No. 60CV-15-2921

IN THE CIRCUIT COURT OF PULASKI COUNTY, ARKANSAS
FIFTH DIVISION

STACEY JOHNSON,
JASON McGEHEE,
BRUCE WARD,
TERRICK NOONER,
JACK JONES,
MARCEL WILLIAMS,
KENNETH WILLIAMS,
DON DAVIS, and
LEDELL LEE PLAINTIFFS

v.

WENDY KELLEY, in her official capacity as
Director, Arkansas Department of Correction, and
ARKANSAS DEPARTMENT OF CORRECTION DEFENDANTS

SECOND AMENDED COMPLAINT
FOR DECLARATORY AND INJUNCTIVE RELIEF

I. Introduction

1. In this action, the Plaintiffs, Arkansas prisoners under death sentences (hereinafter "the Prisoners"), seek equitable relief against Wendy Kelley, the Director of the Department of Correction, and against the Arkansas Department of Correction (collectively, "the ADC"). The Prisoners challenge as unconstitutional Arkansas Act 1096 of 2015 (the new lethal-injection statute), which grants the ADC extensive new discretion and purports to legitimize unnecessarily risky lethal-injection procedures. The

Prisoners also challenge as unconstitutional the particular lethal-injection protocol that the ADC has adopted under the new statute, which creates a demonstrated risk of severe pain that is substantial when compared to known and available alternatives. The Prisoners seek, among other things, a declaration that Act 1096 is unconstitutional, a permanent injunction forbidding the ADC from executing them under Act 1096, and a permanent injunction forbidding the ADC from executing them pursuant to its current lethal-injection procedure.

II. Procedural History

2. The Prisoners originally challenged the lethal-injection statute and protocol in a complaint filed on April 6, 2015 (Case No. 60CV-15-1400), the same day that Act 1096 became law.

3. On April 10, 2015, the ADC noticed the removal of 60CV-15-1400 to federal court.

4. On April 18, 2015, the Prisoners voluntarily dismissed the federal case without prejudice.

5. That same day, with no federal case to block state-court litigation, the Prisoners filed an amended complaint in 60CV-15-1400.

6. On May 5, 2015, the Prisoners—seeking to advance this matter with diligence to avoid any emergency litigation—served the ADC with comprehensive discovery requests in 60CV-15-1400.

7. On May 19, 2015, the ADC filed a motion to dismiss, which raised a formalistic challenge to this Court's jurisdiction. The ADC's motion conceded that this Court did have jurisdiction over the Prisoners' causes of action but complained that the Court needed to exercise that jurisdiction under a different case number.

8. Out of an abundance of caution, and to ensure that there is no question about the jurisdiction of this Court, the Prisoners filed this new action (60CV-15-2921) on June 29, 2015, to get the new case number the ADC insisted they acquire.

9. On July 17, 2015, based on the parties' stipulation, this Court dismissed without prejudice case number 60CV-15-1400 in deference to this case (60CV-15-2921), in which its jurisdiction is undisputed.

10. On September 9, 2015, the State set execution dates for all the Prisoners except Ledell Lee.

11. On September 28, 2015, the Prisoners filed an Amended Complaint asserting eight causes of action: (1) Act 1096 violates the Contracts Clause of the Arkansas Constitution, Art. 2, § 17; (2) Act 1096

violates the Speech Clause of the Arkansas Constitution, Art. 2, § 6; (3) Act 1096 violates the procedural protections of the Cruelty Clause of the Arkansas Constitution, Art. 2, § 9; (4) Act 1096 violates the Due Process Clause of the Arkansas Constitution, Art. 2, § 8; (5) Act 1096 violates separation of powers, Art. 4; (6) Act 1096 substantively violates the Cruelty Clause; (7) Act 1096 violates the Ex Post Facto Clause of the Arkansas Constitution, Art. 2, § 17; (8) Act 1096 violates the Publication Clause of the Arkansas Constitution, Art. 19, § 12.

12. On September 30, 2015, the Prisoners filed an Emergency Motion for Partial Summary Judgment or, Alternatively, for a Preliminary Injunction.

13. On October 5, 2015, the State moved to dismiss the Amended Complaint. The Court dismissed (1) the Separation of Powers claim insofar as it alleged that Act 1096 delegates excessive authority to select execution drugs and (2) the Ex Post Facto Claim. The Court denied the motion to dismiss on all other claims.

14. On October 9, 2015, the Court issued a temporary restraining order ("TRO") preventing the State from executing the Prisoners pending a preliminary-injunction hearing.

15. On October 13, 2015, the State filed a petition for certiorari in the Arkansas Supreme Court, No. CV-15-829, asking the Supreme Court to vacate this Court's TRO.

16. On October 20, 2015, the Supreme Court vacated this Court's TRO but issued its own stay of executions "pending the resolution of the litigation currently pending in Pulaski County Circuit Court, No. 60CV-15-2921."

17. On December 3, 2015, this Court ruled upon the parties' earlier cross-motions for summary judgment. The Court (1) granted summary judgment to State on the Separation of Powers claim insofar as it alleged that the Act infringes upon the authority of the judiciary; (2) granted summary judgment to the Prisoners on their claims under the Contracts Clause, the Speech Clause, the procedural component of the Cruelty Clause, the procedural component of the Due Process Clause, and the Publication Clause; and (3) denied summary judgment on the substantive Cruelty Clause and substantive Due Process claims.

18. On December 3, 2015, the State filed notice of an interlocutory appeal.

19. On June 23, 2016, the Arkansas Supreme Court reversed. In its opinion, the Supreme Court adopted the two-part test stated in *Glossip v.*

Gross, 135 S. Ct. 2726 (2015). That test requires prisoners challenging the method of their execution to (1) show that the method involves a "demonstrated risk of severe pain" and (2) "plead and prove a known and available alternative" that would substantially reduce the risk. *Id.* at 2737, 2739. The Supreme Court held that the Prisoners had not sufficiently pled an alternative execution method. *See Kelley v. Johnson*, 2016 Ark. 268, at 18–19. The opinion said nothing about the Prisoners' evidence that the current execution method poses an unacceptable risk of severe pain.

20. The Arkansas Supreme Court ordered the Prisoners' Amended Complaint dismissed. The order was silent on whether the dismissal was with prejudice or without prejudice. When a court dismisses a complaint for failure to state adequate facts, "it is improper for such a dismissal to be granted with prejudice and without leave to plead further pursuant to [Ark. R. Civ. P. 12(j)]." *Ballard Grp., Inc. v. BP Lubricants USA, Inc.*, 2014 Ark. 276, at 19, 436 S.W.3d 445, 456. Accordingly, the Prisoners have the right to replead those portions of the Amended Complaint that the Arkansas Supreme Court found deficient.

21. The Prisoners now amend their Amended Complaint pursuant to Ark. R. Civ. P. 15(a), which provides, in pertinent part, that "a party may amend his pleadings at any time without leave of court."

III. Summary of Causes of Action

22. In summary form, the Prisoners' causes of action are as follows:

a. Claim 1: Substantive Violations of Art. 2, § 9: Act 1096 and Arkansas's chosen lethal-injection procedure substantively violate the ban on cruel or unusual punishment found in Art. 2, § 9 of the Arkansas Constitution. Under the Act, the ADC has adopted a three-drug procedure (midazolam then vecuronium bromide then potassium chloride). This protocol subjects each Prisoner to an objectively intolerable and objectively unreasonable risk of serious harm. In the best case, it will fail to adequately sedate the Prisoners and will paralyze them so they are unable to express the feeling of suffocation and of being burned alive that the second and third drugs will cause. As a scientific matter, and as manifested in executions in Ohio, Oklahoma, Arizona, and Alabama, there is no chance this protocol will avoid causing the Prisoners torturous pain and a high chance it will lead to a botched execution. Several available alternative execution procedures, specified below, would significantly reduce the risk of pain and suffering. The statute is not severable; accordingly, the entire statute is invalid.

b. Claim 2: Violation of Due Process under Art. 2, § 8. The fundamental fairness guaranteed by the state due-process clause requires that condemned inmates be given access to information necessary to determine whether a cruel-or-unusual-punishment violation exists. Specifically, the Prisoners are entitled to information showing that the drugs come from a reliable (read: FDA-approved) manufacturer and that the drugs meet applicable potency requirements. By permitting the ADC to conceal such information, Act 1096 violates Article 2, § 8 of the Arkansas Constitution.

c. Claim 3: Violation of Due Process under Art. 2, § 9. Act 1096 violates procedural protections implied by Art. 2, § 9 of the Arkansas Constitution. This provision protects any prisoner from cruel or unusual punishment. An implication of the right to be free from cruel or unusual punishment is a right to information necessary to determine whether a punishment would be cruel or unusual. Information showing that the drugs come from a reliable (read: FDA-approved) manufacturer and that the drugs meet applicable potency requirements is necessary to determine whether Arkansas's execution procedure will be cruel or unusual. Act 1096 prevents the Prisoners

from accessing such information and thus violates the state guarantee against cruel or unusual punishment.

d. Claim 4: Violation of Separation of Powers: Act 1096 violates Art. 4 of the Arkansas Constitution (the Separation-of-Powers Article) in two separate respects:

i. First, the Act violates separation-of-powers by unlawfully delegating excessive discretion to the ADC, an executive department. A divided Arkansas Supreme Court very narrowly upheld Ark. Code Ann. § 5-4-617 (2014), the method of execution law as it existed prior to Act 1096. *See Hobbs v. McGehee*, 2015 Ark. 116. Rather than contenting itself with the substantial discretion narrowly allowed by *McGehee*, the General Assembly chose in Act 1096 to vest the ADC with extensive additional discretion. This new discretion is a bridge too far. Act 1096 newly vests the ADC with a discretion unbounded by any meaningful definition of the chemical compounds that will actually comprise the lethal injection and permits the ADC absolute say in choosing among (1) a safe barbiturate approved by the FDA and made by a well-regulated pharmaceutical manufacturer, (2) the incredibly risky grey-market chemicals

cooked up by unregulated compounding pharmacists—chemicals which have resulted in multiple botched executions in other states, or (3) a three-drug protocol that is assured to cause severe pain and suffering while cloaking such torture by paralyzing the subject as he is burned alive from the inside. The new discretion conferred by Act 1096, when considered along with the substantial discretion already provided by § 5-4-617 (2014), renders Act 1096 invalid under *Hobbs v. Jones*, 2012 Ark. 293. The statute is not severable; accordingly, the entire statute is invalid.

ii. Second, the Act violates the separation of powers by impairing the judicial function. The judiciary has the prerogative and responsibility to review actions of the executive department for compliance with constitutional commands. Specifically, the judiciary has the prerogative and responsibility to ensure that a prisoner's right to be free from cruel and unusual punishment is protected, and it has a duty to ensure that the ADC does not violate Art. 2 § 9 in carrying out any execution. Act 1096 shrouds in secrecy information that is critical to the judiciary's ability to exercise these prerogatives and fulfill these duties. Thus, it

violates the separation of powers. The statute is not severable; accordingly, the entire statute is invalid.

e. Claim 5: Violation of the Ex Post Facto Clause: Act 1096 violates the ex post facto clause of the Arkansas Constitution (Art. 2, § 17) because it creates a significant risk that the Prisoners will experience a more painful execution and more anxiety leading up to the execution.[1]

IV. Parties

23. The Plaintiffs are all prisoners under a sentence of death and in the custody of the ADC while awaiting execution.

24. Defendant Wendy Kelley is the Director of the ADC. Defendant Kelley oversees the ADC and all of its employees and agents. She is personally responsible for procuring drugs for use in lethal injection.

25. Defendant Arkansas Department of Correction is an agency of the executive branch of the State of Arkansas. The ADC is responsible for

[1] The Prisoners acknowledge that the Court previously dismissed their Separation of Powers and Ex Post Facto claims. Repleading is necessary here to preserve the right to appeal denial of those claims. *See McMullen v. McHughes Law Firm*, 2015 Ark. 15, at 11, 454 S.W.3d 200, 207 ("[A]n amended complaint, unless it adopts and incorporates the original complaint, supersedes the original complaint."). Though the claims have now been renumbered, this Second Amended Complaint repeats the Separation of Powers and Ex Post Facto Claims verbatim from the Amended Complaint.

carrying out death sentences in general and for procuring and using lethal-injection drugs.

V. Jurisdiction and Venue

26. This Court has jurisdiction over the subject matter of this action pursuant to Arkansas Constitutional Amendment 80, the declaratory-judgment statute, Ark. Code Ann. § 16-111-101 *et seq.,* and Ark. Code Ann. § 17-87-105. This Court has personal jurisdiction over the Defendants under Ark. Code Ann. § 16-4-101(B).

27. Venue in this Court is authorized by Ark. Code Ann. § 16-60-103(3), which allows suits against state agencies and state officers to be brought in Pulaski County.

VI. Statement of Facts

A. Prior Legislation and Litigation

28. Lethal injection has been Arkansas's method of execution since 1983.

29. In 2009, the General Assembly rewrote Arkansas's method-of-execution statute to grant the ADC unfettered discretion to select any chemical or chemicals to use in lethal-injection procedures without providing it any guidance on how to go about making the selection. *See* Arkansas Act 1296 of 2009, Ark. Code Ann. § 5-4-617 (2010).

30. The Arkansas Supreme Court subsequently struck down this statute as an unlawful delegation of legislative authority because it lacked reasonable guidance containing sufficient standards to cabin the ADC's discretion, in violation of the Separation-of-Powers Article. *See Hobbs v. Jones*, 2012 Ark. 293.

31. In response, the General Assembly adopted a new method-of-execution statute, Arkansas Act 139 of 2013, Ark. Code Ann. § 5-4-617 (2014).

32. The 2013 law, among other things, stated: "The Department of Correction shall carry out the sentence of death by intravenous lethal injection of a barbiturate . . ."

33. Significantly, the 2013 statute required the ADC to select a **manufactured** barbiturate. *See* Arkansas Act 139 of 2013 §§ 1(d), 2(c), 2(e)(2)(E).

34. Under an emergency clause, the 2013 statute became effective on February 20, 2013.

35. On April 11, 2013, the ADC adopted a new lethal-injection procedure under the authority of the new statute. The procedure called for condemned inmates to be injected with specified quantities of Lorazepam and Phenobarbital Hydrochloride. *Id*. at 9.

36. On April 26, 2013, the Prisoners filed a lawsuit challenging both the 2013 statute and the specific procedure the ADC had adopted. *See McGehee et al. v. Hobbs et al.*, No. 60CV-13-1794 (Pulaski County Cir. Ct.). Among other things, the Prisoners argued that Act 139 still unlawfully delegated legislative authority to the ADC by granting it unfettered discretion to choose among a broad range of drugs and by granting it unfettered discretion over whom to select for its execution team and whether to train them.

37. On February 21, 2014, this Court entered summary judgment for the Prisoners, striking down Arkansas Act 139 of 2013, Ark. Code Ann. § 5-4-617 (2014), as contrary to the Separation-of-Powers Article of the Arkansas Constitution.

38. On appeal, a divided Arkansas Supreme Court reversed and narrowly upheld the validity of Arkansas Act 139 of 2013, Ark. Code Ann. § 5-4-617 (2014). The opinions in the case make clear that the question was close.

B. Arkansas Act 1096 of 2015

39. On April 6, 2015, the Governor signed Act 1096 of 2015, attached hereto as Exhibit 1.

40. Section 2(a)–(c) of Act 1096 deletes the requirement that the ADC use a barbiturate drug—a requirement that had been imposed by Arkansas Act 139 of 2013, Ark. Code Ann. § 5-4-617 (2014), and was essential to the Arkansas Supreme Court upholding the law.

41. Section 2(c) gives the ADC the discretion to forego using a barbiturate and to use the following drugs instead: "Midazolam, followed by vecuronium bromide, followed by potassium chloride."

42. Act 1096 deletes the requirement that the ADC use safe, FDA-regulated, bulk-manufactured drugs. Specifically, it deletes three references to manufactured drugs that had been in Arkansas Act 139 of 2013, Ark. Code Ann. § 5-4-617 (2014), and, in context, required the ADC to use safe, FDA-regulated, bulk-manufactured drugs.

43. In lieu of a requirement that the ADC use safe, FDA-regulated, bulk-manufactured drugs, Section 2(d) of Act 1096 gives the ADC unfettered discretion to use drugs "[o]btained from a compounding pharmacy."

44. Finally, Section 2(b) of Act 1096 purports to allow private parties and the ADC to deliver, receive, dispense, and administer controlled substances without a prescription.

C. Problems with Compounded Drugs

45. Act 1096 provides the ADC with unfettered discretion to use compounded drugs. *See* Ark. Code Ann. § 5-4-617(d) (2015).

46. The use of compounded drugs in executions would create grave risks as compared to FDA-approved bulk-manufactured drugs. Exh. 9, Aff. of Larry D. Sasich. In contrast to bulk-manufactured drugs, which are subject to stringent oversight by the FDA, the oversight of compounding pharmacies in the United States "is at best haphazard." *Id.* ¶ 8. The use of compounded drugs in executions "carries a substantial risk of causing . . . unnecessary and lingering pain and suffering" because such drugs are "of unknown composition" and are "highly likely to be contaminated" or to be otherwise "compromised" in terms of quality. *Id.* ¶ 30.

47. Act 1096 provides the ADC with unfettered discretion to choose between drugs proven to be pure and effective by FDA approval and compounded drugs, which carry a substantial risk of causing unnecessary and lingering pain and suffering.

D. Differences Within the Class of Barbiturate Drugs

48. Act 1096 provides the ADC with unfettered discretion to choose any drug among the broad class of drugs known as barbiturates. *See* Ark. Code Ann. § 5-4-617(c)(1) (2015).

49. Dr. David Waisel, a practicing anesthesiologist and professor of anesthesia at Harvard, attests to the wide differences among different barbiturates. Exh. 10. As Dr. Waisel explains, barbiturates range from ultra-short-acting, which produce "a rapid onset in the body (typically within seconds)," to long-acting, which "may take considerably longer to take effect in the body, as well as may stay in the body for a significantly longer time." *Id.* ¶¶ 3–4.

50. Thus, considering Section 2(c)(1) in isolation, just that portion of Act 1096 gives the ADC unfettered discretion to execute the prisoners using a drug that would take effect within seconds or to execute the prisoners using a drug that could take an hour to take effect, resulting in a prolonged execution and lingering death.

E. The Lack of Qualification and Training Requirements

51. Act 1096 provides ADC's director with unfettered discretion to determine "the identity . . . of the persons involved with carrying out the sentence of death." Ark. Code Ann. § 5-4-617(g)(1)(G).

52. Arkansas's statute acknowledges that the execution procedure requires the intravenous injection of controlled substances, the use of technical "medical equipment" and "medical supplies" such as "catheters,"

and the proper sterilization of such medical equipment and supplies. Ark. Code Ann. §§ 5-4-617(f), (g)(1), (i)(2)(B).

53. Yet the Act contains no requirement whatsoever that "the persons involved with carrying out the sentence of death" have any relevant medical or technical qualifications or training.

54. The director could, consistent with the Act, pick prison guards, relatives of the decedents, or just random people off the street to carry out the entirety of the execution procedure. The Act is devoid of standards or guidelines to govern the choice of personnel.

F. The ADC Has Adopted a Three-Drug Protocol

55. Act 1096 gives the ADC unfettered discretion to choose between a one-drug barbiturate execution protocol and a three-drug execution protocol that omits the use of any barbiturate drug. Ark. Code Ann. § 5-4-617(c).

56. The ADC exercised its discretion under Section 2(c)(2) of Act 1096 to execute the Prisoners using "Midazolam, followed by vecuronium bromide, followed by potassium chloride." The Lethal Injection Procedure, which is attached hereto as Exhibit 2, provides in pertinent part:

a. The condemned inmate will first be injected with 500 mg of midazolam.

b. After at least five minutes, a member of the execution team "will confirm the inmate is unconscious" using unspecified techniques.

c. The inmate will next be injected with 100 mg of vecuronium bromide.

d. The inmate will then be injected with 240 mEq of potassium chloride.

57. On July 10, 2015, Deputy Attorney General David Curran emailed the Prisoners' counsel to notify them that the ADC had purchased midazolam, vecuronium bromide, and potassium chloride.

58. The ADC's initial batch of vecuronium bromide expired on June 30, 2016. On July 12, 2016, counsel for the Prisoners learned via an ADC press release that the ADC had acquired a new supply of vecuronium bromide that expires on March 1, 2018. The ADC has not informed the Prisoners whether the drugs were made by an FDA-approved manufacturer; obtained from an FDA-registered facility; or obtained from a compounding pharmacy that has been accredited by a national organization that accredits compounding pharmacies.

59. According to invoices the ADC provided to the Prisoners in response to a FOIA request, the ADC conducted a "purity analysis" of the

new batch of vecuronium bromide. The ADC has not informed the Prisoners of the results of the purity analysis.

60. The ADC's supply of potassium chloride expired on January 1, 2017. As of this filing, the ADC has not restocked potassium chloride.

G. The ADC's Three-Drug Protocol is Fundamentally Flawed.

61. The three-drug procedure the ADC has adopted will cause severe pain and suffering.

62. Counsel for the Prisoners have retained Dr. Craig W. Stevens, Ph.D., a Professor of Pharmacology at Oklahoma State University–Center for Health Sciences, to study Arkansas's lethal-injection protocol and author an extensive expert opinion and report. Dr. Stevens's Amended Report is attached hereto as Exhibit 3.

63. Dr. Stevens has extensive experience evaluating lethal-injection protocols. "With regard to the pharmacological issues of lethal injection, [he has] worked as a consultant with the state as well as with attorneys representing condemned inmates." Exh. 3 at 4. Dr. Stevens has also worked with "both the prosecution . . . and the defendant" on criminal "cases involving pharmacological issues." *Id*.

64. After a thorough review of the matter, Dr. Stevens has concluded that the scientific literature mandates a categorical conclusion: "A prisoner

sedated only with midazolam would be conscious of the suffocating effects of vecuronium bromide but, as a result of its paralytic properties, be unable to communicate his or her distress. The prisoner would also be subjected to the burning sensation of the 3rd drug, potassium chloride." *Id.* at 34.

i. The Second and Third Drugs in Arkansas's Execution Procedure Will Cause Severe Pain and Suffering Unless the Prisoner is First Placed under General Anesthesia.

65. As Dr. Stevens explains in detail, the effects of the second drug in Arkansas's Lethal Injection Procedure, vecuronium bromide, are harrowing:

> Vecuronium, like pancuronium, is a drug classified as a neuromuscular blocker or simply called a paralytic drug. Neuromuscular blockers work by blocking the action of acetylcholine which is the neurotransmitter released from a nerve ending onto the muscle that causes the muscle to contract (*Hibbs and Zambon 2011*). Clinical uses of neuromuscular blockers are to provide muscle relaxation for endotracheal intubation, and to ensure patient immobility during surgery or mechanical ventilation (*Kovac 2009, Vecuronium Bromide for Injection Prescribing Information*). Vecuronium is a chemical analog to pancuronium and is about 1.5 to 1.75 times more potent than pancuronium (*Fahey et al. 1981*). Vecuronium has about the same onset time as pancuronium (within 5 minutes) but has a shorter duration of action, and produces no cardiovascular effects or changes in heart rate or blood pressure. With higher doses of vecuronium, the onset time can be reduced to 2.4 minutes (*Hilgenberg 1983*).
>
> The clinical effects of vecuronium are shared by other neuromuscular blockers and include progressive loss of skeletal muscle contraction, first noted by drooping eyelids and muscle weakness (*Hibbs and Zambon 2011*). Motor weakness progresses eventually to a total flaccid paralysis. The small, quick muscles of

the eyes, jaw, and larynx relax before those of the arms, legs, and trunk of the body. Finally, the intercostal muscles that expand the ribs and the diaphragm are paralyzed, and breathing ceases. Without intubation and mechanical ventilation, death ensues from a lack of oxygen (hypoxia).

There are a few studies of the effect of neuromuscular blockers given in human volunteers without an anesthetic agent. In a classic 1947 paper, a complete description of the effects of tubocurarine, an early neuromuscular blocker, on the central nervous system was examined (*Smith et al. 1947*). These researchers found that neuromuscular blockers had no effect on altering consciousness, memory, and had no analgesic effect. They concluded that these paralytic drugs should not be used alone as they may cause "serious psychic trauma." A later study using trained anesthesiologists and the researchers themselves, found that in these awake subjects, vecuronium had no effect on consciousness and, like the earlier study by Smith and colleagues, that the most distress came from a feeling of shortness of breath and 'air hunger', even as they were artificially ventilated with supplemental oxygen at sufficient levels (*Topulos et al. 1993*). As early as 1950 clinicians realized that the use of paralytic drugs like vecuronium and pancuronium without adequate anesthesia leads to the possibility that a patient could be awake but incapable of indicating distress or pain because of muscle paralysis (*Brice 1970*).

While these above studies were done on the researchers themselves that were trained in the procedures and knew what to expect, most research on the adverse effects of vecuronium and other neuromuscular blockers comes from cases where conscious patients were completely paralyzed but unable to communicate with health care workers. In emergency care, patients who experienced paralysis without sedation or anesthesia reported dysphoria and severe pain (*Chong 2014*). Patients in intensive care units who were paralyzed with pancuronium because they were intubated and on mechanical ventilators, but were not sedated and were conscious, reported that they felt "buried alive" and some thought they were already dead (*Perry 1985*). Most of

> these patients said they would rather die than go through 4 days of being paralyzed while conscious again. A study of patients that emerged from anesthesia but were still paralyzed from neuromuscular blockers gave reports of panic, suffocation, and a feeling of already being dead (*Thomsen et al. 2015*). These experiences were horrific enough to trigger post-traumatic stress disorder (PTSD) in some unfortunate patients.
>
> The above papers show that vecuronium or pancuronium, or any other paralytic drug, should only be used in patients that are anesthetized and unconscious. In documented cases where patients or experimental subjects were awake but paralyzed, intolerable and damaging experiences of pain, panic, and suffocation occurred.

Id. at 20–21.

66. Dr. Stevens attests that potassium chloride, the third drug in Arkansas's Lethal Injection Procedure, causes severe "burning pain." *Id.* at 37. He elaborates as follows:

> There are a few cases of high dose potassium chloride injection in awake patients, which only occurs as a result of an accident or intentional homicide in the hospital setting (*Wetherton et al. 2003*). The earliest report of an accidental high dose of IV potassium chloride due to improper mixing was in a male patient who immediately complained of a severe pain moving up his arm (above the site of the IV) and a ringing in his ears (*Lankton et al. 1973*). The patient then lost consciousness, stopped breathing, and his heart stopped beating. Another case study in that same year reported that an IV infusion of potassium chloride produced severe pain at the site of the IV infusion (*Williams 1973*). In a forensic report of four IV potassium chloride-induced deaths at hospital, one man who accidentally received a high dose IV infusion of potassium chloride screamed out in pain (*Wetherton et al. 2003*). Potassium chloride IV injections are also documented as a rare method of suicide in health care workers, but self-

> reports of the effects noted by these persons are unavailable (*Battefort et al. 2012, Bertol et al. 2012*).
>
> The above studies show that IV administration of potassium chloride at high doses leads to severe pain in awake, unanesthetized patients.

Id. at 21–22.

67. Because vecuronium bromide and potassium chloride each cause extreme pain, it is essential that a prisoner reach a state of general anesthesia before these two drugs are administered. *Id.* at 22. Unless the prisoner reaches a state of general anesthesia—which, as Dr. Stevens explains, is distinct from lesser levels of sedation, *id.* at 10–13—he will consciously experience the "serious psychic trauma" caused by the suffocating effects of vecuronium bromide and the severe burning pain caused by potassium chloride. *Id.* at 20–22

68. Furthermore, because vecuronium bromide paralyzes every muscle in the body, a prisoner would manifest no external signs of distress despite experiencing this conscious suffocation and searing pain. *Id.* at 34. Even though the prisoner would subjectively experience extreme agony, the execution would appear peaceful to external observers.

ii. The First Drug in Arkansas's Execution Procedure, Midazolam, is Pharmacologically Incapable of Inducing General Anesthesia at Any Dose, Meaning That the Prisoners Will Consciously Experience the Agonizing Effects of the Second and Third Drugs.

69. As Professor Stevens documents in great scientific detail, midazolam is **physically incapable of inducing general anesthesia**, no matter how much of the drug is given. *Id.* at 5–14, 23–35.

70. Midazolam, unlike barbiturates and other anesthetic drugs, has a "ceiling effect." *Id.* at 8–9, 23–24, 35. That is, there is a maximum amount of sedation midazolam can produce, and no matter how much more of the drug is given, no further effect will be achieved. *Id.*

71. Midazolam has a "ceiling effect" because, unlike anesthetic drugs, midazolam has no independent depressive effect; it produces a depressive effect only by pairing with a neurotransmitter called GABA already present in the body—but present in limited quantities. *Id.* at 7–8, 23–24.

72. "GABA is a limited resource in the brain." *Id.* at 23. When the body's natural supply of GABA has been exhausted, additional midazolam will have no effect whatsoever because, again, midazolam does not have any independent effect but acts only by pairing with GABA.

73. Using a rigorous methodology, Dr. Stevens's Report demonstrates that "a 228 mg IV dose of midazolam would be expected to reach the

threshold concentration of midazolam to produce a ceiling effect."[2] *Id.* at 32. (emphasis in original). The additional 272 milligrams called for by Arkansas's execution procedure is pointless; because no more GABA is available to pair with this additional 272 milligrams, it will have no effect. *Id*. at 7–8, 23–24.

74. More importantly, the maximum level of sedation that can be produced by midazolam—*i.e.*, the state of sedation reached through midazolam doses at or above the "ceiling"—is not sufficient to render any Prisoner insensate to pain or suffering. *Id.* at 35. Thus, whether the ADC injects a Prisoner with 228 milligrams of midazolam, 500 milligrams of midazolam, or 10,000 milligrams of midazolam, the result will be the same: the Prisoner will consciously suffocate to death under the effects of vecuronium bromide, while also consciously experiencing the searing, burning pain produced by potassium chloride. *Id*. at 35.

[2] In the Amended Complaint, Dr. Stevens calculated the ceiling-effect dosage as 20 mg. This calculation resulted from a mathematical error in Dr. Stevens's original report. Specifically, on page 23 of his report, where Dr. Stevens calculated "an initial plasma concentration of 120,000 ng/mL of midazolam after a 500 mg IV dose," he should have calculated "an initial plasma concentration of 12,000 ng/mL of midazolam after a 500 mg IV dose." As Dr. Stevens explains in an introduction to the amended report, the error does not affect his overall conclusion that midazolam cannot render the Prisoners insensate to the pain sure to be caused by the vecuronium bromide and the potassium chloride. Exh. 3 at 1. Additionally, as Dr. Stevens discusses in his report, other researchers using a different methodology—examination of bispectral-index data in patients injected with midazolam—have identified midazolam's ceiling effect as occurring at about 25 mg. *Id.* at 34.

75. In *In re Ohio Execution Protocol Litigation*, No. 11-1016, 2017 WL 378690 (Jan. 26, 2017), the U.S. District Court for the Southern District of Ohio, relying in large part on Dr. Stevens's expert testimony, found that "use of midazolam as the first drug Ohio's present three-drug protocol will create a 'substantial risk of serious harm' or an 'objectively intolerable risk of harm' as required by *Baze* [*v. Rees*, 553 U.S. 35 (2008),] and *Glossip*." *Id.* at *53.

iii. The ADC's "Consciousness Check" Provides No Protection

76. As noted, the ADC's Lethal Injection Procedure states that a member of the execution team "will confirm the inmate is unconscious" using unspecified techniques. However, this consciousness check "does not provide ***any*** assurance" that the Prisoner "will be sufficiently anesthetized or that he will not experience the pain and suffering caused by the second two drugs in Arkansas's protocol." Exh. 3 at 22 (emphasis added).

77. As an initial matter, the Stevens Report documents that even trained anesthesiologists using actual anesthetic drugs and sophisticated techniques frequently misdiagnose patients as being unconscious when, in fact, they are actually aware and sensitive to pain. *Id.* Arkansas's Lethal Injection Procedure does not require an anesthesiologist, a doctor, or even a nurse to check the Prisoners; the person purporting to check a given Prisoner

for consciousness need not have any medical degree or license at all. As Dr. Stevens explains, this increases the risk for error. *Id.*

78. The ADC's "consciousness check" fails on a more fundamental level. Any determination that a prisoner is unconscious in the sense that he would not experience the agonizing effects of the second and third drugs would **necessarily be erroneous** because midazolam (the only sedative drug in the ADC's Lethal Injection Procedure) is **physically incapable of producing general anesthesia**, and absent a state of general anesthesia, the Prisoners will experience an agonizing death. *Id.* at 10–13, 22, 35.

* * *

79. For these reasons, the ADC's Lethal Injection Procedure will cause severe pain and suffering.

H. There Have Been Multiple Botched Executions Using Midazolam.

80. The conclusion in Dr. Stevens's report—that midazolam will not adequately sedate the Prisoners—has been borne out in at least four botched executions using midazolam.

a. On January 16, 2014, Ohio executed Dennis McGuire using a combination of 10 mg midazolam and 40 mg hydromorphone. The execution took twenty-five minutes and "was accompanied by

movement and gasping, snorting and choking sounds." Erica Goode, *After a Prolonged Execution in Ohio, Questions over 'Cruel and Unusual'*, N.Y. TIMES, Jan. 17, 2014, *available at* http://nyti.ms/2glQUyI.

b. On April 29, 2014, Oklahoma executed Clayton Lockett using 100 mg midazolam followed by a paralytic and potassium chloride. Lockett awoke during administration of the second and third drugs. Though the execution was halted, Lockett died forty minutes after the execution began. *See Glossip*, 135 S. Ct. at 2782 (Sotomayor, J., dissenting).

c. On July 23, 2014, Arizona subjected Joseph Wood to an execution in which he was injected with 750 mg midazolam and 750 mg hydromorphone. Wood "gasped and snorted for nearly two hours" before he finally died. *Id.* at 2791.

d. Most recently, on December 8, 2016, Alabama executed Ronald Bert Smith using 500 mg of midazolam followed by 600 mg of rocuronium bromide followed by 240 mEq potassium chloride. During the execution, which took thirty-four minutes, Smith "was apparently struggling for breath as he heaved and coughed for about 13 minutes." Mark Berman & Robert Barnes, *After Divided Supreme Court Allows*

Alabama Execution, Inmate Heaves and Coughs During Lethal Injection, WASH. POST, Dec. 9, 2016, *available at* http://wapo.st/2hnRs7p. According to Spencer Hahn, an attorney for Smith present at the execution, two minutes after the midazolam began flowing, Smith began having "regular asthmatic-sounding barking coughs every ten seconds or so." Exh. 11 ¶7. "He also lifted his head and looked around, moved his arms, clenched his left hand, and moved his lips in what appeared to be an attempt to say something. [His] eyes never closed, and he moved and coughed regularly throughout approximately the next fifteen minutes." *Id.* Smith was awake after the first consciousness check, "as he was still moving his head, hands and arms, coughing, and attempting to speak." *Id.* ¶8. After the second consciousness check, Smith's "eyes remained open" (despite a guard's attempt to push his left eye closed), and Smith "moved his right arm." *Id.* ¶10–11. "Shortly thereafter, they must have administered the paralytic, as [Smith's] breathing became very shallow and he stopped moving. His eyes remained open, with the left eye opening further as his breathing became imperceptible." *Id.* ¶11.

I. Multiple, Superior Alternatives to the ADC's Three-Drug Procedure Are Available.

81. Multiple alternative execution procedures are available that would significantly reduce the risk of pain and suffering.

82. First, execution by firing squad would carry a significantly reduced risk of pain and suffering as compared to the ADC's three-drug lethal-injection protocol. This method provides a more humane and reliable means than the torturous chemical procedure the ADC seeks to use.

a. As it has previously admitted in this litigation, the State of Arkansas has access to guns, ammunition, and personnel skilled in the use of firearms. Ans. to Am. Compl. at 18. A firing squad is thus an available method of execution.

b. Execution by firing squad is feasible, as is evident from the June 18, 2010, firing-squad execution of Ronnie Lee Gardner by the State of Utah and the firing-squad protocol used by the State of Utah in that execution. That protocol, which is attached as Exhibit 5, calls for the following procedures, each of which is possible for the ADC to implement without excessive difficulty:

i. The execution is carried out at a "secure correctional facility operated by the department." Ex. 5 at 51.

ii. The firing squad consists of five certified peace officers designated by the director of the Corrections Department, with two additional officers selected as alternates. *Id.* at 55.

iii. The peace officers selected must "demonstrate proficiency with weapons designated to carry out the execution." *Id*. Each officer must fire each designated weapon from a distance of 21 feet at a target the same dimension as that to be attached to the condemned. *Id.* An officer is disqualified if s/he fails "to accurately hit the specified target with one round from each weapon fired." *Id.*

iv. The leader of the execution team will arrange for .30 caliber rifles, live rounds of ammunition, and blank rounds of ammunition. *Id.* at 62. The execution-team leader will also arrange for practice sessions and ensure that the equipment is clean and that there are backup .30 caliber rifles and ammunition. *Id.*

v. There are at least three rehearsals for the execution. *Id.* at 92–93.

vi. Before the execution, the condemned is escorted to the execution chamber and tied to a chair. *Id.* at 76–77.

vii. The execution-team leader loads the weapons with two rounds each. *Id.* at 89. One weapon is loaded with two blank cartridges, and "[c]are shall be taken to preclude any knowledge by the members of the firing squad of who is issued the weapon with the two blank cartridges." *Id.* at 89–90.

viii. A designated person places a target over the heart of the condemned. *Id.* at 90. This person leaves the chamber and the chamber is opened for public viewing. *Id.*

ix. After the condemned gives his last words, a hood is placed over the head of the condemned. *Id.*

x. Upon confirmation that no stay of execution has been issued, the firing squad fires the first volley. *Id.* If the condemned appears unconscious, the warden waits a maximum of three minutes and calls for the physician to check vital signs. *Id.* at 91. If no vital signs are detected, the physician will certify death. *Id.* If vital signs are still detected after the passage of ten minutes, the firing squad will fire a second volley. *Id.* at 91–92.

xi. If the condemned appears conscious upon the first volley, the firing squad immediately fires the second volley. *Id.* at 92.

xii. Persons who may come in contact with the condemned inmate's body fluids are provided rubber gloves and bloodborne-pathogen-protection supplies and equipment. *Id.* at 63.

c. Dr. Jonathan Groner, a trauma surgeon and professor, attests that a firing-squad protocol like the one used for Gardner's execution "will cause a nearly instantaneous death" and that this "swift death will also be painless." Exh. 4, Aff. of Jonathan Groner, ¶¶ 6–7. Dr. Groner concludes that the "current midazolam protocol has a far greater risk of causing pain and suffering compared to the firing squad." *Id.* ¶9.

d. Available scientific data further suggest that an execution by firing squad causes rapid death. In a 1938 firing-squad execution in Utah, the executioners used an electrocardiograph to measure electrical activity in the condemned inmate's heart. The inmate's heart stopped 15.6 seconds after he was shot. *See* Deborah W. Denno, *The Firing Squad as "a Known and Available Alternative Method of Execution" Post*-Glossip, 49 U. MICH. J.L. REF. 749, 785–86 (2016). By contrast, when Ronald Bert Smith was executed using a midazolam protocol

similar to Arkansas's, he heaved and coughed for thirteen minutes and took thirty-four minutes to die. *See supra* ¶80.d.

e. Available data show that a substantially greater risk of pain attends lethal-injection than attends the firing squad. Of 144 firing-squad executions in the United States, two have been botched—one because the prisoner refused to be tied to a chair (thus creating a moving target), and one because the executioners intentionally missed their mark. Denno, *supra*, at 787. By contrast, in a study of all executions from 1910–2010, lethal-injection was the method that was botched the most, at a rate of just over seven percent. *Id.* at 781.

83. Second, execution using a massive overdose of an anesthetic gas—namely, sevoflurane—as the sole lethal agent would carry a significantly reduced risk of pain and suffering as compared to the ADC's three-drug lethal-injection protocol.

a. As the Stevens Report attests, an execution using sevoflurane as the sole lethal agent would produce a rapid and painless death. Exh. 3 at 35–37. Sevoflurane has the same mechanism of action as barbiturate drugs and, like barbiturate drugs, is sufficient to cause death on its own. *Id.* at 35. Studies have shown that, unlike midazolam, it would produce a state of anesthesia sufficient to prevent the inmate

from feeling the effects of the second and third drugs in the protocol. *Id.* at 36.

b. It would be feasible for ADC to carry out an execution using sevoflurane. As Dr. Stevens explains, the equipment needed to administer sevoflurane is available on the internet for anyone—including ADC employees—to purchase. *Id.* Administration of sevoflurane does not require medical expertise, and the training materials for operating the machinery is available online free of charge. *Id.*

c. Sevoflurane is available for purchase by the ADC for use in executions. On July 18, 2016, an investigator for the Prisoners contacted Piramal Critical, which is based in Bethlehem, PA, and which manufactures sevoflurane. A representative informed the investigator that Piramal would be willing to sell sevoflurane and isoflurane directly to the ADC for use in executions. *See* Exh. 6, Aff. of Joseph Cummings.

84. Third, execution by nitrogen hypoxia would significantly reduce the risk of pain and suffering compared to that inherent in the current lethal-injection protocol.

a. Nitrogen hypoxia refers to a process whereby a person inhales nitrogen gas. The nitrogen displaces a person's oxygen flow to the brain, thereby causing rapid unconsciousness and death within minutes.

b. Hypoxia is distinct from asphyxia. Asphyxia prevents a person from exhaling carbon dioxide, leading to a feeling of air-hunger and panic. Hypoxia permits the exhalation of carbon dioxide and the effects of oxygen loss are not felt. For this reason, right-to-die proponents advocate nitrogen (or helium) asphyxia for use in euthanasia procedures.

c. Because nitrogen is not a controlled substance, there are no legal barriers to acquiring it. Nor are there the sort of market controls on nitrogen attached to pharmaceuticals by companies who wish not to provide their healing products for the purpose of killing.

d. Oklahoma commissioned a study of nitrogen hypoxia, which is attached hereto as Exhibit 7. The study concludes as follows:

i. Nitrogen hypoxia would cause a prisoner to lose consciousness within twenty seconds and would be "painless" and "peaceful." Exh. 7 at 8–9.

ii. Nitrogen hypoxia is simple to administer in a manner that ensures painless death. Specifically, the method requires fitting a bag over the head of the condemned, filling the bag with the gas, and using an elastic band to prevent the bag from slipping off the head. *Id.* at 6. "The parts needed to create the bag are inexpensive and available locally without prescription." *Id.* A restraint system would ensure that the method works as intended even if the inmate tries to resist (*e.g.*, by attempting to move the bag to access oxygen). *Id.* at 11.

iii. Nitrogen hypoxia would not require the involvement of medical personnel. *Id.* at 9–10.

iv. Nitrogen sources for administering this method are widely available and "should be easy to find and readily available for purchase for such purpose." *Id.* at 11.

e. Effective November 1, 2015, Oklahoma law provides that nitrogen hypoxia is the method of execution if lethal injection is held unconstitutional or is otherwise unavailable. 22 Okla. Stat. § 1014(B).

f. In February 2015, a study commissioned by the Louisiana legislature recommended adding nitrogen hypoxia as an alternative execution method. The study, which is attached hereto as Exhibit 8,

concluded that nitrogen hypoxia would be "the most humane method," that "a Gas Chamber would not be used," and that "nitrogen is readily available." Exh. 8 at 11.

g. As is evident from these studies, nitrogen hypoxia is a feasible and readily available execution method that would substantially reduce the risk of excruciating pain that the midazolam protocol involves.

h. On October 10, 2016, the Arkansas Senate and House Judiciary Committees met jointly to consider whether to commission a study of hypoxia as a method of execution. At the meeting, Cory Cox, legislative director for the Attorney General, told the Committees that they should not adopt hypoxia. *See* John Moritz, *Execution by Gas Gets Panel Flak*, ARK. DEM.-GAZ., Oct. 11, 2016, at A1. In objecting to the study, Rep. Laurie Rushing said that those on death row "need to be punished instead of wasting taxpayer money," "even if it's in the least humane way." *Id.* Ultimately the proposal to commission a study of hypoxia was withdrawn.

85. Fourth, execution by a lethal injection of FDA-approved, manufactured pentobarbital is a known and available alternative.

a. There is currently a market for departments of correction to purchase manufactured pentobarbital. This came to light in *In re Missouri Department of Corrections v. Jordan*, No. 16-3072 (8th Cir. 2016). That case concerned whether the Missouri Department of Corrections ("MDOC") should have to respond to a subpoena from prisoners in a different state. As disclosed in a document made publically available (Exh. 12), the prisoners requested that MDOC produce "all drug labels and package inserts for any drug purchased or obtained by the department, from 2010 to the present, for use in lethal injections." Exh. 12 at 6. MDOC argued to the district court that it couldn't respond to the subpoena insofar as it addressed pentobarbital purchases, because any response would reveal whether MDOC possessed manufactured, FDA-approved pentobarbital. Manufactured drugs have labels and package inserts; compounded drugs don't. By saying there were responsive (though privileged) documents, MDOC would be admitting it possessed manufactured pentobarbital. Nevertheless, MDOC provided the district court a privilege log admitting it had privileged documents in response to the prisoners' request, *id.* at 6–7, thereby admitting that it has been able to obtain manufactured pentobarbital.

See also Chris McDaniel, *Missouri Execution Drug Purchases Revealed*, BUZZFEED, Jan. 8, 2017, *available at* http://bzfd.it/2mg1UQJ.

b. In *Kelley v. Johnson*, the Arkansas Supreme Court upheld the part of the method-of-execution statute that shields drug suppliers from disclosure. MDOC also has a confidentiality provision that allows it not to disclose the source of its execution drugs, which has allowed it to obtain pentobarbital consistently over many years. With this guarantee of confidentiality, ADC will be able to obtain manufactured pentobarbital.

c. Manufactured pentobarbital would substantially reduce the pain and suffering that the current midazolam protocol is certain to cause.

86. Fifth, execution by a lethal injection of compounded pentobarbital is a known and available alternative.

a. As discussed above, compounded drugs carry significant risk. *See supra* Part VI.C. However, that risk is substantially less than that inherent in current three-drug protocol, which is certain to cause the Prisoners excruciating pain for want of adequate sedation.[3]

[3] With appropriate safeguards in place, an execution procedure using compounded pentobarbital would significantly reduce the known risks of harm presented by the use of midazolam. As discussed in ¶46 and in Dr. Sasich's affidavit, compounded

b. Compounded pentobarbital is available to the ADC, as shown by the successful efforts of other departments of correction to obtain compounded pentobarbital for executions. Specifically, the states of Georgia and Texas have recently obtained and used compounded pentobarbital.

c. This execution method is feasible. The ADC has previously carried out lethal injections. Substitution of drugs does not affect the ADC's ability to perform the execution.

87. Sixth, execution using a two-drug protocol consisting of midazolam and potassium chloride would significantly reduce the risk of pain inherent in the current protocol.

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pharmaceuticals carry their own specific risks of causing substantial suffering. For this reason, it is imperative to institute safeguards, including use of a reputable pharmacy that is licensed to compound sterile injectable drugs and testing of the drug shortly before the execution to ensure its identity, potency, and reliability. Once the appropriate safeguards are in place, this method would be acceptable. By suggesting compounded pentobarbital as an alternative, the Prisoners do not waive their right to challenge that method should the ADC one day adopt a protocol using a single injection of compounded pentobarbital. The Prisoners would be entitled to challenge the ADC's choice to use compounded pentobarbital in lieu of other methods that would essentially eliminate the risk caused by injection of compounded drugs (*e.g.*, firing squad).

Any possible challenge to compounded pentobarbital is not ripe for review, however. *Kelley v. Johnson*, 2016 Ark. 268, at 21 n.3. The question at this juncture is not whether compounded pentobarbital would cause substantial pain and suffering, but rather whether it would reduce the pain and suffering midazolam would cause. Surely the ADC would agree that, whatever the risks involved with compounded pentobarbital, it is a superior alternative to a method of execution that is certain to inflict unnecessary pain and suffering on the Prisoners, as exhibited by troublesome executions using midazolam and the scientific evidence in this case.

a. Removal of vecuronium bromide from the current protocol eliminates the feeling of air hunger and being buried alive that the Prisoner is certain to feel absent adequate sedation. Though the execution will still cause the Prisoner pain—because he will still be injected with potassium chloride—this step is certain to reduce a major component of suffering inherent in the current protocol. By choosing a three-drug cocktail rather than a two-drug cocktail, ADC has elected to inflict unnecessary suffering on the Prisoners. The Arkansas Constitution forbids this.

b. This execution method is readily available. The ADC has acquired these drugs in the recent past and has at least one of necessary drugs on hand as of this filing.

c. This execution method is feasible. The ADC stands prepared to execute the Prisoners using a three-drug protocol. Removing one drug from the protocol requires minimal effort.

VII. Claims for Relief

Claim 1: Substantive Violations of Art. 2, § 9:

88. All of the allegations set forth elsewhere in this Second Amended Complaint are incorporated by this reference as if fully set forth herein.

89. The ADC's three-drug Lethal Injection Procedure will cause extreme pain and suffering.

a. Midazolam cannot, at any dosage, render a person unconscious and insensate to pain and suffering.

b. The second and third drugs in the listed protocol indisputably cause extreme pain and suffering.

90. There exist multiple available, alternative methods of executions that would avoid or significantly reduce the risk of pain and suffering. These include:

a. execution by firing squad;

b. execution using a massive overdose of an anesthetic gas—namely, sevoflurane—as the sole lethal agent;

c. execution by nitrogen hypoxia;

d. execution by a lethal injection of manufactured pentobarbital by itself;

e. execution by a lethal injection of compounded pentobarbital by itself;

f. execution by a two-drug cocktail of midazolam followed by potassium chloride.

91. The General Assembly has refused even to study the question of whether nitrogen hypoxia is a more humane execution method, preferring to inflict extreme suffering on the Prisoners rather than "wasting taxpayer money" that would be required to change the protocol.

92. By refusing to remove vecuronium bromide from the protocol, the ADC sanctions a substantial and needless risk that the Prisoners will feel they are being buried alive during the executions. Vecuronium bromide is unnecessary to cause the Prisoners' deaths.

93. Accordingly, both Act 1096 and the ADC's Lethal Injection Procedure substantively violate the ban on cruel or unusual punishments found in Art. 2, § 9 of the Arkansas Constitution.

Claim 2: Violation of Procedural Due Process

94. All of the allegations set forth elsewhere in this Second Amended Complaint are incorporated by this reference as if fully set forth herein.

95. The Prisoners have a liberty interest in freedom from an unconsented and torturous injection.

96. The fundamental fairness guaranteed by the due process clause requires that condemned inmates be given a meaningful opportunity to protect that liberty interest.

97. Without information showing that the drugs to be used in their executions are reliable, the Prisoners will have no meaningful opportunity to protect their liberty interest.

98. Act 1096 prevents the Prisoners from accessing information showing that the drugs to be used in their executions are reliable.

99. Act 1096 thus violates the procedural due process guaranteed by Art. 2, § 8 of the Arkansas Constitution.

Claim 3: Procedural Violation of Art. 2, § 9

100. All of the allegations set forth elsewhere in this Second Amended Complaint are incorporated by this reference as if fully set forth herein.

101. Art. 2, § 9 of the Arkansas Constitution bans cruel or unusual punishment.

102. The substantive rights of Art. 2, § 9 imply certain procedural safeguards, including access to information necessary to determine whether a Art. 2, § 9 violation is present.

103. Information showing the reliability of the execution drugs is necessary to determine whether Arkansas's execution procedure will be cruel or unusual.

104. Act 1096 prevents the Prisoners from accessing such information and thus violates the state constitutional guarantee against cruel or unusual punishment.

Claim 4: Violation of Separation of Powers

105. All of the allegations set forth elsewhere in this Second Amended Complaint are incorporated by this reference as if fully set forth herein.

106. Article 4 of the Arkansas Constitution provides:

> The powers of the government of the State of Arkansas shall be divided into three distinct departments, each of them to be confided to a separate body of magistracy, to-wit: Those which are legislative, to one, those which are executive, to another, and those which are judicial, to another.
>
> No person or collection of persons, being of one of these departments, shall exercise any power belonging to either of the others, except in the instances hereinafter expressly directed or permitted.

107. Act 1096 violates Art. 4 of the Arkansas Constitution in two separate respects:

a. Act 1096 violates Art. 4 by unlawfully delegating excessive discretion to the ADC.

i. Under Art. 4, the legislature may delegate discretion to an executive agency only if it provides reasonable guidelines that include appropriate standards.

ii. Act 1096 delegates excessive discretion to the ADC, an executive agency, by failing to provide meaningful definition and regulation of its power in relation to executions.

iii. First, Act 1096 provides the ADC with the leeway to choose between, on one end, a barbiturate-only execution procedure and, on the other end, a completely different execution procedure that omits barbiturate drugs entirely: "Midazolam, followed by vecuronium bromide, followed by potassium chloride." Act 1096 fails to provide reasonable guidelines and appropriate standards and thus is devoid of any meaningful definition or regulation to guide the ADC's ostensible discretion in choosing a procedure between these two widely divergent poles.

iv. Second, assuming the ADC chooses the barbiturate-only procedure, Act 1096 provides the ADC with unfettered discretion to choose among the broad range of chemicals that qualify as barbiturates. *See Hobbs v. McGehee*, 2015 Ark. 116 (Wynne, J., dissenting).

v. Third, Act 1096 provides the ADC with unfettered discretion to choose between pure, FDA-approved manufactured drugs and compounded drugs that are likely to cause serious pain

and suffering. The Act fails to provide reasonable guidelines and appropriate standards to guide the ADC's discretion in choosing between these two options.

vi. Fourth, Act 1096 provides the ADC with unfettered discretion to select the members of the execution team without any reasonable guidelines and appropriate standards to provide guidance about who should be chosen.

vii. Fifth, Act 1096 provides the ADC with unfettered discretion about whether and how members of the execution team should be trained.

viii. In its totality, the discretion granted to the ADC under Act 1096 exceeds what it is permitted under Art. 4.

ix. The statute is not severable; accordingly, the entire statute is invalid.

b. The Act violates the separation of powers by impairing the judicial function.

i. The judiciary has the prerogative and responsibility to review actions of the executive department for compliance with constitutional commands.

ii. Specifically, the judiciary has the prerogative and responsibility to ensure that prisoners' rights to be free from cruel and unusual punishment are protected, and it has a duty to ensure that the ADC does not violate Art. 2 § 9 in carrying out executions.

iii. Act 1096 makes secret information that is critical to the judiciary's ability exercise these prerogatives and fulfill these duties.

iv. Act 1096 thus violates Art. 4.

v. The statute is not severable; accordingly, the entire statute is invalid.

Claim 5: Violation of the Ex Post Facto Clause

108. All of the allegations set forth elsewhere in this Second Amended Complaint are incorporated by this reference as if fully set forth herein.

109. Act 1096 creates a significant risk that the Prisoners will experience a substantially more painful or agonizing execution than they would have suffered under the law in effect at the time of their offenses.

110. Act 1096 creates a significant risk that the Prisoners will experience substantially more mental anxiety leading up to the execution

than they would have experienced under the law in effect at the time of their offenses.

111. Act 1096 thus violates the ex post facto clause of the Arkansas Constitution (Art. 2, § 17).

VIII. Prayer for Relief

WHEREFORE, the Prisoners pray for the following relief:

i. That Act 1096 be declared unconstitutional in its entirety, both as applied and on its face;

ii. That ADC's three-drug execution protocol, consisting of midazolam, followed by vecuronium bromide, followed by potassium chloride, be declared unconstitutional;

iii. That this Court order the ADC to immediately disclose information showing the drugs it intends to use in the Prisoners' executions are reliable, including the names and addresses of the persons and entities producing and supplying its execution drugs;

iv. That this Court enjoin the ADC from carrying out executions pursuant to Act 1096;

v. That this Court explicitly reserve enforcement jurisdiction to ensure compliance with its injunction pending any appeal by the Defendants; and

vi. That this Court grant all other relief to the Prisoners to which they may be entitled and which this Court deems just and proper.

Dated: February 24, 2017

Respectfully submitted,

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CERTIFICATE OF SERVICE

I, John C. Williams, hereby certify that I have served a copy of the foregoing on all counsel of record through the electronic filing system this 24th day of February, 2017.

/s/ John Williams
JOHN C. WILLIAMS

2015 Arkansas Laws Act 1096 (H.B. 1751)

ARKANSAS 2015 SESSION LAWS

90th GENERAL ASSEMBLY, REGULAR SESSION, 2015

Additions are indicated by **Text**; deletions by
~~Text~~ .
Vetoes are indicated by ~~Text~~ ;
stricken material by ~~**Text**~~ .

ACT 1096
H.B. 1751
CORRECTIONAL INSTITUTIONS—EXECUTIONS—LETHAL INJECTION

AN ACT CONCERNING THE ADMINISTRATION OF A LETHAL INJECTION AT THE DEPARTMENT OF CORRECTION; TO DECLARE AN EMERGENCY; AND FOR OTHER PURPOSES.

Subtitle

CONCERNING THE ADMINISTRATION OF A LETHAL INJECTION AT THE DEPARTMENT OF CORRECTION; AND TO DECLARE AN EMERGENCY.

BE IT ENACTED BY THE GENERAL ASSEMBLY OF THE STATE OF ARKANSAS:

SECTION 1. DO NOT CODIFY. **Legislative findings.**

(a) The laws of Arkansas impose the sentence of death for its most serious offenses. The General Assembly finds it necessary to provide a means of carrying out the sentence of death while also complying with the constitutional prohibition on cruel and unusual punishment.

(b) To address objections to the method of lethal injection previously provided by law and to address the problem of drug shortages, the General Assembly finds that it should adopt alternative methods of lethal injection to bring about the death of the condemned prisoner.

(c) The General Assembly finds that this act meets those goals and satisfies the separation-of-powers doctrine by setting forth the state's policy and the procedural guidelines for carrying out the sentence of death.

SECTION 2. Arkansas Code § 5–4–617 is amended to read as follows:

<< AR ST § 5–4–617 >>

5–4–617. Method of execution.

(a) The Department of Correction shall carry out the sentence of death by intravenous lethal injection of ~~*a barbiturate*~~ ***the drug or drugs described in subsection (c) of this section*** *in an amount sufficient to cause death.*

(b) The Director of the Department of Correction or his or her designee may order the dispensation and administration of the drug or drugs described in subsection (c) of this section for the purpose of carrying out the lethal-injection procedure, and a prescription is not required.

(c) The department shall select one (1) of the following options for a lethal-injection protocol, depending on the availability of the drugs:

(1) A barbiturate; or

(2) Midazolam, followed by vecuronium bromide, followed by potassium chloride.

(d) The drug or drugs described in subsection (c) of this section used to carry out the lethal injection shall be:

(1) Approved by the United States Food and Drug Administration and made by a manufacturer approved by the United States Food and Drug Administration;

(2) Obtained from a facility registered with the United States Food and Drug Administration; or

(3) Obtained from a compounding pharmacy that has been accredited by a national organization that accredits compounding pharmacies.

~~*(b) Before the intravenous lethal injection is administered, the condemned prisoner shall be intravenously administered a benzodiazepine.*~~

~~*(c)*~~ ***(e)*** *The drugs set forth in* ~~*subsections (a) and (b)*~~ ***subsection (c)*** *of this section shall be administered along with* ~~*any substances that the manufacturer has mixed with the drugs and*~~ *any additional substances, such as saline solution, called for in the* ~~*manufacturer's*~~ *instructions.*

~~*(d)*~~ ***(f)*** *Catheters, sterile intravenous solution, and other equipment used for the intravenous injection of the* ***drug or*** *drugs set forth in* ~~*subsections (a) and (b)*~~ ***subsection (c)*** *of this section shall be sterilized and prepared in a manner that is safe and commonly performed in connection with the intravenous administration of drugs of that type.*

~~*(e)*~~ ***(g)*** *The* ~~*Director of the Department of Correction*~~ ***director*** *shall develop logistical procedures necessary to carry out the sentence of death, including:*

(1) The following matters:

(A) Ensuring that the drugs and substances set forth in ~~*subsections (a) - (d) of*~~ *this section and other necessary supplies for the lethal injection are available for use on the scheduled date of the execution;*

(B) Conducting employee orientation of the lethal injection procedure before the day of the execution;

(C) ~~*Logistics*~~ ***Determining the logistics*** *of the viewing;*

(D) Coordinating with other governmental agencies involved with security and law enforcement;

(E) Transferring the condemned prisoner to the facility where the sentence of death will be carried out;

(F) Escorting the condemned prisoner from the holding cell to the execution chamber;

(G) ~~*The*~~ ***Determining the*** *identity, arrival, and departure of the persons involved with carrying out the sentence of death at the facility where the sentence of death will be carried out; and*

(H) Making arrangements for the disposition of the condemned prisoner's body and personal property; and

(2) The following matters pertaining to other logistical issues:

(A) Chaplaincy services;

(B) Visitation privileges;

*(C) Determining the condemned prisoner's death, which ~~must~~ **shall** be pronounced according to accepted medical standards; **and***

~~*(D) Confirming the type and concentration of the drugs and substances set forth in subsections (a)–(d) of this section when they have been received by the department; and*~~

*~~(E)~~ **(D)** Establishing a protocol for any necessary mixing or reconstitution of the drugs and substances set forth in ~~subsections (a)–(d) of~~ this section in accordance with the ~~manufacturer's~~ instructions.*

*~~(f)~~ **(h)** The procedures for carrying out the sentence of death and related matters are not subject to the Arkansas Administrative Procedure Act, § 25–15–201 et seq.*

*~~(g)~~ **(i)(1)** The procedures under subdivision ~~(e)(1)~~ **(g)(1)** of this section**, ~~and~~** the implementation of the procedures under subdivision ~~(e)(1)~~ **(g)(1)** of this section**, and the identities of the entities and persons who participate in the execution process or administer the lethal injection** are not subject to disclosure under the Freedom of Information Act of 1967, § 25–19–101 et seq.*

(2) The department shall keep confidential all information that may identify or lead to the identification of:

(A) The entities and persons who participate in the execution process or administer the lethal injection; and

(B) The entities and persons who compound, test, sell, or supply the drug or drugs described in subsection (c) of this section, medical supplies, or medical equipment for the execution process.

(3) The department shall not disclose the information covered under this subsection in litigation without first applying to the court for a protective order regarding the information under this subsection.

(j) The department shall make available to the public any of the following information upon request, so long as the information that may be used to identify the compounding pharmacy, testing laboratory, seller, or supplier is redacted and maintained as confidential:

(1) Package inserts and labels, if the drug or drugs described in subsection (c) of this section have been made by a manufacturer approved by the United States Food and Drug Administration;

(2) Reports obtained from an independent testing laboratory; and

(3) The department's procedure for administering the drug or drugs described in subsection (c) of this section, including the contents of the lethal-injection drug box.

*~~(h)~~ **(k)** The department shall carry out the sentence of death by electrocution if **execution by lethal injection under** this section is invalidated by a final and unappealable court order.*

(l) Every person that procures, prepares, administers, monitors, or supervises the injection of a drug or drugs under this section has immunity under § 19–10–305.

SECTION 3. SEVERABILITY CLAUSE. ***If any provision of this act or its application to any person or circumstance is held invalid, the invalidity does not affect other provisions or applications of this act which can be given effect without the invalid provision or application, and to this end the provisions of this act are severable.***

SECTION 4. EMERGENCY CLAUSE. ***It is found and determined by the General Assembly of the State of Arkansas that the courts now require heightened legislative oversight and control over the procedures used in carrying out capital punishment. In addition, victims' families need assurance that capital sentences will be carried out in compliance with prevailing case law. Therefore, an emergency is declared to exist, and this act being immediately necessary for the preservation of the public peace, health, and safety shall become effective on:***

(1) The date of its approval by the Governor;

(2) If the bill is neither approved nor vetoed by the Governor, the expiration of the period of time during which the Governor may veto the bill; or

(3) If the bill is vetoed by the Governor and the veto is overridden, the date the last house overrides the veto.

lslHouse

APPROVED: 4/6/2015

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LETHAL INJECTION PROCEDURE (Attachment C)

SECTION I. General

1. The Deputy Director, or designee, is responsible for assuring that the chemicals for lethal injection, the gurney, straps, and other necessary items, are available for use on the scheduled date of execution. The Deputy Director, or the designee, shall be healthcare trained, educated, and/or experienced in matters related to the establishment and monitoring of IVs, the mixing and administration of the chemicals, and assessing the presence or absence of consciousness.

2. When the chemicals have been received, the Deputy Director, or the designee, shall verify as to type and concentration, and thereafter supervise any necessary mixing or reconstituting of the chemicals in such a manner as will meet the injection requirements (see Chart A) and in accordance with manufacturer's instructions. The mixed or reconstituted chemicals shall be transferred to an appropriate syringe(s) and thereafter placed in a designated Injection Drug Box. The box will be secured and conveyed to the Cummins Unit.

3. The Deputy Director, or designee, shall maintain physical custody of the Injection Drug Box and physically convey the box directly to the execution chamber for use. If not used, the Deputy Director, or designee, shall secure the Drug Box until used or destroyed.

4. Orientation of the executioner(s) to the Department's *Lethal Injection Procedure*, if needed, will be conducted prior to the day of the execution and provided by the Director and/or designee(s).

5. On the evening of the execution, the executioner(s) shall, under the supervision of the Director, or designee, enter the injection room prior to the scheduled time of the execution and shall immediately inventory the Injection Drug Box to ensure that all chemicals are accounted for and that the infusion device(s) are in readiness.

6. The execution gurney will be positioned in the death chamber so that the Deputy Director, or designee, and the executioner(s) can directly observe the condemned inmate's face and IV infusion site(s).

SECTION II. IV Set-Up Procedure

1. The Deputy Director, or designee, shall have an intravenous infusion device placed in each arm, or other standard anatomical venous point of entry, of the condemned inmate and a solution of N.S. (Normal Saline) available for an infusion medium. The individual(s) engaged in this activity will be referred to as the IV Team and shall be qualified as set forth in Section V.

2. An IV administration set shall be inserted into the outlet of the bag of N.S. IV solution. Two (2) IV bags will be set up in this manner.

3. The administration set tubing for each set-up will be connected to the receiving port of the three-way control devices; one left arm/side, the other for the right arm/side.

4. IV extension tubing will be connected to the discharge ports on the right/left three-way control devices and shall be thereafter connected to the applicable right and left IV insertion site(s). Extension tubing will be of sufficient length to accommodate the distance from control device to IV insertion site(s).

5. The tubing shall be cleared of air and made ready for use.

6. Intravenous catheters shall be initiated through standard procedure for such devices. Once the infusion of the IV solution has been assured, the IV devices shall be secured as appropriate.

7. At this point, the administration sets shall be running at a slow rate of flow (KVO), and ready for the insertion of syringes containing the chemicals. The Deputy Director, or designee, shall maintain observation of IV infusion(s) to ensure that the rate of flow is uninterrupted. NO FURTHER ACTION shall be taken until the prearranged signal to start the injection of chemicals is given by the Warden.

8. In the event that a patent intravenous infusion site cannot be established, the IV Team shall be directed by the Deputy Director, or designee, to evaluate other possible infusion sites. All effort will be made to establish two (2) unrelated intravenous infusion sites. If one (1) patent infusion site is established, and a second site proves to be a futile effort, the Deputy Director, or designee, may direct the IV Team to suspend further action to establish a second site and proceed with one site. In the case that no patent infusion site is established after reasonable attempts as determined by the IV Team, the Deputy Director, or designee, will direct the IV Team to suspend further action and thereafter summon trained, educated, and experienced person(s) necessary to establish a primary IV line as a peripheral line or as a central venous line.

EVERY EFFORT WILL BE EXTENDED TO THE CONDEMNED INMATE TO ENSURE THAT NO UNNECESSARY PAIN OR SUFFERING IS INFLICTED BY THE IV PROCEDURE. STANDARD PRACTICE OF USING A LOCAL ANESTHETIC (1% LIDOCAINE) WILL BE ACCOMMODATED AS NECESSARY.

SECTION III. Preparation of Chemicals

1. The Deputy Director, or the designee(s), and a member of the IV Team shall prepare the designated chemicals and syringes for a total of one (1) complete set of chemicals. One (1) complete set of syringes is used in the implementation of the death sentence and an additional complete set of the necessary chemicals shall be obtained and kept available. The specific chemical contained in each syringe will be identified with the following information as set forth in the chemical charts:

   a. Assigned number

   b. Chemical name

   c. Chemical amount

   d. Designated color

2. The quantities of chemicals prepared and administered shall not be changed in any manner without prior documented approval of the director.

3. All prepared chemicals shall be utilized or properly disposed of in a timely manner after the time designated for the execution to occur.

4. The chemical amounts as set forth in the Chemical Chart are designated for the execution of persons weighing 500 pound or less. The chemical amounts shall be reviewed and may be revised as necessary for an offender exceeding this body weight.

5. CHEMICAL CHART

   a. **CHART A**: Three (3) Drug Protocol with Midazolam, Vecuronium Bromide and Potassium Chloride

CHEMICAL CHART	
Syringe No.	**Label**
1A	250 mg midazolam, **GREEN**
2A	250 mg midazolam, **GREEN**
3A	60 ml saline, **BLACK**
4A	50 mg vecuronium bromide, **YELLOW**
5A	50 mg vecuronium bromide, **YELLOW**
6A	60 ml saline, **BLACK**
7A	120 mEq potassium chloride, **RED**
8A	120 mEq potassium chloride, **RED**
9A	60 ml saline, **BLACK**

(1) Syringes 1A and 2A shall each have a dose of 250 milligrams midazolam for a total dose of 500 milligrams. Each syringe containing midazolam shall have a **GREEN** label which contains the name of the chemical, the chemical amount and the designated syringe number.

(2) Syringes 4A and 5A shall each have a dose of 50 milligrams vecuronium bromide for a total dose of 100 milligrams. Each syringe containing the selected bromide shall have a **YELLOW** label which contains the name of the chemical, the chemical amount and the designated syringe number.

(3) Syringes 7A and 8A shall each contain 120 milliequivalents potassium chloride for a total dose of 240 milliequivalents. Each syringe containing potassium chloride shall have a **RED** label which contains the name of the chemical, the chemical amount and the designated syringe number.

(4) Syringes 3A, 6A, and 9A shall each contain 60 milliliters of saline solution. Each syringe shall have a **BLACK** label which contains the name of the solution, amount of solution, and the designated syringe number.

SECTION IV. Injection Procedure

1. The three-way control device facilitates the movement of infusion fluid from saline bag or infusion fluid with the chemicals from the syringes. A valve serves to direct which fluid source is entering the IV set up.

2. When the signal to commence is given by the Warden, the executioner(s) shall administer the chemicals in the order they appear in chart A under the direction of the Deputy Director, or designee, as follows:

   a. Syringe 1A shall be inserted into the designated chemical receiving port of the three-way control device.

   b. The flow of IV solution will be interrupted by moving the three-way valve assembly to allow the infusion of chemical from Syringe 1A.

   c. The contents of Syringe 1A shall commence with a steady even flow of the chemical and continue until the full dose of the chemical has been administered. Only the force necessary to activate the syringe plunger will be used.

   d. When the contents of Syringe 1A have been injected, the three-way valve assembly will be moved so as to shut off the chemical receiving port and resume infusion of IV solution.

e. Syringe 1A will be replaced by Syringe 2A and the procedure described in subparagraphs a-d for Syringe 1A will be repeated. This process will be repeated for all subsequent syringes.

f. Following the administration of syringe numbers 1A, 2A, and 3A, and after at least five (5) minutes have elapsed since commencing the administration of syringe 1A, the Deputy Director, or designee, will confirm the condemned inmate is unconscious by using all necessary and medically-appropriate methods. The Deputy Director, or designee, shall also confirm that the IV line(s) remains affixed and functioning properly.

g. Once the Deputy Director, or designee, determines that the condemned inmate is unconscious, the remaining chemicals will be administered in the order they appear in Chart A.

h. In the unlikely event that the Deputy Director, or designee, determines that the condemned inmate remains conscious following the administration of the chemicals in syringe numbers 1A, 2A, and 3A, the back-up syringes of the first chemical (Syringe 1B and 2B) and saline (Syringe 3B), shall be administered via the secondary or alternative IV line.

(1) Following the administration of syringe numbers 1B, 2B, and 3B, and after at least five (5) minutes have elapsed since commencing the administration of syringe 1B, the Deputy Director, or designee, will confirm the condemned inmate is unconscious by using all necessary and medically-appropriate methods. The Deputy Director, or designee, shall also confirm that the IV line(s) remains affixed and functioning properly.

(2) Once the Deputy Director, or designee, determines that the condemned inmate is unconscious, the remaining chemicals will be administered via the secondary or alternative IV line in the order they appear in Chart A.

i. Throughout the chemical infusion process, the Deputy Director, or designee, will closely monitor the infusion site for evidence of infiltrate, vein collapse, or other challenge to the patency of the infusion site.

(1) Should a problem be suspected, the Deputy Director, or designee, will direct reduction of chemical flow rate or redirect chemical to the secondary or alternative site.

(2) In the use of a singular infusion site pursuant to Section II (8), if the infusion site is suspected to be compromised, chemical flow rate will be reduced. If problem persists, the:

(a) injection procedure will cease;

(b) curtain to death chamber will close; and

(c) the IV Team summoned, and the infusion site problem corrected.

(3) If all efforts to re-establish patent infusion site fail, the Deputy Director, or designee, will direct the IV Team to suspend further action and trained, educated, and experienced person(s) necessary to establish a primary IV line as a peripheral line or as a central venous line will be summoned to facilitate an IV infusion site.

(4) When the infusion compromise is corrected, the IV Team and the summoned person(s) will be excused, the curtain reopened, and the lethal injection procedure continued.

Section V. IV Team Qualifications

Each member of the IV team shall have at least two (2) years of professional experience and certification or licensure in at least one of the following fields:

1. Emergency Medical Technician-Intermediate, or

2. Emergency Medical Technician-Paramedic, or

3. Nurse, or

4. Physician Assistant, or

5. Physician.

AMENDED SUBMISSION

THE PHARMACOLOGY OF ARKANSAS'S LETHAL INJECTION PROCEDURE: FACTS, INTERPRETATIONS, AND ALTERNATIVES

January 2, 2017

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Reason for an Amended Report

The reason for the submission of an amended report is the discovery of a calculation error in section 5C of the original report. This was a simple error which led to an initial calculation of a higher blood concentration of a 500 mg IV midazolam dose.

The original report stated as follows: "This study gave peak blood concentrations of nearly 120 ng/mL (nanogram per milliliter) after a 5 mg IV dose. It follows then that with a 500 mg IV dose, the initial amount after direct IV bolus infusion is 100 times of what occurred with the 5 mg dose, which gives an initial blood concentration of ***120,000 ng/mL*** of midazolam after a 500 mg IV dose." [p 23 in original report, calculation error in bold, italics]. 120 ng/mL times 100 equals **12,000 ng/mL** (not 120,000 ng/mL). This has been corrected in the present version in section 5Bii in the amended report on p. 29. Subsequent calculations were corrected accordingly to arrive at a new ceiling-effect dosage of 228 mg IV midazolam.

The discovery of the calculation error does not essentially alter the summary and conclusions of the original report: that Midazolam's ceiling-effect dosage is lower than the 500 mg dose in the State's lethal-injection protocol and that a 500 mg dose of Midazolam cannot be relied on to render someone unconscious and insensate to the noxious stimuli that will occur from the application of the remaining drugs in the Arkansas lethal injection protocol.

Sections

1. Introduction

A. Author Qualifications

I am a full-time faculty member in the department of Pharmacology and Physiology at the College of Osteopathic Medicine, a unit of the Oklahoma State University, Center for Health Sciences campus in Tulsa, Oklahoma.

After receiving my Ph.D. in Pharmacology from the Mayo Clinic, in Rochester, Minnesota, I completed a 2 year postdoctoral fellowship at the University of Minnesota Medical School in Minneapolis, Minnesota, and secured a position as an Assistant Professor of Pharmacology with my present employer in 1990. I advanced through the academic ranks to Associate Professor of Pharmacology in 1993, and Professor of Pharmacology in 2000.

Besides my regular duties of teaching medical students, pursuing research and scholarly activities, and serving on college committees, I work part-time as a litigation consultant/expert witness on cases involving pharmacological issues. I have consulted in both civil and criminal cases, working with both the prosecution or plaintiff and the defendant.

With regard to the pharmacological issues of lethal injection, I have worked as a consultant with the state as well as with attorneys representing condemned inmates.

My *curriculum vitae* (CV) is attached as Appendix A to this report.

B. Materials Considered

Attorney Josh Lee, who retained me to study Arkansas's lethal injection procedures, provided me with several documents that I reviewed and relied upon in preparing this Expert Report. These materials were: (1) an email from Deputy Attorney General David Curran, to which was appended redacted package inserts and labels for the drugs that Arkansas intends to use in its execution procedure; (2) an email from Assistant Attorney General Jennifer Merritt, to which was appended a document titled "Lethal Injection Procedure (Attachment C)"; and (3) Arkansas's 2015 lethal injection statute, Ark. Code Ann. § 5-4-617 (2015). In addition to the above materials provided by Mr. Lee, I also considered pharmacological textbooks, reviews, and research studies (listed in Section 8, below), as well as *Baze v. Rees*, 128 S. Ct. 1520 (2008), and *Glossip v. Gross*, 135 S. Ct. 2726 (2015), which set the standard for when a lethal injection procedure may be said to violate the federal ban on cruel and unusual punishment. After Mr. Josh Lee left the Federal Public Defenders Office, my work as a pharmacology consultant continued with Mr. John C. Williams in the same office. Before submitting this amended report, I reviewed the Arkansas Supreme Court's opinion in *Kelley v. Johnson*, 2016 Ark. 268, and portions of the briefing in that case.

C. Brief Description of Arkansas's Execution Protocol

The execution procedure appended to the email from Deputy Attorney General Jennifer Merritt is a three-drug lethal injection protocol. First, the prisoner is to be injected with 500 mg. of the drug Midazolam. Next, after waiting five minutes, a member of the execution team ostensibly "confirm[s] the condemned inmate is unconscious," using unspecified methods. Then, the prisoner is to be injected with 100 mg (milligrams) of the muscle-paralytic drug, vecuronium bromide. Finally, the prisoner is to be injected with 240 mEq (milli-equivalents) of the heart-stopping drug, potassium chloride.

D. Referral Questions

Mr. Lee asked me to offer my expert opinion on several issues. First, Mr. Lee asked me to discuss the pharmacology of all the different drugs authorized by Arkansas's lethal injection statute, i.e., barbiturates, Midazolam, vecuronium bromide, and potassium chloride—with particular attention to any similarities and differences between barbiturates and Midazolam. Second, Mr. Lee asked for my opinion on whether Arkansas's chosen lethal injection procedure (Midazolam, followed by vecuronium bromide, and potassium) is sure or very likely to cause serious pain and suffering. Third, Mr. Lee asked me to address whether alternative execution procedures would significantly reduce the risk of pain and suffering and, if they would, to describe some of those procedures.

A thorough discussion of these issues follows. A summary of my opinions on the referred questions can be found in Section 7 of this Report.

2. Midazolam and Fast-Acting Barbiturates are Fundamentally Different Drugs

A. Pharmacological Equivalency and Pharmacological Substitution

Each drug has a unique chemical (atomic) structure and exerts a unique profile of pharmacological effects. Drugs are classified both by their chemical structures and by their therapeutic uses. Drugs that have very similar chemical structures are grouped together based on that structure. Drugs that have similar therapeutic uses are also grouped together by their therapeutic or pharmacological effects.

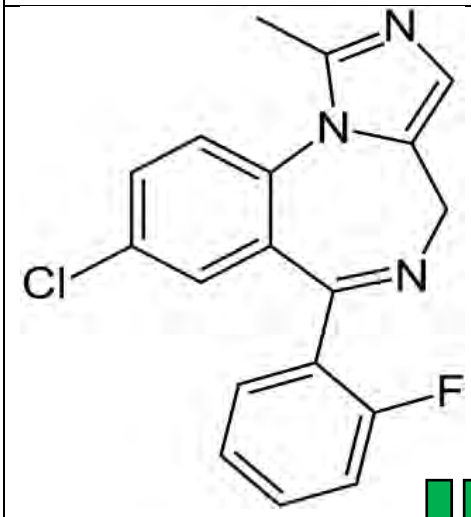
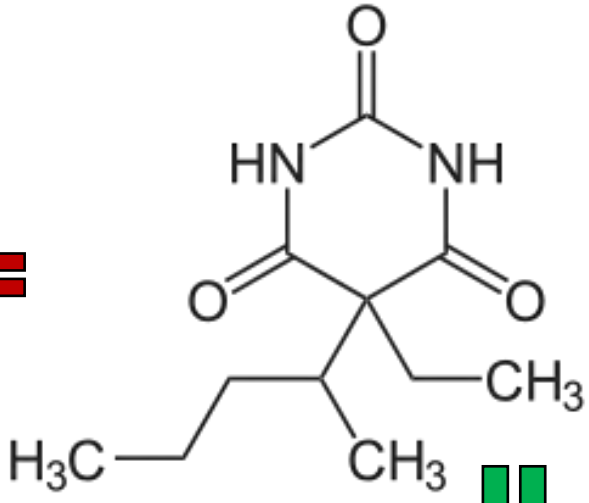
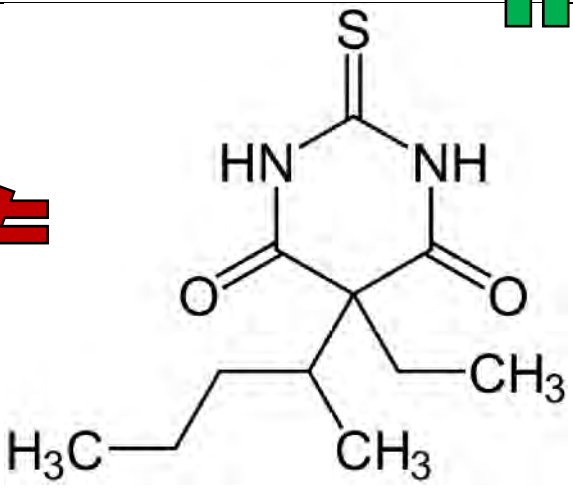
Pharmacological equivalency is present when two or more drugs exhibit the same or closely similar pharmacological properties. It is a working principle used by physicians who often substitute drugs due to drug allergies or for reasons of cost. Pharmacological equivalency is also the guiding principle for the FDA to accept a generic version of the same branded drug (e.g. Walgreen's ibuprofen, the generic form, is *pharmacologically equivalent* to Advil®, the branded formulation of ibuprofen. See *Meredith 2003, Borgheini 2003*).

Pharmacological substitution is the act of using one drug in the place of another. It is axiomatic that in order to maintain the same pharmacological and therapeutic effect of two drugs, the drug that is substituted must have pharmacological equivalency to the new drug.

There is no question that midazolam and fast-acting barbiturates (such as thiopental or pentobarbital) are different drugs. The key question in substituting drugs for lethal injection is one of a pharmacological nature: Does midazolam have *pharmacological equivalency* to fast-acting barbiturates such that a valid pharmacological substitution can be made? Pharmacological equivalency between midazolam, a benzodiazepine, and fast-acting barbiturates, is examined herein with respect to **pharmacological classification by chemical (atomic) structure, mechanisms of action, partial and full effects of these agents and the 'ceiling effect', therapeutic uses, and DEA scheduling of these agents.**

B. Pharmacological Classification of Midazolam and Fast-Acting Barbiturates

Table 1. Visual comparison of benzodiazepine and barbiturate chemical structures.

BENZODIAZEPINES	BARBITURATES
	
Midazolam (Versed®)	Pentobarbital (Nembutal®)
	
Diazepam (Valium®)	Thiopental (Pentothal®)

Midazolam belongs to the class of drugs called benzodiazepines whereas drugs like pentobarbital and thiopental are members of the barbiturate class of drugs (*Brenner and Stevens, 2013*). The

chemical structure of midazolam and pentobarbital are shown in the first row of Table 1 above to provide an accessible first exposure to the differences between the two drugs. The untrained eye clearly recognizes that midazolam and pentobarbital do not have similar structures and are not close analogs. The second row in Table 1 shows examples of other drugs from the same class of drugs as midazolam and pentobarbital. Most notably, at the center of the benzodiazepines there is 7-sided ring with two nitrogen atoms (N) attached to a 6-sided ring with one chloride atom (Cl). Quite differently, the two barbiturates do not contain such a core structure and instead consist of a single 6-sided ring containing two nitrogen atoms. The non-expert can see that the benzodiazepine, midazolam, is similar to diazepam (Valium®), and the barbiturate, pentobarbital (Nembutal®), is a close analog of thiopental (Pentothal®). There is an irrefutable difference between midazolam and fast-acting barbiturates at the atomic level.

In summary, Table 1 shows that that there is no chemical, structural **pharmacological equivalency between midazolam and fast-acting barbiturates.** However, Table 1 does show that the substitution of thiopental with pentobarbital (from one fast-acting barbiturate to another fast-acting barbiturate) does meet the test for pharmacological equivalency by chemical structure.

C. Mechanism of Action of Midazolam and Fast-Acting Barbiturates

The pharmacology of drugs ranges from effects on the whole organism, to effects on specific tissues or organs, down to the actual mechanism of action at the molecular level. For many drugs, the action at the molecular level can be traced upward to the effect on the whole organism, yielding a nearly complete description of drug action.

Starting at the molecular level, both midazolam and pentobarbital act on the $GABA_A$ receptor-chloride ion channel complex (henceforth $GABA_A$ receptor). GABA is the acronym for gamma-aminobutyric acid, an inhibitory neurotransmitter in the brain that is the natural activator of $GABA_A$ receptors (*Sigel and Steinmann 2012, Sieghart 2015*). When inhibitory neurons of the brain release GABA onto other brain neurons, the recipient neurons are inhibited and become more quiescent. This is an ongoing neurotransmitter action, occurring without the presence of any drugs or exogenous substances in the brain. The $GABA_A$ receptor is shaped like a funnel with a lid on it. When GABA binds to the receptor, the lid opens and chloride ions rush from the outside of the neuron to the inside. The chloride ions rushing inside the neuron causes the neuron to decrease its electrical activity.

Benzodiazepines act at the $GABA_A$ receptor on brain neurons where GABA itself acts (*Chang et al. 1981, Sigel and Barnard 1984*) but at a different molecular site than GABA on the $GABA_A$ receptor (*Cromer et al. 2002, Ernst et al. 2003*). Midazolam and all benzodiazepines do not increase the synthesis of the inhibitory neurotransmitter GABA but enhance the effect of GABA at the $GABA_A$ receptor (*Greenblatt et al. 1983*). GABA must be released by inhibitory neurons and be acting on the $GABA_A$ receptor at the same time as the benzodiazepine for drugs like midazolam to enhance GABA inhibition (*D'Hulst et al. 2009, Sieghart et al. 2012*). GABA acts on the receptor and opens the lid to the chloride ion channel (funnel) and midazolam increases the frequency that the lid opens (*Study and Barker 1981, Rogers et al. 1994*). In that way,

midazolam helps GABA have a greater inhibitory effect. However without GABA present, midazolam does little to the $GABA_A$ receptor.

Barbiturates such as pentobarbital also act at the $GABA_A$ receptor on brain neurons where GABA itself acts (*Olsen and Snowman 1982, Greenfield LJ 2013*). Barbiturates bind to a different spot on the $GABA_A$ receptors than benzodiazepines (*Cestari et al. 1996*). Unlike midazolam, pentobarbital and other barbiturates enhance GABA inhibition by increasing the time that the ion channel lid remains in the open position (*Study and Barker 1981*). Contrary to the mechanism of action of midazolam, pentobarbital, like all barbiturates, can cause neuronal inhibition even when GABA is not present (*Mathers and Barker 1980, Jackson et al. 1982*). Barbiturates therefore can open the lid on the ion channel by themselves and keep it open longer than benzodiazepines (*MacDonald et al. 1989, Sancar and Czajkowski 2011*). As a result, the flow of chloride ions into the neuron is not limited to enhancement only when GABA is present, but barbiturates can increase the rush of chloride ions into the neuron in the absence of GABA so that the activity of the neuron is completely shut down. Thus, barbiturates are more potent drugs at the $GABA_A$ receptor than benzodiazepines.

In summary, a large body of pharmacological research on the mechanisms of action of midazolam and fast-acting barbiturates **clearly demonstrates that benzodiazepines, like midazolam, and barbiturates, such as pentobarbital, do NOT exhibit pharmacological equivalency with regard to their detailed mechanism of action**. Compared to barbiturates, benzodiazepines bind to a different site on the $GABA_A$ receptor, need GABA to co-activate the $GABA_A$ receptor to work, and increase the frequency of the opening of the chloride ion channel, not the time it remains open.

D. The Pharmacology of the Partial Agonist, Midazolam, and the Full Agonists, Barbiturates

Most drugs that are used clinically do something to cells or neurons that they affect. They bind to (act on) a target receptor and the receptor does something, like open an ion channel. These types of drugs that do something are called agonists. Other types of clinically-used drugs, like the antihypertensive drugs called 'beta-blockers', bind to a receptor and prevent another substance from doing something. These drugs are called antagonists.

Agonists are further subdivided into partial agonists and full agonists. As their name suggests, full agonists produce a full pharmacological effect and partial agonists only produce a partial pharmacological effect. The difference between one drug being a partial agonist and another drug being a full agonist arises from the drugs' differing mechanism of action.

As noted above, midazolam, like all benzodiazepines, increases the frequency (not the duration) of ion channel opening only when GABA is present. As GABA is a neurotransmitter synthesized by inhibitory brain neurons, the amount of GABA released onto $GABA_A$ receptors is limited. Because midazolam depends on the co-activation of GABA to produce its effects, midazolam's effects on the brain is therefore also limited. In this regard, **midazolam is a partial agonist**.

Barbiturates, to the contrary, do not need co-activation by GABA to produce their effects. Therefore, the neuronal inhibition produced by barbiturates is not limited. In this regard, **fast-acting barbiturates are full agonists**.

By definition, partial agonists will exhibit a 'ceiling effect' in which greater doses will not produce a greater pharmacological effect. The ceiling effect of benzodiazepines, and the lack of ceiling effect for barbiturates, is so well-accepted that many medical pharmacology textbooks contain a Figure illustrating this fact. Fig. 1 below shows one such example.

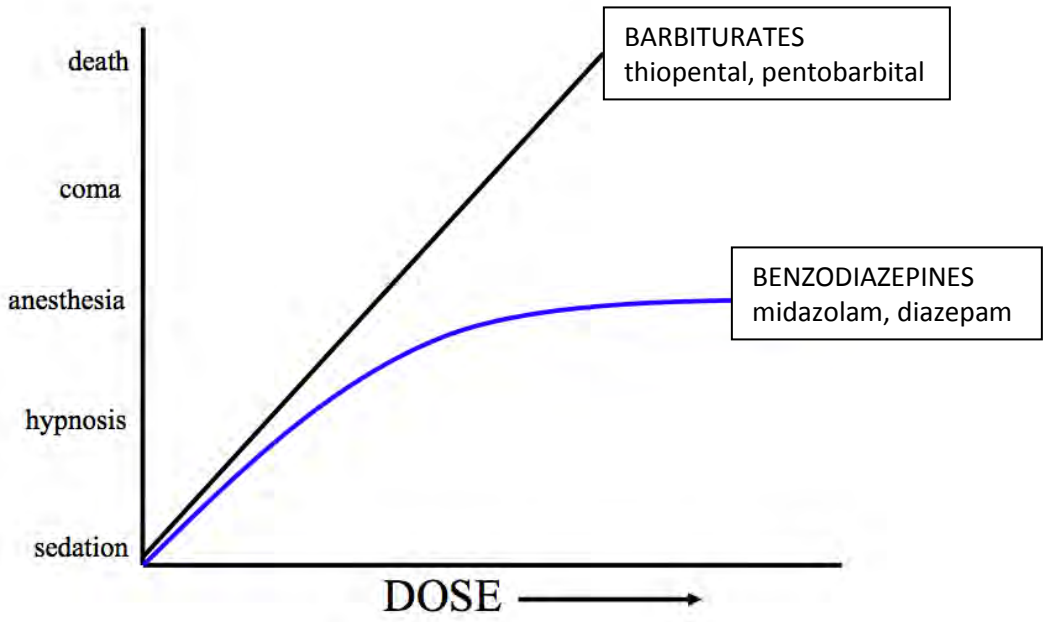


Fig. 1. Typical textbook example of a graph showing the differences between barbiturates (top line) and benzodiazepines (bottom line). The dose increases along the horizontal axis as you move to the right; the effects in humans increases as you move up the vertical axis. Note the **ceiling effect shown for benzodiazepines** versus the lack of ceiling effect for barbiturates. As the dose of benzodiazepine increases, a plateau ('ceiling') is reached before reliable general anesthesia is obtained. Increasing doses of barbiturates reliably produce anesthesia, coma, and death. Note: the term 'hypnosis' is medical terminology for 'sleep'. Adapted from *Brenner and Stevens 2013*.

In summary, **the fact that midazolam is a partial agonist, and that fast-acting barbiturates are full agonists, arises directly from their mechanisms of action, as barbiturates can act in the absence of GABA and increase the inhibition of brain neurons whereas midazolam and other benzodiazepines are limited with their effect only when GABA is present and thus cannot inhibit neurons as much as barbiturates. This pharmacological fact demonstrates that pharmacological equivalency is NOT met by substitution of a barbiturate with a benzodiazepine**. The ceiling effect of a midazolam and other benzodiazepines, and the lack of ceiling effect with the use of barbiturates, is beyond controversy and taught to all medical and pharmacology students.

E. Therapeutic Uses of Benzodiazepines and Barbiturates

The therapeutic use of a drug is a direct result of the drug's pharmacological properties, including, most importantly, a drug's mechanism of action. As noted above, while both benzodiazepines and barbiturates act on the $GABA_A$ receptor, they do so in very different ways. Because of the difference in their mechanism of action, the FDA approves benzodiazepines and barbiturates for difference therapeutic uses. Whereas barbiturates can be used as the sole agent for general anesthesia, benzodiazepines cannot.

i. The Anesthesia Continuum

Before examining the FDA-approved uses of midazolam, pentobarbital, and other agents, it is necessary to understand the terminology used in describing sedative and anesthetic effects. The authoritative professional organization for Anesthesiologists, the American Society for Anesthesiology (ASA), has published standards and definitions for the level of sedation and general anesthesia. There can be no question that these definitions serve as the foundation for any fact-finding. For this reason, the Continuum of Depth of Sedation Table from the ASA is presented below as Table 2 (next page).

There are four levels defined for the Continuum of Depth of Sedation. Of these four levels, there are three levels of sedation and only one level of general anesthesia (see Table 2, column headers). These are, in order of increasing depth of sedation, Minimum Sedation Anxiolysis, Moderate Sedation/Analgesia ("Conscious Sedation"'), Deep Sedation/Analgesia, and General Anesthesia.

Two important facts come from Table 2. First, there is only one level for complete anesthesia, called General Anesthesia. This is the level which renders the patient, or a condemned inmate, to a state of unconsciousness (stated in the text below the Table, underlined) and insensate to all conscious sensation including pain (in the Table itself, end of row one, under General Anesthesia, boxed). The other three levels of sedation are characterized by response to pain and drug-induced *depression* of consciousness *without loss* of consciousness. For this reason, it is clear that any drug used as the first drug in the Arkansas lethal injection protocol must produce a state of General Anesthesia.

Second, the specific use of the term 'General' in the name of the deepest level, 'General Anesthesia,' emphasizes overall brain-activity depression characterized by lack of pain sensation and unconsciousness. Use of the just the word 'anesthesia' does not mean 'general anesthesia.' As stated in the major authoritative pharmacology textbook, *Goodman and Gilman's The Pharmacological Basis of Therapeutics*:[1] "*The clinical literature often refers to the anesthetic effects and uses of certain benzodiazepines, but the drugs do not cause a true general anesthesia because awareness usually persists.*" It is clear that many uses of the word 'anesthesia' in the medical literature do not mean 'general anesthesia' and should not be interpreted as such unless there was loss of all sensation (including pain) and unconsciousness.

[1] Mihic SJ and Harris RA (2011) Chapter 17 Hypnotics and Sedatives, p 460, in Brunton LL et al. (Eds.), Goodman & Gilman's Pharmacological Basis of Therapeutics, Macmillan Co., New York, NY.

American Society of Anesthesiologists

CONTINUUM OF DEPTH OF SEDATION:
DEFINITION OF GENERAL ANESTHESIA AND LEVELS OF SEDATION/ANALGESIA*

Committee of Origin: Quality Management and Departmental Administration

(Approved by the ASA House of Delegates on October 13, 1999, and last amended on October 15, 2014)

	Minimal Sedation Anxiolysis	*Moderate Sedation/ Analgesia ("Conscious Sedation")*	*Deep Sedation/ Analgesia*	*General Anesthesia*
Responsiveness	Normal response to verbal stimulation	Purposeful** response to verbal or tactile stimulation	Purposeful** response following repeated or painful stimulation	Unarousable even with painful stimulus
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Spontaneous Ventilation	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular Function	Unaffected	Usually maintained	Usually maintained	May be impaired

Minimal Sedation (Anxiolysis) is a drug-induced state during which patients respond normally to verbal commands. Although cognitive function and physical coordination may be impaired, airway reflexes, and ventilatory and cardiovascular functions are unaffected.

Moderate Sedation/Analgesia ("Conscious Sedation") is a drug-induced depression of consciousness during which patients respond purposefully** to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained.

Deep Sedation/Analgesia is a drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully** following repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.

General Anesthesia is a drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, and positive pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired.

Because sedation is a continuum, it is not always possible to predict how an individual patient will respond. Hence, practitioners intending to produce a given level of sedation should be able to rescue*** patients whose level of sedation becomes deeper than initially intended. Individuals administering Moderate Sedation/Analgesia ("Conscious Sedation") should be able to rescue*** patients who enter a state of Deep Sedation/Analgesia, while those administering Deep Sedation/Analgesia should be able to rescue*** patients who enter a state of General Anesthesia.

** Reflex withdrawal from a painful stimulus is NOT considered a purposeful response.

*** Rescue of a patient from a deeper level of sedation than intended is an intervention by a practitioner proficient in airway management and advanced life support. The qualified practitioner corrects adverse physiologic consequences of the deeper-than-intended level of sedation (such as hypoventilation, hypoxia and hypotension) and returns the patient to the originally intended level of sedation. It is not appropriate to continue the procedure at an unintended level of sedation.

Table 2. Continuum of Depth of Sedation Table from the ASA [Emphasis added]

Instead of anesthesia, the term 'Moderate Sedation' or another one of the three sedation-level descriptors should be used, if loss of consciousness and insensibly to pain were not present. Textbooks or review articles that state that IV benzodiazepines can produce anesthesia mean that these agents, in general, can produce levels of sedation along the anesthesia scale (Table 2), not that they produce the specific, deepest level of anesthesia called General Anesthesia. Likewise, midazolam is sometimes referred to as 'an anesthetic' or able to produce 'anesthesia,' but this does not mean midazolam can produce 'general anesthesia'.

As shown in the next subsection, the FDA-approved indications (therapeutic uses) for midazolam do not include 'General Anesthesia' (Table 3). Section 5 below discusses clinical studies showing that midazolam is unable to produce a state of General Anesthesia.

ii. FDA-approved Labeling of Anesthetic Effects.

Table 3 below is a list of therapeutic uses for benzodiazepines and barbiturates. Entries marked with a 'YES' indicate that this class of drugs (benzodiazepine or barbiturate) is FDA-approved for this indication and list which particular drug(s) is approved for this therapeutic use.

Table 3. Comparison of therapeutic uses for five benzodiazepines and five barbiturates.

Therapeutic Use	**Benzodiazepines**	**Barbiturates**
Anxiety disorders	YES, alprazolam, diazepam, lorazepam	YES but only for 'sedation' with butabarbital
Panic Disorder	YES, alprazolam, clonazepam	NO
Acute Alcohol Withdrawal	YES, diazepam	NO
Skeletal Muscle Spasm	YES, diazepam	NO
Seizure Disorders	YES, clonazepam, diazepam	YES, pentobarbital (IV), phenobarbital (IV), thiopental (IV)
Preoperative Sedation	YES, midazolam (IM/IV)	YES, pentobarbital (IV), secobarbital
Outpatient Sedation	YES, midazolam (IV)	NO
Anesthesia Induction	YES, midazolam (IV)	YES, thiopental (IV)
Sole Anesthesia (brief)	NO	YES, thiopental (IV)
Sedation for Intubated Ptx	YES, midazolam (IV cont.)	NO
Co-Anesthesia (Adjunct)	YES, midazolam (IV)	YES, thiopental (IV)
Insomnia (short-term)	NO	YES, butabarbital, secobarbital, pentobarbital (IV)
Induce Coma in Brain Trauma	NO	YES, thiopental (IV)
Psychiatric Use (Narcoanalysis)	NO	YES, thiopental (IV)

Note: Benzodiazepine data of therapeutic uses are from the FDA-approved Prescribing Information labels of alprazolam (Xanax®), clonazepam (Klonopin®), diazepam (Valium®), lorazepam (Ativan®), and midazolam (Versed® injection). Barbiturate data are from current FDA-approved labels—for butabarbital (Butisol®), pentobarbital (Nembutal® injection), phenobarbital (Luminal®), secobarbital (Seconal®)—excepting the discontinued label for thiopental (Pentothal®), which is no longer marketed. All drug formulations are oral tablets except where noted; IV=intravenous, IM=intramuscular.

As shown in Table 3, there are 14 therapeutic uses for the benzodiazepine and barbiturate drugs. Among these 14 therapeutic uses, only 5 (or 35.7%) are common to both benzodiazepines and barbiturates. These shared indications are Anxiety Disorders, Seizure Disorders, Preoperative

Sedation, Anesthesia Induction, and Adjunct/Co-Anesthesia (used with a general anesthetic). It should be noted that benzodiazepines for the treatment of Anxiety Disorders have almost universally supplanted the older barbiturate drugs for this use (*Howie 1975*, *Pieters and Snelders 2007*). Five indications are for the use of benzodiazepines only; Panic Disorder; Acute Alcohol Withdrawal; Skeletal Muscle Spasms; Outpatient Sedation; and Sedation for Intubated Patients. Four indications are for the use of barbiturates only: Sole Anesthesia (for brief procedures); Insomnia (for short-term treatment of 2 weeks); Induce Coma in Brain Trauma; and Psychiatric Use (Narcoanalysis), *i.e.*, the limited and historical use of thiopental to get the therapy patient to talk, as in 'truth serum'.

Both midazolam and thiopental are indicated for use in Anesthetic Induction. Anesthetic Induction is a procedure to **start the anesthesia process**. Although midazolam is used for Anesthetic Induction, this use does not mean that midazolam can produce a state of General Anesthesia. Both midazolam and thiopental are indicated for use in Co-Anesthesia as adjunct anesthetics along with other agents. Use of midazolam as an adjunct agent in a Co-Anesthesia protocol does not indicate that midazolam by itself can produce a state of General Anesthesia.

Thiopental, **but not midazolam**, is indicated for Sole Anesthesia, for brief (15 minute) procedures. Thiopental, a barbiturate, is able to be used by itself to provide general anesthesia, but midazolam, like other benzodiazepines, is limited in its potency and cannot produce general anesthesia but only sedation.

Use of midazolam for Preoperative Sedation or Outpatient Sedation—both uses not reaching the level of General Anesthesia—is not germane to drug use for lethal injection. Likewise, use of midazolam to treat Anxiety disorders, Panic Disorder, Acute Alcohol Withdrawal, Skeletal Muscle Spasm, or Seizure Disorders is not pertinent to the production of General Anesthesia, the level of anesthesia needed to administer the second and third drugs used in Arkansas's lethal injection protocol without pain.

With regards to specific drugs, out of five indications for midazolam, midazolam shares only one therapeutic use with pentobarbital: Preoperative Sedation.

In sum, comparison of the FDA-approved labels for benzodiazepines and barbiturates—and more specifically for midazolam and pentobarbital—**demonstrates that pharmacological equivalency of barbiturates and benzodiazepines is NOT met considering the criteria of approved therapeutic uses.** Most importantly, midazolam is not approved for use as a Sole Anesthetic as it cannot produce General Anesthesia. In contrast, the barbiturate thiopental was approved as a Sole Anesthetic for brief procedures. Midazolam cannot produce General Anesthesia, whereas barbiturate drugs like pentobarbital and thiopental are more potent (with no ceiling effect) and can produce a state of General Anesthesia. Evidence supporting these facts is elaborated below in Section 5.

F. DEA Scheduling of Midazolam and Fast-Acting Barbiturates

Most prescription drugs are safe and without the potential for abuse and dependence. Thus, the vast majority of drugs prescribed by physicians do not come under the purview of the Drug Enforcement Administration (DEA). Drugs that pose a special danger of abuse or drug dependence are tightly regulated by the DEA and are called controlled substances.

Midazolam and barbiturates are controlled substances according to the DEA, as promulgated by the Controlled Substances Act of 1970. The DEA places dangerous drugs into five schedules, with Schedule I drugs having no approved medical use and being the most dangerous. Schedule II-V are drugs with medical uses but with decreasing danger of abuse and dependence. Midazolam, as with most of the other benzodiazepines like diazepam (Valium®) and lorazepam (Ativan®) are placed into Schedule IV. Fast-acting barbiturates are considered much more dangerous drugs to abuse so they are scheduled the highest level for drugs still used medically, as Schedule II controlled substances. This is evidence that midazolam is deemed safer to use by the DEA, with less evidence of abuse and drug dependence than fast-acting barbiturates. Simply put, the DEA decision to schedule midazolam and the fast-acting barbiturates differently **reflects the DEA finding that midazolam and fast-acting barbiturates do NOT exhibit pharmacological equivalency in causing drug dependence and abuse.**

G. Summary

Pharmacological equivalency between benzodiazepines and barbiturates, and more specifically between midazolam and fast-acting barbiturates, was investigated by examining key aspects of the pharmacology of the two drug classes. The findings from this section are:

i. There is no pharmacological equivalency between midazolam and fast-acting barbiturates using the criterion of chemical structures for benzodiazepines and barbiturates.

ii. There is no pharmacological equivalency when examining the different mechanisms of action of benzodiazepines (midazolam) and barbiturates (pentobarbital, thiopental).

iii. There is no pharmacological equivalency between the magnitude of pharmacological effects produced by benzodiazepines (partial agonists) and barbiturates (full agonists). In particular, it is well-known that midazolam has a ceiling effect that is not present barbiturates.

iv. There is no pharmacological equivalency when examining the different therapeutic uses of benzodiazepines and barbiturates, or between midazolam and fast-acting barbiturates. In particular, midazolam is does not produce General Anesthesia and could not be used as a Sole Anesthetic, whereas barbiturates are used as Sole Anesthetics and do produce General Anesthesia.

v. There is no pharmacological equivalency in the drug abuse and dependence properties of benzodiazepines and barbiturates as confirmed by the different scheduling of these drugs by the DEA.

3. Dosage and Characteristics of Pentobarbital Used in Lethal Injection

A. Therapeutic, Toxic, and Lethal Dosages of Intravenous (IV) Pentobarbital

Barbiturates are a class of sedative-hypnotic drugs, largely replaced in clinical therapeutics by the benzodiazepine class of sedative-hypnotics (*Brenner and Stevens 2013*). Examples of common barbiturate drugs are thiopental, pentobarbital, phenobarbital, and methohexital.

Nembutal® Sodium Solution (Pentobarbital Sodium for Injection, USP) is an FDA-approved drug formulation that is manufactured by Akorn, Inc. a subsidiary of Oak Pharmaceuticals, Inc., headquartered in Lake Forest, IL (*FDA 2015*). Its official indications are listed on the FDA label for use as: a. Sedatives; b. Hypnotics, for the short-term treatment of insomnia; c. Preanesthetics; and d. Anticonvulsant, in anesthetic doses, in the emergency control of certain acute convulsive episodes, *e.g.* status epilepticus (*Nembutal® Sodium Solution* Prescribing Information, Oak Pharmaceuticals). Pentobarbital sodium IV solution is also used 'off-label' for the induction and maintenance of coma to reduce intracranial pressure in brain-injured patients (*Woodcock et al. 1982*).

Clinical studies and forensic toxicology studies have determined the therapeutic, toxic, and lethal blood concentrations of pentobarbital (*Musshoff et al. 2004; Regenthal et al. 1999; Schulz et al. 2012; Winek et al. 2001*). These values are given in blood concentration ranges from the most recent paper, as shown in Table 4 below.

Table 4. Therapeutic, toxic, and lethal ranges of pentobarbital blood concentrations. Concentrations given in mg/L (milligram per Liter) which is equal to mcg/mL (microgram per milliLiter). Half-life (t1/2) is given in the last column and is the time in hours it takes for half the amount of drug to be cleared from the bloodstream. From Schulz et al. 2012.

Substance	Blood-plasma concentration (mg/L)			$t_{½}$ (h)
	therapeutic ("normal")	toxic (from)	comatose-fatal (from)	
Pentobarbital	1-5 (-10)	10-19	15-25	20-40

There are no clinical studies determining the lethal dose of IV pentobarbital sodium in humans for obvious reasons. However, the largest IV pentobarbital sodium dose ever administered to human volunteers is reported in an early pharmacokinetic study from the 1950s (*Brodie et al. 1953*). In two volunteers, 2.5 grams pentobarbital was injected IV over 50 minutes. While blood concentrations were not determined in these volunteers, the authors note that following these large doses of IV pentobarbital, the volunteers were deeply anesthetized and had to be put on a ventilator with oxygen "until spontaneous ventilation was deemed adequate." Such studies could not be performed today due to safety and ethical concerns, but it is clear that a 2.5 gram dose given IV was a lethal dose in these two individuals as it caused them to stop breathing on

their own. These volunteers would have died without the supportive measures of the artificial ventilator and oxygen supplementation.

The most straight-forward approach to determining the lethality of pentobarbital sodium used in lethal injection protocols is to pharmacologically model the blood concentrations of pentobarbital after a 5 gram IV bolus injection of pentobarbital sodium. Once a reasonable estimate is made of the pentobarbital blood concentrations after a 5 gram IV pentobarbital sodium dose, the blood levels obtained can be compared to lethal pentobarbital concentrations as shown in Table 4, above.

B. Blood Levels of 5 gram Pentobarbital after IV Bolus Dose in Humans

The study of drug movement after administration is called pharmacokinetics. The pharmacokinetics of pentobarbital sodium are characterized by a rapid distribution of pentobarbital throughout the body and into the brain. With direct IV administration, there is no absorption phase of the drug like when a pill is swallowed. For this reason, the peak blood concentration of IV pentobarbital is observed with the first time point of sampling after the IV bolus injection.

As mentioned above, there are no studies in the literature that give the blood concentrations of pentobarbital following a 5 gram IV dose, as this is higher than approved clinical doses. However, it is possible to examine the pentobarbital blood concentrations in humans from studies following the administration of lower doses of IV pentobarbital sodium. The data from these studies can then be used to model the blood concentrations of pentobarbital after a 5 gram IV dose.

In 1953, the first study of the fate of pentobarbital in humans estimated the peak amount of pentobarbital in the blood after IV bolus administration of 1 gram (= 1000 mg) pentobarbital sodium (*Brodie et al. 1953*). This study gave peak blood concentrations of about 25 mg/L after the IV dose. Twenty years later, the first study using modern techniques in pharmacokinetic analysis determined the blood concentration of pentobarbital after an IV dose of 50 mg pentobarbital sodium (*Smith et al. 1973*). These authors found that a 50 mg IV dose of pentobarbital gave an initial peak blood concentration of about 1.5 mg/L. In a second pharmacokinetic study of IV pentobarbital sodium, a 100 mg IV dose yielded an initial pentobarbital blood concentration of about 3.0 mg/L (*Ehrnebo 1974*). A figure from this second modern paper is included below (as Fig. 2, top of next page) to portray the pentobarbital blood concentration curve over time following IV administration.

Given that a 50 mg IV dose of pentobarbital gave an initial pentobarbital blood concentration of 1.5 mg/L and that a 100 mg IV dose of pentobarbital (Fig. 2, below) gave an initial pentobarbital blood concentration of 3.0 mg/L (i.e. doubling the IV dose, doubled the initial blood concentration) it follows that a 5,000 mg IV dose of pentobarbital would give an initial pentobarbital blood concentration of 150 mg/L. This is calculated from the fact that a 5,000 mg IV dose (= 5 grams) is 100 times greater than the 50 mg IV dose and 100 times 1.5 mg/L equals

150 mg/mL. By examining Table 4 above, this initial pentobarbital blood concentration of 150 mg/mL is 6 to 15 times greater than the lethal drug range listed as 10-25 mg/mL.

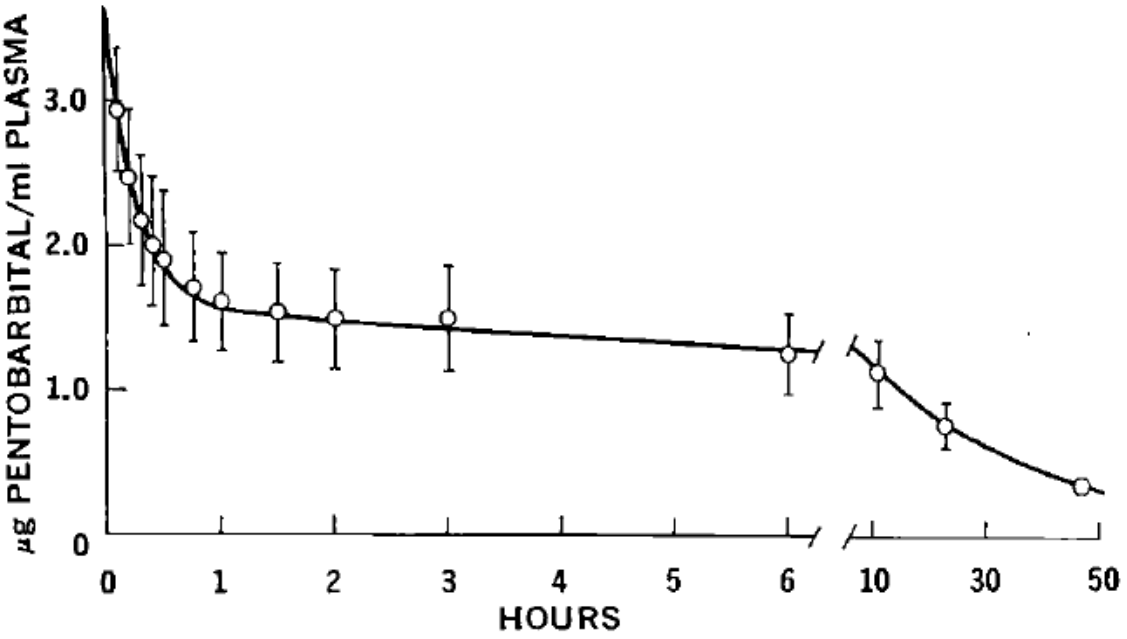


Fig. 2. Blood levels of pentobarbital following rapid IV injection of 100 mg to seven human subjects. Data points are the mean values of pentobarbital blood concentrations, plus and minus one standard deviation error bars. From *Ehrnebo 1974*. Note: µg/mL is equal to mg/L.

Given the above calculation that 5 grams of IV pentobarbital sodium yields an initial lethal blood concentration of 150 mg/L, the next determination is to model the fall of the pentobarbital blood concentration over time. It can be seen from Figure 2 above that the fall of pentobarbital blood concentrations occurs in two parts; the decrease in pentobarbital occurs more rapidly for the first hour, then the decrease slows down and changes slowly from the pentobarbital levels seen at one hour. The first rapid phase of the decrease in pentobarbital concentrations is due to the distribution of pentobarbital from the blood to the brain and other tissues. The second, slower phase in the decrease of pentobarbital is due to the elimination of pentobarbital from the blood by metabolism and excretion. The time it takes for the pentobarbital blood level to decrease by one-half is called the 'half-life' ($t_{1/2}$). The first rapid phase of pentobarbital decrease has a smaller half-life than the half-life of the second slower phase of pentobarbital decrease.

In order to determine the fall of pentobarbital concentrations over time, it is necessary to use the half-life data for IV pentobarbital from the pharmacokinetic studies cited above. Both of the modern pharmacokinetic studies of IV pentobarbital sodium show a rapid distribution of pentobarbital out of the blood of with a half-life of about 1 hour (*Ehrnebo 1974; Smith et al. 1973*) which lasts for about 2 hours, then a longer elimination half-life of about 22-50 hours. Using these half-life values, the pharmacokinetic modeling of a 5 gram (5000 mg) IV dose was done using an Excel® spreadsheet, as noted previously in the scientific literature (*Chamberlain 2003*).

The resulting graph of the decrease in pentobarbital blood levels after IV injection of 5 grams (5000 mg) is shown in Figure 3 below. This graph shows that with an initial blood concentration of 150 mg/L pentobarbital, the blood levels of pentobarbital decrease to 37.5 mg/L after 120 minutes. Within the first 5 minutes, the blood levels decrease to 141 mg/L (inset graph, Figure 3, below). Comparing these blood levels of pentobarbital with the lethal concentrations summarized in Table 4 above, after the first 5 minutes, the 5 gram IV dose of pentobarbital sodium yields blood levels of pentobarbital that are 5.6 to 14 times higher than lethal pentobarbital concentrations. After 120 minutes, the 5 gram dose gives blood levels that remain elevated above the lethal pentobarbital concentrations.

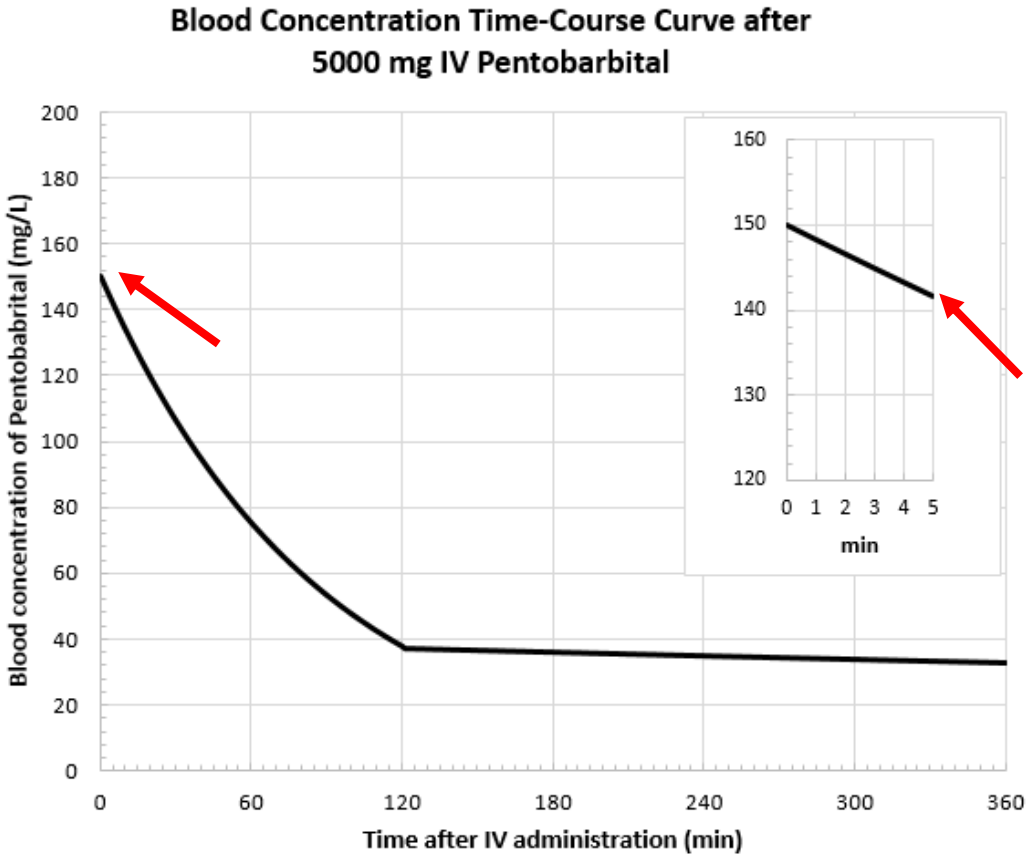


Fig. 3. Blood levels of pentobarbital following IV injection of 5 grams (5000 mg) as modeled by the best available data. The initial blood concentration was 150 mg/L (at left arrow). The rapid decrease (distribution phase) used a half-life of 60 min that lasted for 2 hours. The slower elimination phase used a half-life of 20 hours. Inset graph in upper right corner shows an enlargement of the first 5 minutes after IV injection (right arrow).

C. Differences Among Barbiturate Drugs

Barbiturate drugs were discovered and used to a great degree before the advent of the benzodiazepine drugs in the 1960s (*Harvey 1980*). All benzodiazepines have the same mechanism of action, which differs from barbiturates' mechanism of action (see Section 2C above). Barbiturate drugs potentiate and replace the action of GABA to greatly inhibit neurons, whereas benzodiazepines need GABA present to work and are limited in their pharmacological effects (i.e. are partial agonists, see Section 2D).

The differences in various barbiturate drugs lie primarily in their pharmacokinetic characteristics, and are subclassified according to how long they exert their pharmacological effects. The barbiturates are also classified by their therapeutic effects, such that there are anesthetic barbiturates, such as thiopental, pentobarbital, amobarbital, and anticonvulsant barbiturates, such as mephobarbital and phenobarbital (*Macdonald and Barker 1979*).

Barbiturates also differ by their individual chemical nature, most importantly in a term called lipophilicity. Lipophilicity, which means 'fat-loving,' describes a physical characteristic of drugs that correlates with how rapidly a drug can cross from the bloodstream to the brain. Rapid-onset, ultrashort-acting anesthetic barbiturates, like amobarbital and pentobarbital, are more lipophilic than anticonvulsant barbiturates like mephobarbital or phenobarbital (*Toon and Rowland 1983*). Because of this, the highly lipophilic barbiturates (amobarbital and pentobarbital) have a faster onset of action, usually within 30 seconds to 1 minute after an IV bolus dose (*Sessions et al. 1954*).

Finally, the barbiturates differ in terms of their potency: anesthetic barbiturates (pentobarbital and amobarbital) are more potent in their inhibition of brain neurons than anticonvulsant barbiturates like mephobarbital and phenobarbital (*Macdonald and Barker 1979*).

The pharmacological differences between barbiturates precludes a substitution of pentobarbital with any other barbiturate except another fast-acting barbiturate.

D. Summary

The findings from this section are:

i. The normal therapeutic blood concentration of pentobarbital ranges from 1-10 mg/L. Toxic blood concentrations of pentobarbital range from 10-19 mg/L and lethal concentrations of pentobarbital range from 15-21 mg/L and higher.

ii. A 5 gram IV bolus dose of pentobarbital sodium produces initial pentobarbital blood concentrations of about 150 mg/L, which is 6 to 15 times greater than the accepted lethal dose range. After 5 minutes, the blood concentration of pentobarbital is 5.6 to 14 times greater than the lethal blood concentrations of pentobarbital. After 2 hours, the blood concentration of pentobarbital remains above the lethal blood concentration range.

iii. All barbiturates share the same mechanism of action but differ in potency, time of onset, duration of action, and therapeutic indications. Only fast-acting barbiturates like thiopental or pentobarbital are suitable for use in lethal injection protocols.

4. Pharmacology of Vecuronium and Potassium Chloride

According to the Arkansas method-of-execution statute, § 5-4-617, the Director of the Arkansas Department of Corrections shall select one of the following options for a lethal injection protocol: a one-drug protocol using a barbiturate, or a three-drug protocol using midazolam, followed by vecuronium bromide, followed by potassium chloride. The pharmacology and mechanism of action of the first drug in the three-drug protocol, midazolam, was detailed above (Section 2) and the ceiling effect of midazolam is discussed below (Section 5). The second and third drugs listed in the Arkansas three-drug lethal protocol are vecuronium bromide, at a dose of 100 mg, and potassium chloride, at a dose of 240 mEq, which are discussed here.

A. Pharmacology and Clinical Effects of Vecuronium

Vecuronium, like pancuronium, is a drug classified as a neuromuscular blocker or simply called a paralytic drug. Neuromuscular blockers work by blocking the action of acetylcholine which is the neurotransmitter released from a nerve ending onto the muscle that causes the muscle to contract (*Hibbs and Zambon 2011*). Clinical uses of neuromuscular blockers are to provide muscle relaxation for endotracheal intubation, and to ensure patient immobility during surgery or mechanical ventilation (*Kovac 2009, Vecuronium Bromide for Injection Prescribing Information*). Vecuronium is a chemical analog to pancuronium and is about 1.5 to 1.75 times more potent than pancuronium (*Fahey et al. 1981*). Vecuronium has about the same onset time as pancuronium (within 5 minutes) but has a shorter duration of action, and produces no cardiovascular effects or changes in heart rate or blood pressure. With higher doses of vecuronium, the onset time can be reduced to 2.4 minutes (*Hilgenberg 1983*).

The clinical effects of vecuronium are shared by other neuromuscular blockers and include progressive loss of skeletal muscle contraction, first noted by drooping eyelids and muscle weakness (*Hibbs and Zambon 2011*). Motor weakness progresses eventually to a total flaccid paralysis. The small, quick muscles of the eyes, jaw, and larynx relax before those of the arms, legs, and trunk of the body. Finally, the intercostal muscles that expand the ribs and the diaphragm are paralyzed, and breathing ceases. Without intubation and mechanical ventilation, death ensues from a lack of oxygen (hypoxia).

There are a few studies of the effect of neuromuscular blockers given in human volunteers without an anesthetic agent. In a classic 1947 paper, a complete description of the effects of tubocurarine, an early neuromuscular blocker, on the central nervous system was examined (*Smith et al. 1947*). These researchers found that neuromuscular blockers had no effect on altering consciousness, or memory and had no analgesic effect. They concluded that these paralytic drugs should not be used alone as they may cause “serious psychic trauma.” A later study, using trained anesthesiologists and the researchers themselves, found that in these awake subjects vecuronium had no effect on consciousness and, like the earlier study by Smith

and colleagues, that the most distress came from a feeling of shortness of breath and 'air hunger,' even as they were artificially ventilated with supplemental oxygen at sufficient levels (*Topulos et al. 1993*). As early as 1950 clinicians realized that the use of paralytic drugs like vecuronium and pancuronium without adequate anesthesia leads to the possibility that a patient is awake but incapable of indicating distress or pain because of muscle paralysis (*Brice 1970*).

While these above studies were done on the researchers themselves, who were trained in the procedures and knew what to expect, most research on the adverse effects of vecuronium and other neuromuscular blockers comes from cases where conscious patients were completely paralyzed but unable to communicate with health care workers. In emergency care, patients who experienced paralysis without sedation or anesthesia reported dysphoria and severe pain (*Chong 2014*). Patients in intensive care units who were paralyzed with pancuronium because they were intubated and on mechanical ventilators, but were not sedated and were conscious, reported that they felt "buried alive"; some thought they were already dead (*Perry 1985*). Most of these patients said they would rather die than go through 4 days of being paralyzed while conscious again. A study of patients who emerged from anesthesia but were still paralyzed from neuromuscular blockers gave reports of panic, suffocation, and a feeling of already being dead (*Thomsen et al. 2015*). These experiences were horrific enough to trigger post-traumatic stress disorder (PTSD) in some unfortunate patients.

The above papers show that vecuronium or pancuronium, or any other paralytic drug, should only be used in patients that are anesthetized and unconscious. In documented cases where patients or experimental subjects were awake but paralyzed, intolerable and damaging experiences of pain, panic, and suffocation occurred.

B. Pharmacology and Clinical Effects of Potassium Chloride

Potassium chloride for injection is an electrolyte solution used for the treatment of hypokalemia, which means low blood-potassium levels (*Potassium Chloride for Injection Prescribing Information*). Hypokalemia can be life-threatening and can lead to dysfunction of excitable tissues such as cardiac, skeletal, and smooth muscle (*Kruse and Carlson 1990*). The low potassium of hypokalemia may result in muscular paralysis, respiratory failure, and cardiac abnormalities, which can be fatal.

Potassium chloride for injection is also used in late-term abortions of a fetus with genetic or severe, non-viable abnormalities (*Isada et al. 1992, Senat et al. 2002, Sfakianaki et al. 2014*). In these cases, potassium chloride is delivered directly into the fetal heart chamber or into the umbilical vein.

There are a few cases of high-dose potassium-chloride injection in awake patients, which only occurs as a result of an accident or intentional homicide in the hospital setting (*Wetherton et al. 2003*). The earliest report of an accidental high dose of IV potassium chloride due to improper mixing was in a male patient who immediately complained of a severe pain moving up his arm (above the site of the IV) and a ringing in his ears (*Lankton et al. 1973*). The patient then lost

consciousness, stopped breathing, and his heart stopped beating. Another case study in that same year reported that an IV infusion of potassium chloride produced severe pain at the site of the IV infusion (*Williams 1973*). In a forensic report of four IV potassium-chloride-induced deaths at hospital, one man who accidentally received a high-dose IV infusion of potassium chloride screamed out in pain (*Wetherton et al. 2003*). Potassium-chloride IV injections are also documented as a rare method of suicide in health care workers, but self-reports of the effects noted by these persons are unavailable (*Battefort et al. 2012, Bertol et al. 2012*).

The above studies show that IV administration of potassium chloride at high doses leads to severe pain in awake, unanesthetized patients.

C. Importance of Achieving General Anesthesia

In the case of lethal injection using a three-drug protocol, it is crucial to insure that the first drug achieves General Anesthesia because of the intolerable effects of the second drug (muscle paralytic) and third drug (potassium chloride).

Clinical experience with non-responsive patients shows that a cautious approach to the risk evaluation of midazolam's ability to produce General Anesthesia should be taken. Patients that are non-responsive are diagnosed of being in a vegetative state after repeated tests of consciousness show no evidence of sustained, reproducible, purposeful, or voluntary behavioral response to visual, auditory, tactile, or noxious stimuli (*MacDonald et al. 2015).* These tests in non-responsive patients are the same as tests used by anesthesiologists to detect the surgical plane of anesthesia. In the non-responsive patients, studies show that up to 43% of these patients that are diagnosed as vegetative are actually aware or conscious. Additionally, studies document that some patients are not unconscious even when strong general anesthetics, like pentobarbital or inhalation agents, are used. (*Escallier et al. 2014*) These findings mandate a conservative approach to questions of the first drug used in a three-drug lethal injection protocol. In other words, even under the best circumstances, clinicians assessing non-responsive patients and anesthesiologists inducing general anesthesia appear to get it wrong a significant percentage of the time and their patients are not unconscious (or anesthetized) as often as they think.

Because even trained anesthesiologists using powerful anesthetic drugs fail to detect awareness or consciousness a significant proportion of the time, the "consciousness check" articulated in Section IV.2.h(1) of Arkansas's lethal injection protocol does not provide any assurance that the condemned inmate will be sufficiently anesthetized or that he will not experience the pain and suffering caused by the second two drugs in Arkansas's protocol. According to Section 1.1 of the protocol, the "Deputy Director, or designee" who performs the consciousness check need not even be a physician or nurse, much less an anesthesiologist. Further, because it is pharmacologically impossible for midazolam to produce a state of General Anesthesia, as discussed above in Section 2 and further below in Section 5, any determination that the prisoner is unconscious when not in a state of General Anesthesia would by definition be erroneous.

D. Summary

i. Vecuronium administration produces paralysis of muscles, including muscles that promote breathing, preventing movement in patients undergoing surgery.

ii. Vecuronium administered to unanesthetized subjects in clinical studies gives rise to pain, panic, and suffocation, without a means to communicate this to others due to complete muscle paralysis.

iii. Potassium chloride is used to produce cardiac arrest (stop the heart) in the condemned inmate.

iv. Studies show that use of potassium chloride by IV injection in an awake and unanesthetized patient leads to severe pain radiating from the site of the IV infusion and cessation of breathing and heart function while conscious.

v. The condemned inmate must be in a state of General Anesthesia, noted by loss of consciousness and the inability to respond to a noxious stimulus, before the administration of vecuronium and potassium chloride.

5. Calculation of the 'Ceiling Effect' Dosage of Midazolam Used in Lethal Injection

This section discusses the concept of the "ceiling effect" in further detail. It calculates the ceiling-effect dose of midazolam using a methodology described below; it then discusses other clinical studies regarding midazolam's ceiling effect and their bearing on the calculation contained herein.

A. Introduction to the Issue of the 'Ceiling Effect' With an IV Bolus Dose of Midazolam

The 'ceiling effect' refers to the fact that greater doses of midazolam do not produce a greater pharmacological effect. The ceiling effect is well-known for midazolam and all similar drugs in the class called benzodiazepine sedative-hypnotics. By way of contrast, there is no ceiling effect seen with barbiturate sedative-hypnotics like thiopental and pentobarbital (see Section 2D above). The ceiling effect of midazolam and other benzodiazepines is not controversial and is portrayed in many introductory pharmacology textbooks (see Fig. 1 above).

As detailed in Section 2D above, benzodiazepines (including midazolam) act by enhancing the inhibitory effect of the neurotransmitter, GABA, on brain neurons. The decrease in neuronal activity produced by the inhibitory neurotransmitter, GABA, is not 'all or none'. GABA simply decreases the ongoing activity of neurons by a graded amount, depending on how much GABA is present. GABA is a limited resource in the brain, as it is made and released by inhibitory brain neurons, which are finite in number. Therefore midazolam is limited in its action by the amount of GABA present, whereas barbiturates are not limited by the amount of GABA present.

A little more pharmacology of benzodiazepines' mechanism of action and an analogy is needed. Midazolam and other benzodiazepines potentiate the binding of GABA at the $GABA_A$ receptor, but at a site different than where GABA binds. This is called allosteric modulation. To use an analogy, the allosteric action of midazolam might be thought of as a Boy Scout helping an elderly woman (GABA) across the street. The woman can cross the street without the Boy Scout (midazolam) but his presence and assistance helps the elderly woman move faster. Midazolam and other benzodiazepines can only enhance GABA action and have no inhibitory action on brain neurons on their own. By this allosteric mechanism of action, benzodiazepines have an innate 'ceiling effect' and can only produce sedation on a limited plateau. Using our analogy, the Boy Scout can move the elderly woman across the street only so fast, the act of getting the woman across the street is still limited by the ability of the woman to ambulate on her own two legs. There is a 'ceiling effect' in how fast the woman can cross the street, even if two or more Boy Scouts were to help her.

Most telling that midazolam has a ceiling effect is the lack of a fatal blood level range for midazolam in the latest compendium of therapeutic, toxic, and fatal blood levels of over 1,000 drugs (*Schulz et al. 2012*). **Table 5 below shows the blank space for the fatal blood levels of midazolam**. **There are few fatalities.**

Table 5. Therapeutic, toxic, and lethal ranges of pentobarbital and midazolam blood concentrations. Note the lack of fatal concentration ranges for midazolam. From Schulz et al. 2012.

Substance	Blood-plasma concentration (mg/L)			$t_{½}$ (h)
	therapeutic ("normal")	toxic (from)	comatose-fatal (from)	
Pentobarbital	1-5 (-10)	10-19	15-25	20-40
Midazolam	0.04-0.1 (-0.25)[134]	1-1.5		1.5-3[46]

B. Calculation of Ceiling Effect

This subsection calculates midazolam's ceiling effect using a modeling approach based on extrapolation from *in vitro* and cell-culture testing. The calculation considers that the Arkansas Lethal Injection Protocol employs two syringes with 250 mg midazolam each for a total of 500 mg. The State's procedure also states that "*after at least five (5) minutes have elapsed since commencing the administration of syringe 1A* [the first 250 mg midazolam syringe]*, the Deputy Director, or designee, will confirm the condemned inmate is unconscious by using all necessary and medically-appropriate methods."* Accordingly, the present subsection ultimately seeks to answer whether midazolam's ceiling effect is reached at or below (1) the brain concentration of midazolam produced immediately after the IV bolus administration[2] of a 500 mg midazolam dose and (2) the brain concentration 5 minutes after IV midazolam administration.

The first step of this modeling approach is to determine the concentration at which midazolam's ceiling effect occurs in studies done *in vitro* (using brain cells in a laboratory dish). Second, a calculation of the blood concentration of midazolam following a 500 mg IV bolus dose

[2] Bolus means a single IV injection all at one time as opposed to continuous infusion at a lower rate.

is made based on blood concentrations of midazolam following clinically-used doses. Third, based on the pharmacological data of midazolam crossing into the brain in preclinical studies, the extent of the 500 mg midazolam dose that enters the brain is calculated. Fourth, published studies are researched to calculate the concentration of midazolam in the brain after a 500 mg IV dose. Finally, by comparing the concentration of midazolam that produces a ceiling effect in studies done *in vitro* with the calculated concentration of midazolam in the human brain after a 500 mg dose, the ceiling-effect dose is calculated.

i. Ceiling Effect of Midazolam and Other Benzodiazepines Observed In Vitro

This subsection will highlight cell culture *in vitro* studies and preclinical (animals) studies from the medical literature that determined the ceiling effect of midazolam and other benzodiazepines. These studies will provide specific numerical values that can be used to model the concentration in the brain of a condemned inmate after a 500 mg IV dose of midazolam.

Table 6 below shows the threshold dose(s) that produced the observed ceiling effect in published studies of in vitro experiments. Most studies of diazepam show a ceiling effect threshold at 100 nM and all three studies of midazolam gave 100 nM as the concentration producing a ceiling effect.[3]

[3] Drug concentrations are measured with different units in different types of experiments or clinical studies. The in vitro studies presented in this subsection use Molar Concentration, which is basically a certain number of grams (1 Mole) in a liter of solution. 1 Mole of a drug in 1 Liter of solution gives a 1.0 M concentration. Then, using the metric system prefixes, we know that 1 M = 1000 mM (milli-Mole) which equals 1,000,000 µM (micro-Mole), which is equal to 1,000,000,000 nM (nano-Mole). For these types of studies, the drug solutions are mixed to make up different strengths, like 1 nM, 10 nM, 100 nM, and 1000 nM, and these different solutions are bathed on different sets of cells in a Petri dish and the pharmacological effects measured. The results shown below for the in vitro studies of benzodiazepine effects use drug solutions in the units of nM.

Other units are used in other studies below. Concentration of drug in blood is often given in ng/mL (nano-grams per milli-Liter). Again using the metric system prefixes, we know that 1 g (gram) equals 1000 mg (milli-grams) equals 1,000,000 µg (or mcg; micro-gram) equals 1,000,000,0000 ng (nano-gram). Finally, doses of drugs are administered on a per weight basis, such as 2 mg/kg, or as the same dose for everybody, such as 500 mg dose of midazolam administered intravenously (IV).

Table 6. Summary of selected studies showing ceiling effect of diazepam and midazolam

Benzodiazepine	**Ceiling effect at:**	**Preparation**	**Reference**
Diazepam	10 nM[a]	Cell culture (mouse spinal neurons)	*Skerritt and Macdonald (1984)*
Diazepam	100 nM	Cell culture (oocytes)	*Sigel and Baur (1988)*
Diazepam	50-100 nM	Cell culture (mouse spinal neurons)	*Rogers et al. (1994)*
Diazepam	100 nM	Cell culture (HEK cells)	*Li et al. (2013)*
Diazepam	100 nM	Cell culture (oocytes)	*Rüsch and Forman (2005)*
Midazolam	100 nM	Brain slices (rat)	*Rovira and Ben-Ari (1999)*
Midazolam	100-200 nM	Brain slices (rat)	*Bai et al. (2001)*
Midazolam	100 nM	Cell culture (oocytes)	*Rüsch and Forman (2005)*

[a] nM stands for 'nanomolar' which is a concentration term relating the number of drug molecules in a liter of solution.

A ceiling effect, which is really just a limit on the potency of a drug (see discussion of partial agonists in Section 2D), was noted with benzodiazepines, including diazepam (Valium®) and midazolam (Versed®), in the research studies that determined the mechanism of action for benzodiazepine drugs. Samples of figures from these original research papers are reproduced below (next two page) so that it will be obvious that a ceiling effect is documented and pervasive in the scientific and pharmacological literature.

Figures 4-7 on the next two pages show the actual graphs that confirm a ceiling effect for the benzodiazepines diazepam and midazolam from *in vitro* studies. The ceiling effect on these figures is denoted by a horizontal dashed blue line; this is the plateau that is reached where benzodiazepines given at higher concentrations do not produce greater effects.

Figure legends under the graphs further explain the graphs and the ceiling effect concentration. This is the lowest concentration of drug that produces the plateau effect or ceiling effect.

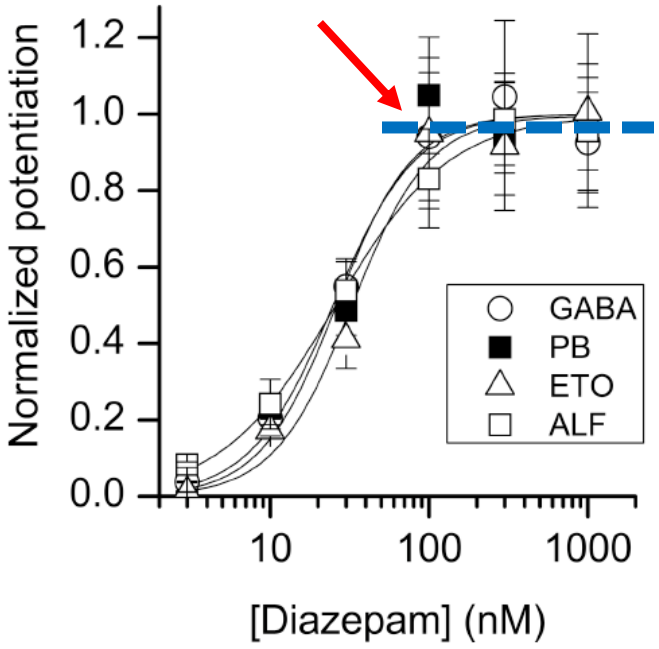


Fig. 4. Various doses of the benzodiazepine, Diazepam, were added with GABA (open circles) and other drugs and the current measured on the vertical scale (Y-axis). Arrow shows ceiling effect threshold at 100 nM. Horizontal dash line shows the ceiling effect. From Fig. 4 in *Li et al. 2013.*

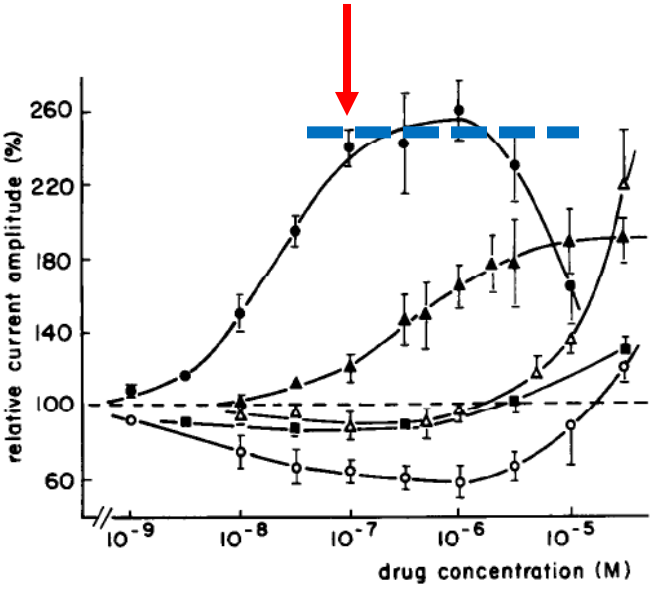


Fig. 5. Various doses of the benzodiazepine, Diazepam (closed circle, top curve) were applied to cells in the presence of GABA and the current measured on the vertical scale (Y-axis). Arrow shows ceiling effect threshold at 10^{-7} M which is equal to 100 nM. Horizontal dash line shows the ceiling effect. From Fig. 4 in *Sigel and Baur 1988.*

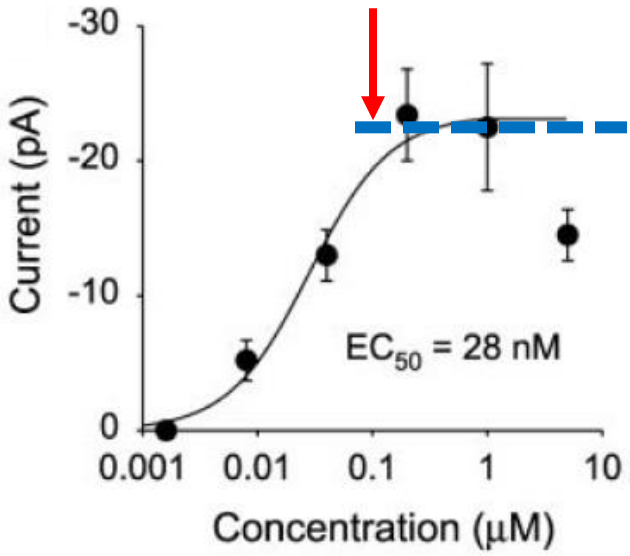


Fig. 6. Various doses of Midazolam (closed circle, top curve) along the horizontal scale (x-axis) were applied to cells in the presence of GABA and current measured on the vertical scale (Y-axis). Arrow shows ceiling effect threshold at 0.1 µM which is equal to 100 nM. Horizontal dash line shows ceiling effect. From Fig. 5B in *Bai et al. 2001.*

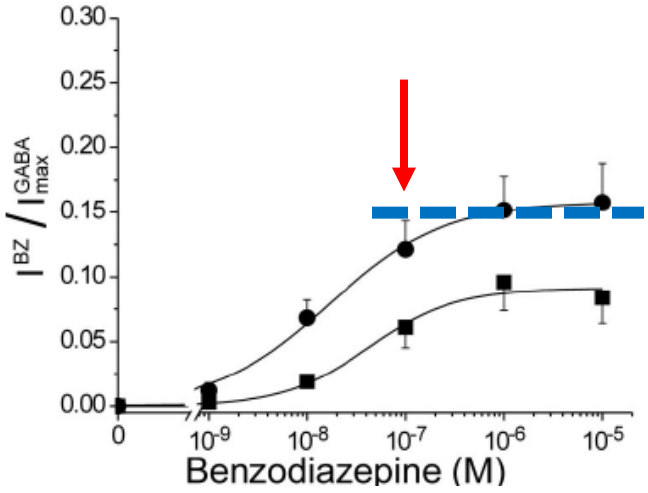


Fig. 7. Various doses of Midazolam (closed circle, top curve) or Diazepam (closed squares, bottom curve) along the horizontal scale (x-axis) were applied to cells in the presence of GABA and current measured on the vertical scale (Y-axis). Arrow shows ceiling effect threshold at 10^{-7} M which is equal to 100 nM. Horizontal dash line shows ceiling effect. From Fig 2A in *Rüsch and Forman 2005.*

ii. Blood Levels of 500 Mg Midazolam after IV Bolus Dose in Humans

As mentioned above, there are no studies in the literature that give the blood concentrations of midazolam following a 500 mg IV dose in humans, as this is higher than approved clinical doses. However, it is possible to review the blood concentrations in humans from studies examining the blood concentrations after clinical doses of IV midazolam. The data from these studies can then be used to model the blood concentrations of midazolam after a 500 mg IV dose.

A clinical study measured the peak amount of midazolam in the blood after IV bolus administration of 5 mg midazolam in eight healthy volunteers (*Schwagmeier et al. 1998*). This study gave peak blood concentrations of nearly 120 ng/mL (nanogram per milliliter) after a 5 mg IV dose. It follows then that with a 500 mg IV dose, the initial amount after direct IV bolus infusion is 100 times of what occurred with the 5 mg dose, which gives an initial blood concentration of 12,000 ng/mL of midazolam after a 500 mg IV dose.

A direct linear modeling of the 500 mg IV dose from the 5 mg dose is supported by other studies. In a more recent study using half of the above 5 mg IV dose, a 2.5 mg IV dose of midazolam, the peak blood concentration of 51.2 ng/mL which is about half the peak blood concentration seen in the above clinical study using a 5 mg IV dose of midazolam (*Veldhorst-Janssen et al. 2011*). Therefore it is not unreasonable to use this linear relationship to extrapolate as is done above

Given the estimate that the initial concentration of midazolam in the blood after a 500 mg IV bolus dose is 12,000 ng/mL, the next determination is to model the fall of midazolam blood concentration over time to determine the amount of midazolam that is available for transfer to the brain during the first 5 minutes. Five minutes is a crucial time point, as the Arkansas Department of Corrections Lethal Injection Procedure mandates that the offender being put to death will be checked for unconsciousness at least 5 minutes after the infusion of midazolam begins.

In order to determine the midazolam blood concentrations over time, it is necessary to have established pharmacokinetic data for IV midazolam. A key paper in this regard examined the pharmacokinetic data after dosing volunteers with 0.1 mg/kg midazolam IV infusions after 1 minute, 1 hour, and 3 hour lengths of infusion (*Greenblatt et al. 2004*). The dosing of midazolam with a 1 minute bolus infusion in this study comes closest to the method to be used by the Arkansas Department of Corrections (see above). Using these data from this study,[4] it was possible to model the blood concentration curve over time following the IV dose of 500 mg midazolam (see Fig. 8 next page). The modeling of the blood concentration curve following a 500 mg IV midazolam dose was done using an Excel spreadsheet, as noted in the scientific literature (*Chamberlain 2003*) and was done above in Section 3B.

[4] The Greenblatt study found that a midazolam IV dose given in 1 minute had a half-life of immediate distribution (t½ alpha) of 21 min and a half-life of elimination (t½ beta) of 171.6 minutes. These parameters were plugged into the spreadsheet formula to give the model data plotted in Fig. 8.

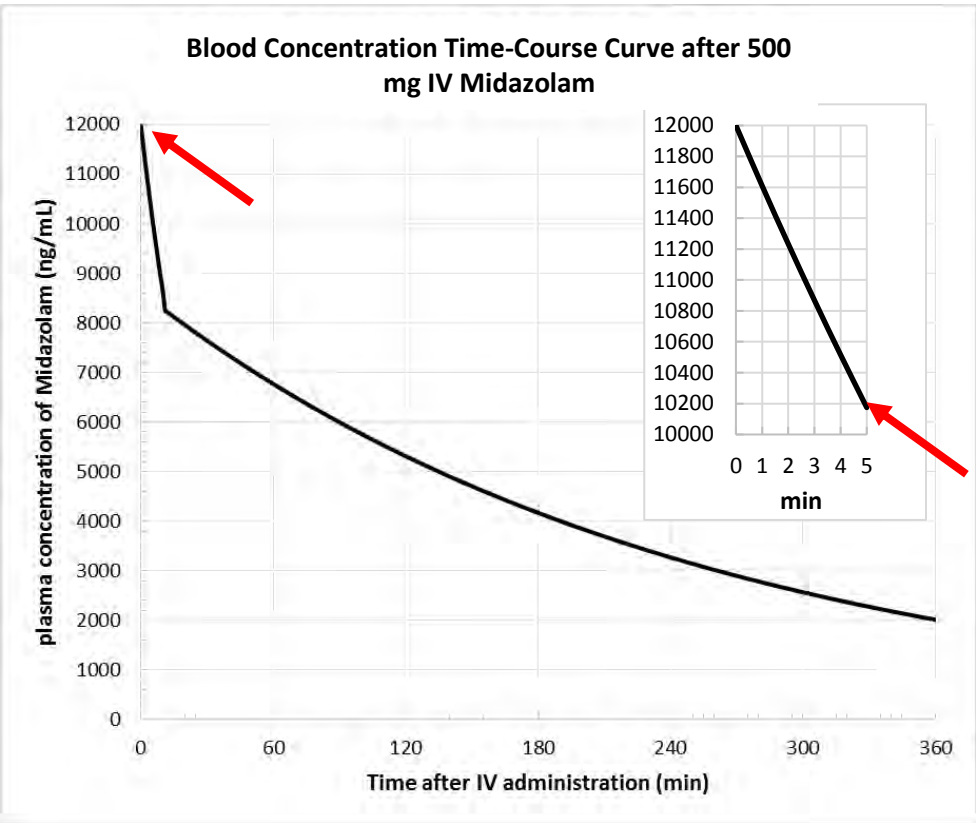


Fig. 8. Blood concentration curve following a single IV bolus dose of 500 mg midazolam. Inset shows the region of the plot from 0-5 minutes. See text for further details. Arrows denote the initial blood concentration of midazolam and midazolam concentration after 5 minutes (inset).

The key parameters calculated above are that following the 500 mg IV dose of midazolam, the initial highest concentration of midazolam is 12,000 ng/mL and after 5 minutes, the concentration of midazolam is 10,200 ng/mL.

iii. Extent of Midazolam Entering the Human Brain after an IV Bolus Dose

Studies that show the amount or extent of midazolam that enters the human brain would be best done by administering an IV dose in numerous people and then sampling brain tissue at various time points afterwards. These studies, of course, cannot be done. However, a number of preclinical studies in animals provide reliable data about the fraction of midazolam that crosses into the brain from the blood. These studies are reviewed next and will provide a value that can be used to determine the amount or extent of midazolam that enters the human brain after a 500 mg IV dose.

It should first be noted that drugs in the blood bind to blood proteins such as albumin and gamma-globulins and the amount of protein binding varies with each drug. This is important as only the free (unbound) drug is available to cross from the blood into the brain to exert its effect. Midazolam is a drug with high blood-protein binding, on the order of 94-97% (*Fragen*

1997). Using 95% as an estimate, this gives only 5% of the amount of midazolam in the blood available for crossing the blood-brain barrier and entering the brain. Taking this into account for the two key parameters of interest noted above, a 500 mg IV bolus of midazolam gives an initial free-drug blood concentration of 600 ng/mL (12,000 X 0.05) and a free-drug blood concentration at 5 minutes of 510 ng/mL (10,200 X 0.05).

Preclinical studies of the fraction of midazolam that enters the brain after an IV dose are done by sampling the cerebrospinal fluid (CSF) along with the blood at various times after midazolam administration (*Arendt et al. 1983, Jones et al. 1988*). The CSF is a good surrogate for the fluid surrounding the brain cells, as it is relatively protein-free so there is little to no binding of drugs to proteins like that which occurs in the blood. The CSF circulates around and through the brain and spinal cord, bathing these tissues (*Lin 2008*). Fig. 9 below shows the concentration of midazolam in the blood and in brain CSF at the same time points from the paper by *Arendt 1983*.

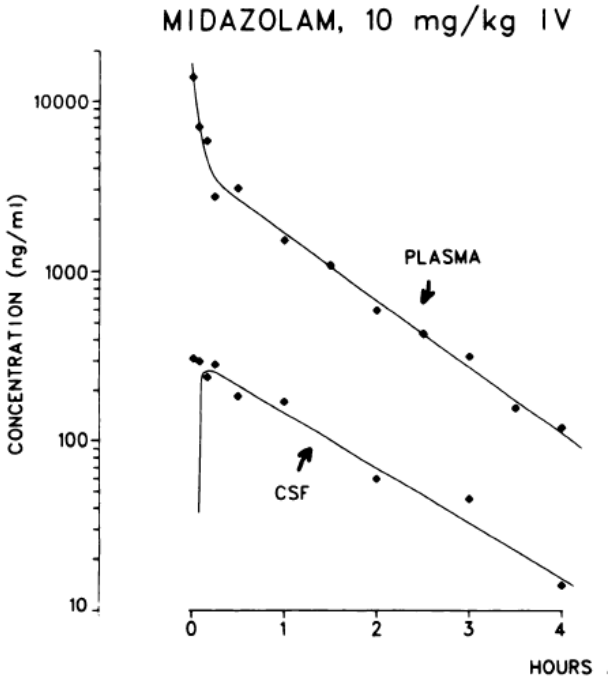


Fig. 9. Midazolam-concentrations curve in blood (plasma, top curve) and in brain CSF (bottom curve) after a single 10 mg/kg IV bolus dose. Note that the CSF concentration is much less than blood at all time points but mirrors the blood curve. From Fig. 2 (left panel) in *Arendt et al. (1983).*

The calculations performed in the study shown in Fig. 9 yielded a brain CSF/blood concentration ratio of 0.14 or 14% (*Arendt et al. 1983*). This ratio can be used in our determinations of brain concentration after 500 mg IV dose of midazolam to calculate that an initial blood concentration of 600 ng/mL midazolam equals 84 ng/mL in the brain (600 X 0.14) and at 5 minutes after start of infusion, the blood concentration of 510 ng/mL is equal to 71.4 ng/mL (510 X 0.14) in the brain.

iv. Dosage of IV Midazolam That Produces a Ceiling Effect in Humans

The above data gave the measurement of midazolam in blood in the units of ng/mL, or nanogram per milliliter, is a weight per volume measure, like mixing a teaspoon of salt in a glass of water). However, the existing data on the concentration of midazolam that produces a ceiling effect from *in vitro* studies reviewed above gave a value of 100 nM (nanomolar), which is in different units. The brain concentration of midazolam, as calculated in ng/mL above, must be converted to nanomolar terms to compare it with the existing *in vitro* data showing that midazolam's ceiling effect occurs at a midazolam concentration of 100 nM. This conversion is done by using the molecular weight of midazolam which gives the relationship between grams and moles.[5] For example, a concentration of midazolam of 32.6 ng/mL in the brain equals 100 nM in molar terms.

The calculated values of the brain concentrations of midazolam following a 500 mg IV dose gave an estimate of 84 ng/mL when the infusion begins and 71.4 ng/mL after 5 minutes elapsed from the start of the infusion. These two values expressed in nM are: 84 ng/mL = 257.9 nM and 71.4 ng/mL = 219.2 nM.

Given that midazolam shows ceiling effects at 100 nM concentration (see Table 6 above), the estimated initial brain concentration for midazolam using a 500 mg IV dose is about 2.6 times higher (at 257.9 nM) than the concentration of midazolam that produces a ceiling effect (100 nM). Five minutes[6] after the 500 mg IV midazolam administration, the brain concentrations for midazolam are estimated to be 219.2 nM or approximately double the ceiling effect concentration of 100 nM shown in preclinical studies (Table 6).

The midazolam dose that results in a 100 nM concentration of midazolam, the ceiling effect concentration, is obtained by using the values of brain concentration obtained with a 500 mg IV dose above after 5 minutes. A 500 mg IV dose gives a brain concentration of 219.2 nM after 5 minutes which is 2.192 times the ceiling effect concentration of 100 nM. Therefore, a dose that is 2.192 times less than 500 mg is 228 mg. Thus, a 228 mg IV dose of midazolam would be expected to reach the threshold concentration of midazolam to produce a ceiling effect after 5 minutes.

C. Comparison to clinical studies

Midazolam's anesthetic effects have also been studied in the clinical setting. This section provides an overview of bispectral analysis (BIS), reports results based on BIS, and discusses discrepancies between the ceiling effect calculated using the above modeling method and the ceiling effect noted in BIS-based studies.

[5] Calculations were assisted by the Molar solution concentration calculator found at *www.physiologyweb.com.*

[6] Five minutes was chosen as the time point to examine as that is the time after midazolam administration that the first consciousness check is performed according to the Arkansas lethal injection protocol.

i. Bispectral Analysis (BIS)

Scientific models of consciousness rely on the measurement of activity in different areas of the brain and the known functions associated with them. When a general anesthetic is given, there is inhibition of the activity in the higher-order association areas of the brain more so than in the primary processing areas of the brain (*MacDonald et al. 2015*). Most telling, as patients come out of general anesthesia, there is dramatic and sudden activation of the higher-order association areas of the brain regions that correlates with patient responding to verbal commands (*Långsjö et al. 2012*). To a first approximation, consciousness is correlated to activity in brain-association areas and therefore unconsciousness is correlated to lack of activity in these brain association areas.

Researchers and clinicians have developed a way to measure the depth of general anesthesia using the technique of electroencephalograms (EEG). The EEG recordings are processed by the computer with a method called bispectral analysis, or BIS (*Escallier et al. 2014*). BIS gives a single number, on the scale from 100 (completely awake and alert) to 0 (coma and EEG burst suppression). BIS values are the most common objective means for assessing the effects of anesthetic agents, with lower values correlated to greater degrees of brain-activity depression.

Clinical signs of anesthesia correlate moderately well with BIS scores (*Weaver et al. 1970*). BIS values less than 60 are targeted during general anesthesia procedures as that is the depth of anesthesia associated with lack of awareness (*Weaver et al. 1970*). In this study, BIS values of 60 or less correlated with General Anesthesia, 65 with Deep Sedation and 80 to Moderate Sedation (see ASA table in section 2E above). Later studies have verified that a BIS value of 40-60 is considered to reflect the state of General Anesthesia (*Escallier et al. 2014*). For example, one study showed the BIS levels of patients who moved at skin incision (mean BIS value of 65) was greater than patients who did not move in response to skin incision (mean BIS value of 40) (*Johansen and Sebel 2000*).

Using thiopental doses to induce (but not maintain general anesthesia) gave BIS values as low as 60 (*Yoo et al. 2012*). Pentobarbital has decreased the depth of General Anesthesia in cases of intractable seizures to BIS values as low as 3 to induce barbiturate coma (*Jaggi et al. 2003*). These studies show that barbiturates are capable of reducing BIS levels consistent with General Anesthesia, and that high-dose administration of barbiturates can reduce cortical brain activity to near zero.

ii. Clinical studies of midazolam and BIS

Generally, midazolam is used as a premedicant before general anesthesia or for regional anesthesia (*Khanderia and Pandit 1987*). Midazolam is a less reliable induction agent than thiopental and induction of anesthesia using midazolam alone is unpredictable. Clinically, benzodiazepines such as midazolam are not used as much for anesthesia or induction of anesthesia but for conscious sedation (*Giovannitti and Trapp 1991*). Conscious sedation is a drug-induced state of relaxation where the patient remains conscious with reflexes intact and

little effect on cardiovascular or respiratory function (see ASA table in section 2E above). Midazolam is often used with an opioid analgesic in outpatient procedures such as colonoscopy and oral surgery.

Clinical studies examining the relationship of midazolam's BIS values to the level of sedation are considered first. BIS values of in the range of 77-92 were reported after repeated IV doses of midazolam in a surgical outpatient study (*Sandler 2000*). In surgery patients, the BIS threshold for responding to a verbal command after midazolam was 80, whereas patients did not respond to verbal command when a BIS score of 77 was observed (*Ibrahim et al. 2001*). In a clinical study using adult healthy volunteers, IV midazolam was infused until patients become unresponsive to mild prodding or shaking (*Lui et al. 1996*). Midazolam at total doses ranging from 4.5 to 20 mg IV decreased the BIS to a mean value of 69.

Clinical studies that show a ceiling effect of midazolam with regard to lowering the BIS values are described next. These studies noted that increasing doses of IV midazolam do not produce greater pharmacological effects in lowering the BIS values. One study noted that an IV midazolam dose of 0.3 mg/kg (25 mg for a typical 180 lb. adult) did not produce greater depression of the brain (as noted by the BIS value) than a dose of 0.2 mg/kg, or about 16 mg (*Miyake et al. 2010*). The authors note that a greater maximal effect was not seen in previous studies where IV midazolam showed a maximal dose of brain activity depression yielding a BIS value of 70, but not lower (*Ibrahim et al. 2002, Kuizenga et al. 2001*). These data suggest that a ceiling effect in humans occurs after an IV infusion dose of 25 mg.

The sedation that can be produced by midazolam, **and the lack of General Anesthesia at any dose**, is insufficient to render the prisoner insensate to the torturous effects of vecuronium bromide and potassium chloride. A prisoner sedated only with midazolam would be conscious of the suffocating effects of vecuronium bromide but, as a result of its paralytic properties, be unable to communicate his or her distress. The prisoner would also be subjected to the burning sensation of the 3rd drug, potassium chloride.

iii. Comparison between modeling and clinical studies

The dose of IV midazolam that produces a ceiling effect in clinical studies is lower (25 mg) than the theoretical ceiling-effect dose calculated above (228 mg). The difference in these results are not unexpected. The ceiling-effect dose of 25 mg comes from clinical studies examining midazolam's effects in patients. The calculated ceiling dose of 228 mg midazolam is mainly based on in vitro and preclinical studies. It is likely that that *in vitro* data using cell cultures are less sensitive to midazolam compared to the clinical effects of midazolam in patients.

Significantly, the ceiling effect of midazolam in the range of 25 to 228 mg IV means that increasing doses of midazolam do not produce increasing effects. The ceiling effect of midazolam is the reason why midazolam cannot produce the general anesthesia needed for a first drug in a three drug protocol.

D. Summary

The findings from this section are:

i. The ceiling effect of midazolam is a direct result of midazolam's mechanism of action. Pentobarbital and other barbiturates have a different mechanism of action and therefore do not exhibit a ceiling effect.

ii. Research done *in vitro* shows that the ceiling effect of midazolam occurs, under those conditions, at a concentration of 100 nM.

iii. An IV bolus dose of 500 mg midazolam produces a brain concentration that is 2 times higher than the concentration of midazolam that produces a ceiling effect at 5 minutes.

iv. An IV bolus dose of 228 mg midazolam is sufficient to reach the threshold of midazolam's ceiling effect at 5 minutes after administration. Amounts beyond that dose are not expected to produce a greater effect.

v. Clinical studies show that the ceiling effect of IV midazolam occur at infusion doses of about 25 mg. These studies show that greater midazolam doses do not produce greater depression of brain activity and cannot produce a state of General Anesthesia.

vi. Midazolam at a dose of 500 mg IV cannot be relied on to render someone sufficiently unconscious to block the noxious stimuli that will occur from the application of the remaining drugs in the protocol.

6. Pharmacological Considerations of Alternative One-Drug Protocols for Lethal Injections

Anesthetic Gases Produce General Anesthesia and Overdose Death

While IV anesthetics like thiopental, pentobarbital, or propofol are used to induce anesthesia, inhalational agents (gases) are generally used to maintain general anesthesia during surgical procedures (*Potyk 1998*). Halothane was the prototypical inhalational agent, but is no longer available in the U.S. due to a high incidence of hepatic toxicity with its use (*Rosenberg and Weaver 1991*). General anesthesia for most surgical operations is done using newer inhalational agents, like sevoflurane, desflurane, or isoflurane (*Ghatge et al. 2003*). Inhalational agents, like barbiturates, are potent activators of the $GABA_A$ receptor (*Franks and Lieb 1994*). Like barbiturates and unlike benzodiazepines, inhalational general anesthetics can produce their potent effects at the $GABA_A$ receptor with or without GABA present. Inhalational general anesthetics like sevoflurane, desflurane, and isoflurane also act on a number of other ion channels to shut down brain activity (*Franks 2006*).

Desflurane and isoflurane irritate the respiratory tract during induction of anesthesia, so they are used for maintaining general anesthesia once induction with another agent has occurred (*Rosenberg and Weaver 1991*). For that reason, only sevoflurane will be considered further in

this section. Sevoflurane is an ideal inhalational agent, as it can be also be used for induction of anesthesia and therefore substitute for an IV general anesthetic like thiopental, pentobarbital, or propofol (*Ghatke et al. 2003*). Sevoflurane is not pungent to the patient and produces a rapid onset of general anesthesia. A state of general anesthesia occurs within 2 minutes after administration of sevoflurane for induction and is quicker than after administration of isoflurane (*Ghatge et al. 2003, Sakai et al. 2005*).

As detailed in Section 5C above, a calculation based on the EEG activity (the BIS value) during administration of an anesthetic provides an objective measure of the level of sedation. A BIS value of 40-60 is considered to reflect the state of General Anesthesia (*Escallier et al. 2014*). Sevoflurane administration reliably produces a state of General Anesthesia and decreases BIS to values consistent with General Anesthesia or deeper, with BIS values as low as 10-20 (*Kreuer et al. 2008*). In a study of women undergoing C-section, sevoflurane decreased BIS to a mean value of 39 (*Zand et al. 2014*). For interventional radiology, BIS levels titrated to the range of 40-49 were needed to prevent movement of patients undergoing procedures with sevoflurane anesthesia (*Jung et al. 2015).*

Sevoflurane administration can lead to death by cardiac and respiratory depression, as shown by the forensic reports of cases involving sevoflurane overdose deaths (*Levine et al. 2007, Rosales et al. 2007*).

The procedures for administering an anesthetic gas requires less training than placement and delivery of a drug by IV. With sevoflurane, there is no need for IV access to induce anesthesia; sevoflurane is non-irritating and can be used directly for mask induction (*Sakai et al. 2005*). There is a cost for the equipment, and the anesthesia machine should include a waste gas scavenger system.[7] Because inhalational agents like sevoflurane are even more potent than barbiturates, they can be used in over-dosage as the sole lethal agent and would produce a rapid and painless death.

Equipment costs are relatively inexpensive, with used Anesthesia Machines, including sevoflurane and isoflurane vaporizers, available on Ebay and other medical-equipment-resale sites for around $2,000.[8] Newly manufactured machines may go for 3-5 times that cost depending on the model and features. Online training for personnel operating the Anesthesia Machines is available from manufacturers' websites.[9]

[7] Examples of various waste gas scavenger systems are given in the 2013 white paper entitled "Management of Waste Anesthetic Gases" from the American Association of Nurse Anesthetists (AANA) available at: www.aana.com/resources2/professionalpractice/Documents/PPM%20Management%20Waste%20Gas.pdf

[8] Ebay Anesthesia Machines at: *www.ebay.com/bhp/anesthesia-machine*

[9] For example, at http://static.draeger.com/trainer/apollo/apollo_trainer/start.html#id=A1100

The inhalant drugs sevoflurane, desflurane, and isoflurane are commercially available in FDA-approved forms. Sevoflurane is available from Abbvie Pharmaceuticals in North Chicago, IL; Piramal Critical in Bethlehem, PA; Baxter Health Corporation in Deerfield, IL; Halocarbon Products in Peachtree Corners, GA; and Shanghai Hengrui, in Shanghai, China. Desflurane (Suprane®) is sold by Baxter Health Corporation of Round Lake, IL. Isoflurane (Forane®) is also available from Baxter Health Corporation and four other manufacturers.

In summary, FDA-approved, fast-acting inhalant anesthetics are commercially available, and a massive overdose of such drugs would produce a rapid and painless death.

7. Overall Summary and Conclusions

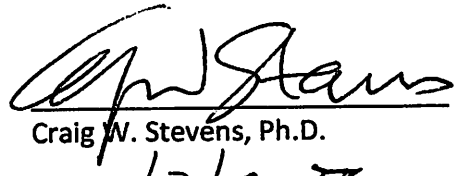
i. The State's decision to substitute midazolam for pentobarbital or thiopental as the first drug in the three-drug lethal injection protocol was made without sound medical or scientific reasoning or expert pharmacological advice. Pharmacological substitution is a legitimate method to provide equal pharmacological effects when one drug may no longer be available. For example, the muscle paralytic pancuronium, the second drug in the three-drug lethal injection protocol, can be substituted with the muscle paralytic vecuronium without violating pharmacological equivalency, as the two drugs are in the same drug class and have the same mechanism of action. Pancuronium and vecuronium have pharmacological equivalency.

However, it is not pharmacologically defensible to substitute barbiturates (like pentobarbital or thiopental) with the benzodiazepine midazolam, because no pharmacological equivalency exists. The final evidence of midazolam's non-equivalency with thiopental or pentobarbital is the fact that no state has attempted to use midazolam in a one-drug lethal injection protocol. If midazolam and pentobarbital (or thiopental) were pharmacologically equivalent, midazolam could be used as the sole agent in a one-drug lethal injection protocol using, as many states have done, using a single barbiturate drug, namely pentobarbital. **The lack of one-drug lethal injection protocols using midazolam by any State in the Union is a tacit admission that midazolam and pentobarbital (or thiopental) are not pharmacologically equivalent**.

ii. Because midazolam cannot induce General Anesthesia, a prisoner sedated with midazolam would consciously experience the suffocating effects of the vecuronium bromide and the burning pain of the potassium-chloride injection. The consciousness check specified by Arkansas's lethal injection protocol provides no protection; inasmuch as midazolam is pharmacologically incapable of providing adequate anesthesia, any determination that the prisoner is adequately anesthetized would necessarily be erroneous. As such, Arkansas's lethal injection protocol is sure or very likely to cause serious pain and suffering. Due to the paralytic effects of vecuroniun bromide, such serious pain and suffering would likely be invisible to observers of the execution procedure.

iii. A single-drug execution protocol would significantly reduce the risk of pain and suffering. FDA-approved, fast-acting inhalant anesthetics are commercially available and would produce a rapid and painless death.

I declare that I have examined this report and all statements contained herein, and to the best of my knowledge and belief, they are true, correct and complete. My opinions stated herein are based on high-level of scientific and medical certainty.



Craig W. Stevens, Ph.D.

1/3/2017

Date

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STATE OF OKLAHOMA)
) **SS**
COUNTY OF TULSA)

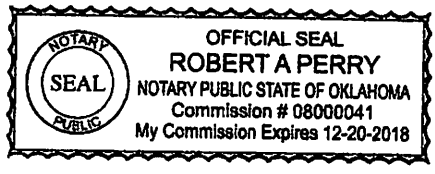
Now on this 3 day of January, 2017, Craig W. Stevens, a person whose identity was satisfactorily proven, appeared before me and, after first being placed under oath, did acknowledged his signature above to be his own voluntary act and deed, and affirmed that the facts contained herein were true.

Witness my hand and official seal

Robert A. Perry
Notary Official Signature

Robert A. Perry
Print Name

My Commission Expires 12/20/2018



No. 60CV-15-2921

IN THE CIRCUIT COURT OF PULASKI COUNTY, ARKANSAS
FIFTH DIVISION

STACEY JOHNSON, et al.

Plaintiffs,

v.

WENDY KELLEY, in her official capacity as
Director, Arkansas Department of Correction, and
ARKANSAS DEPARTMENT OF CORRECTION

Defendants.

AFFIDAVIT OF JONATHAN I. GRONER, M.D.

I, Jonathan I. Groner, M.D., do declare as follows:

1) I am a medical doctor and Professor of Clinical Surgery at The Ohio State University College of Medicine. I graduated from Northwestern University Medical School in 1984. I completed my residency in General Surgery at the Medical College of Wisconsin and in Pediatric Surgery at Nationwide Children's Hospital. I became licensed to practice medicine in the State of Ohio in 1992 and remain licensed to practice in Ohio. I was appointed to the faculty of The Ohio State University College of Medicine in 1994. I practice surgery and train medical students and residents in the practice of surgery. My

particular specialties include pediatric surgery, general surgery, and trauma surgery.

2) I hold a certification in General Surgery and Pediatric Surgery from the American Board of Surgery and have served as an Examiner for the American Board of Surgery's General Surgery Qualifying Examination. I also hold multiple certifications in advanced burn life support and in advanced trauma life support. I have served as the president of the Central Ohio Trauma Center and served on the Ohio Emergency Medical Services Board.

3) I have done extensive research in the areas of pediatric surgery, general surgery, and trauma surgery. My related research interests include the impact of trauma on minority children, firearm trauma, ATV injuries, child abuse, and physician participation in lethal injection. I have published multiple peer-reviewed articles on the administration of capital punishment by lethal injection. I am also the author of *The Hippocratic Paradox: the Role of the Medical Profession in Capital Punishment in the United States*, 35 FORDHAM URB. L.J. 883 (2008). In that article, I wrote that, assuming the shooters hit their mark (the heart), execution by firing squad would be "nearly instantaneous and painless." That is because the "[d]isruption of blood flow to the brain, which would result from lacerations to the heart by

multiple bullets, causes almost immediate loss of consciousness, resulting in rapid death with little or no pain."

4) Counsel for the Plaintiffs asked me to opine further upon the comments I made in the Fordham article. I hold all opinions expressed to a reasonable degree of medical certainty.

5) My analysis assumes the following execution procedure. This procedure is consistent with the procedure the State of Utah used in the 2010 execution of Ronnie Lee Gardner. I have reviewed the protocol Utah followed during that execution.

A. The inmate is placed in a chair and strapped into position so that he/she is not capable of moving. The chair and restraints allow maximum exposure of the chest (as the inmate sits in a straight, upright position).

B. A prison official examines the inmate and locates the position of the inmate's heart by physical exam (palpation of the chest for pulse) or the use of a stethoscope (point of loudest audible heartbeat).

C. The official pins a target to the inmate's clothing indicating the location of the inmate's heart.

D. Four to five law enforcement officers aim high-caliber, long-barreled weapons at the target at close range.

E. When the order is given, the officers fire their guns at the target on the inmate's chest.

6) This procedure will cause a nearly instantaneous death for the following reasons:

A. The location of the palpable heartbeat or the loudest audible heartbeat corresponds to the left ventricle, the largest pumping chamber of the heart. This is the chamber that pumps the blood out of the heart to the body.

B. A single bullet entering the left ventricle would tear a large hole in the left ventricle; multiple bullet holes would accelerate the process.

C. Blood that would normally flow out of the left ventricle into the aorta would immediately begin to flow out through the hole in the ventricle and fill the chest cavity with blood.

D. Cessation of blood flow in the aorta would cause immediate cessation of blood flow to the carotid arteries, which are the major blood supply to the brain.

E. Cessation of blood flow to the brain causes unconsciousness within seconds.

F. Death would follow soon after (3 to 4 minutes) from exsanguinating hemorrhage.

7) This swift death will also be painless. From my experience as a trauma surgeon, it is clear that patients with gunshot wounds to the heart with exsanguinating hemorrhage (loss of most of the blood volume) are unconscious and do not react to pain. In fact, the rescue maneuver for a person that has penetrating trauma to the heart who arrives at the emergency department with waning signs of life—in other words, someone who is bleeding to death from a hole in the heart—is to perform an "Emergency Department thoracotomy," meaning that the chest is cut open immediately in an attempt to repair the hole in the heart. This operation is done without anesthesia. It involves cutting through skin and muscle between the ribs on the left side under the nipple. The incision is usually at least 10-12 inches long. An instrument is used to spread the ribs apart allowing visualization of the heart and aorta. An attempt is made to repair the wound in the heart.

8) It is my opinion that Utah's execution of Ronnie Lee Gardner by firing squad caused a swift and painless death. The media reported that Mr. Gardner pushed his left arm forward "about 2 inches against the restraints," and "in that same motion, he closed his hand

and made a fist." *See* Nate Carlisle, *Firing Squad: An Eyewitness Account of Gardner's Execution*, Salt Lake Tribune, June 18, 2010, *available at* http://bit.ly/2eyfTND. This motion is consistent with reflex contractions following massive trauma to his left pectoralis muscle and ribs from the multiple high-velocity, large-caliber gunshot wounds. There was no report of verbal reaction, which is probably the most common manifestation of pain.

9) The current midazolam protocol has a far greater risk of causing pain and suffering compared to the firing squad. Midazolam is not a general anesthetic and, to my knowledge, is not used as a sole agent for any surgical procedure. The administration of drugs to cause respiratory arrest and cardiac arrest in an inmate medicated only with midazolam is far more likely to cause a painful death.

10) In sum, based on my medical expertise and my review of Utah's functioning firing-squad protocol, I reaffirm my earlier conclusion that execution by firing squad will cause rapid death with little to no pain.

JONATHAN I. GRONER, M.D.

11/29/2016

Date

State of Ohio)
)
County of Franklin)

Now, on this 29 day of November, 2016, Jonathan I. Groner, a person known to me (or whose identity was satisfactorily proven), appeared before me and, after first being placed under oath, did acknowledge his signature above to be his own voluntary act and deed, and affirmed that the facts contained herein are true.

Joyce A Blake
Notary Public
My commission expires:
8/23/2017

TMF 01/01.00 GENERAL PROVISIONS

TMF 01/01.01 Purpose of Technical Manual
TMF 01/01.02 Cross Reference
TMF 01/01.03 Policy
TMF 01/01.04 Definitions

TMF 01/01.00 GENERAL PROVISIONS

TMF 01/01.01 Purpose of Technical Manual

A. The purpose of this Technical Manual is to provide the Department's policies, procedures and post orders for planning and carrying out the sentence for the execution of a person convicted of a capital offense.

B. This chapter shall include policies and procedures related to:

1. planning and preparation;

2. execution of the sentence;

3. post-execution requirements and process;

4. security and control;

5. witnesses and official visitors

6. news media access limitations and briefing;

7. delays, stays, and commutations;

8. support services functions;

9. briefing and training; and

10. documentation, review and audit.

C. Post orders are included for the staff and others involved in the execution planning, implementation, documentation and review.

TMF 01/01.02 Cross Reference

A. Department Policies and Procedures Manuals

AGr05 Media Relations
FDr14 Inmate Property

B. Other Authority

UCA 77-19-6 Judgement of death-Warrant-Delivery of warrant-Determination of execution time.

UCA 77-19-10	Judgement of death-Location and procedures for execution.
UCA 77-19-11	Who may be present-Photographic and recording equipment.
UCA 77-19-12	Return upon death warrant.
UCA 26-4-6	Investigation of deaths by county attorney-Requests for autopsies.
UCA 26-4-7	Deaths over which medical examiner has jurisdiction.
BPPPM 3.12	Commutation Hearings for Death Penalty Cases

TMF 01/01.03 Policy

It is the policy of the Department that:

A. execution of persons sentenced to death under Utah law by a court of competent authority and jurisdiction be carried out in the legally prescribed manner;

B. the Department shall make every effort in the planning and preparation of the execution event to ensure that the execution process:

1. adheres to the intent of the law;

2. is handled in a manner which minimizes negative impact on the safety, security and operational integrity of the prison;

3. accommodates the need for public access to information concerning the event;

4. reasonably addresses the privacy interests of those persons for whom the law, Department policy or commonly-held principles of decency require such privacy;

5. provides sufficient staffing to ensure that unplanned problems can be accommodated and overcome;

6. prepares for stays of execution, commutations and other delays in the execution count-down;

7. provides an opportunity for interested persons to exercise their First

Amendment rights to demonstrate for or against capital punishment in a lawful manner;

8. ensures a firm and adequate response to unlawful civil disobedience, trespass, or other violations of the law by persons attempting to disrupt, prevent or other-wise frustrate the lawful process associated with the execution; and

9. anticipates and provides for sufficient support needs for the execution and the prison as a whole;

C. the Department shall arrest and encourage the prosecution of persons, including but not limited to, those who:

1. violate 77-19-11 UCA prohibitions against filming, taping, sketching, broadcasting or otherwise electronically documenting the death of the condemned;

2. trespass or otherwise enter upon prison property without proper permission and clearance from the Department;

3. participate in unlawful demonstrations;

4. unlawfully attempt to or disrupt, prevent or otherwise interfere with the execution;

5. being inmates, are involved in disruptive, assaultive or other proscribed behavior; or

6. unlawfully threaten, intimidate or terrorize persons involved in the execution process;

D. staff involved in the execution make every effort within the requirements and limits of these polices and procedures and the laws of the State of Utah to:

1. minimize the anxiety and negative impact of the execution on the victim's and inmate's family and friends witnessing the execution;

2. display appropriate levels of professionalism, restraint, and courtesy in interaction with witnesses, demonstrators, news media, and other non-staff persons during the execution process; and

3. not permit interactions, emotion or intimidation to prevent their proper handling of missions and duties;

E. the Department review the adequacy and/or the performance of:

1. the policies and procedures employed;

2. the Department staff members involved in the execution;

3. members of allied agencies assisting with the execution; and

4. statutes and other authority impacting the execution; and

F. the evaluation of each execution event be used to improve operational procedures for the future.

TMF 01/01.04 Definitions

allied agency	refers to another criminal justice agency
Attorney General's Office	staff at the Attorney General's Office or any designated contract attorney approved to carry out the responsibilities described in this technical manual
attorney of record	the condemned inmate's attorney and other assisting legal personnel

broadcast media	refers to radio and television media
civilians	any person not a member of the Department, allied law enforcement agency, nor mutual aid agencies
Command Post Director	the member who is assigned to supervise the command post functions and activities
commutation	the change from a greater to a lesser punishment after conviction
drug injection box	box or boxes each of which shall contain one complete set-up for lethal injection; with or without drugs
execution building	refers to the area containing the execution chamber
execution chamber	the immediate enclosed areas containing the condemned at the moment of execution

mutual aid	agencies or personnel that provide medical, fire suppression, and other support services to the Draper site
news magazines	magazines having a national circulation being sold by news stands to the general public and by mail circulation
news media	collectively refers to those involved with news gathering for newspapers, news magazines, radio, television or news services
news media members	persons over the age of eighteen who are primarily employed in the business of gathering or reporting news for newspapers, news magazines, national or international new services or radio or television stations licensed by the Federal Communications Commission
newspaper	for purposes of this chapter, the publication:

1. circulates among the general public;

2. publishes legal notices in the community in which it is located or the area to which it distributes; and

3. contains items of general interest to the public such as political, commercial, religious or social affairs

pardon	an act of grace by an appropriate authority exempting a person from punishment for a crime
press	refers to the print media; also see "news media", generally
reprieve	the temporary suspension of the execution
respite	see "reprieve"
security curtains	the curtains which cover the viewing room windows in the executionchamber
Warden	warden assigned to the Draper site
witness viewing	the areas from which the

area	execution is viewed by government witnesses, inmate's witnesses and news media witnesses

TMF 01/02.00	PRE-EXECUTION CHECKLIST
TMF 01/02.01	General Provisions
TMF 01/02.02	Prior to Receiving Death Warrant
TMF 01/02.03	Receipt of Death Warrant to Thirty Days Prior to Execution
TMF 01/02.04	Twenty-Nine to Fourteen Days Prior to the Execution
TMF 01/02.05	Thirteen to Seven Days Prior to Execution
TMF 01/02.06	Six to Three Days Prior to Execution
TMF 01/02.07	

TMF 01/02.00 PRE-EXECUTION CHECKLIST

TMF 01/02.01 General Provisions

A. Purpose of Chapter

1. The purpose of this chapter is to provide a checklist of procedures and events which should occur between the issuing of the death warrant and 24 hours prior to the execution.

2. Full detail will not be provided for each procedure or event in this chapter. For detail, reference will be made to Chapter TMF 01/05 and other chapters where such detail may be found.

3. This chapter will be divided to cover the following time periods:

   a. prior to the death warrant being issued;

   b. issuing of death warrant to 30 days prior to the execution;

   c. 14 to 29 days prior to the execution;

   d. 7 to 13 days prior to the execution;

   e. 3 to 6 days prior to the execution; and

   f.

B. Policy

1. It is the policy of the Department that the count-down to the execution be completed in a systematic manner to ensure that all procedures and events which are necessary in the preparation of the execution are completed in a timely manner.

2. This count-down, though offering flexible application, should be observed and followed as written unless deviation or adjustment is required for carrying out the execution.

3. The Executive Director/designee may direct deviation from or adjustment to the policies and procedures in this manual at any time when necessary for the good of the Department's mission in carrying out the execution. Approval for the changes shall be documented in writing.

TMF 01/02.02 Prior to Receiving Death Warrant

A. Execution Planning Team

When it appears an execution is imminent, prior to the issuing of the death warrant, the Warden shall select an Execution Planning Team. The Team mayinclude:

1.

2.

3.

4.

5.

6.

7.

8.

9.

10.

11.

B. Involve Additional Planning Assistance

Other persons who may be invited to attend on a meeting-by-meeting basis, include:

1. a representative or representatives from the Attorney General's Office;

2. a representative from the office of the County Attorney which prosecuted the condemned;

3. a representative from the Board of Pardons and Parole;

4. representatives from the law enforcement agencies which investigated the case involving the condemned;

5. representatives from law enforcement and other allied agencies who may be asked to assist with various aspects of the execution; and

6. any other persons deemed necessary or appropriate by the Executive Director/designee, DIO Director or Warden.

C. Develop Assignments

When it is reasonable to believe a death warrant will be issued in the near future, the Execution Planning Team and those additional persons deemed appropriate shall meet to:

1. review the Execution Plan (TMF 01);

2. make assignments for the pending execution;

3. develop a schedule of events;

4. assign responsibilities related to revision of the Execution Plan, if needed; and

5. take any other steps necessary to prepare for the issuance of the

deathwarrant and begin the execution count down.

D. Identify Possible Execution Dates

1. The Execution Planning Team shall review the Department's schedule of events and identify favorable and unfavorable dates within the period of time in which the execution may be ordered.

2. Information concerning the Department's requests/concerns related to scheduling shall be communicated to the Attorney General's Office to be communicated to the sentencing court.

TMF 01/02.03 Receipt of Death Warrant to Thirty Days Prior to Execution

Upon receipt of a death warrant from a competent court, the following procedures shall be initiated and should be completed at least 30 days prior to execution.

A. Receipt of Death Warrant

1. Upon receipt of the death warrant and as soon as practical thereafter, a meeting of the Execution Planning Team shall be scheduled by the Warden.

2. The Execution Planning Team shall then coordinate the implementation of the procedures set forth in this technical manual under the direction of the Warden.

B. Time and Place of Execution

1. Date

The date for the execution shall be that day set by the sentencing judge.

2. Time

"The Department of Corrections shall determine the hour, within the appointed day, at which the judgment is executed." 77-19-6(3)

3. Location

C. Condemned Inmate's Choice of Witnesses

1. The condemned inmate shall be informed that he may designate religious representatives, friends, or relatives not exceeding a total of five in number to witness the execution. 77-19-11 (2) (d)UCA

2. Refer to TMF 01/07.

D. Disposition of Personal Property

1. The inmate shall be contacted for instructions concerning the disposition of his personal property.

2. Refer to TMF 01/05.06.

E. Disposition of Funds in Inmate's Account

1. The condemned shall be contacted for instructions concerning the disposition of the funds in any accounts controlled or administered by the prison or Department.

2. Refer to TMF 01/05.06 and TMF 01/05.07.

F. Organ Donation

Organ donation is not an option for condemned inmates.

G. Disposition of Body

1. The condemned shall be asked for instructions concerning the disposition of his remains following the execution.

2. Refer to TMF 01/05.08.

H. Designate Persons Required to Assist with Execution

1. Those persons necessary to carry out the execution shall be identified.

   a. The Executive Director/designee, DIO Director or Warden shall be responsible for identifying, selecting and obtaining the services of the executioners. See TMF 01/05.03 and TMF 01/05.04.

   b. The Public Affairs Director shall be responsible for coordinating the notification of the news media and selection of individual news media witnesses. See TMF 01.08.02.

   c. The Warden shall be responsible for designating those persons necessary to carry out and support the execution.

2. Redundancy in assignment may be developed for all vital or important positions. The Warden, DIO Director, and Executive Director/designee shall determine which positions require back-up and shall ensure adequate coverage is provided.

3. "Compensation for members of a firing squad or persons administering intravenous injections shall be in an amount determined by the director of the Division of Finance." 77-19-10 (4)UCA

   a. The Department shall negotiate with the executioners and Division of Finance the fee to be paid to the executioners.

b.

c.

I. Other Approved Witnesses

The Executive Director/designee shall designate other approved witnesses as outlined in TMF 01/07.03.

J. Contact with State Medical Examiner

1. Contact shall be made withthe State Medical Examiner to coordinate the Medical Examiner's role.

2. The Medical Examiner shall be requested to provide direction concerning:

a. transfer of custody of the executed inmate from the Warden to the Medical Examiner;

b.

c.

3. Refer to TMF 01/04.

K. Support Services

1. The Support Services Deputy Warden coordinates the functions of Support Services Section Personnel.

2. Support Services units shall include, but not be limited to:

a. the Food Services Unit (See TMF 01/05.19); and

b. the Maintenance Unit (See TMF 01/05.18).

L. The Correctional Medical Administrator coordinates functions of the Medical Unit personnel. (See TMF 01/05.18)

M. Brief Prison Administrators

1. It is necessary to maintain as nearly as possible a normal prison operation during the execution and the activities preceding and following the execution.

2. Prison administrators should be briefed as appropriate on plans for the execution, restrictions on access, crowd control, additional security procedures, etc., on an on-going basis.

3. Briefings should begin as soon as plans begin to evolve which will effect the general prison operation, and should continue until the operation returns to normal.

TMF 01/02.04 Twenty-Nine to Fourteen Days Prior to the Execution

A. Witnesses

1. The Executive Director/designee shall develop a final list of witnesses consistent with the requirements of 77-19-11 (2) and (3) UCA.

2. Any changes to the Government witness list shall be approved by the Executive Director.

3. Each witness shall be required to sign an agreement prior to being cleared and added to the witness list.

4. The Executive Director may make additions to the witness list when necessary.

5. Refer to TMF 01/05.05.

B. News Media

1. Witness requests shall be received and processed by the Public Affairs Office in accordance with TMF 01/08.02.

2. Alternate coverage/accommodations for members of the press selected to be present at alternate site shall be handled consistent with TMF 01/08.03.

C. Inmate Property and Accounts

1. Finalize arrangements for disposition of the condemned inmate's property and accounts 14 days prior to execution.

2. Refer to TMF 01/05.06 and TMF 01/05.07.

D. Disposition of Body

1. Finalize, if possible, decision concerning disposition of the body.

2. Refer to TMF 01/05.08.

E. Selection of Executioners

1. Finalize the selection of executioners and their back-ups.

2. Refer to TMF 01/05.03 and TMF 01/05.04.

F. Medical/Medical Examiner

1. Finalize arrangements for a physician consistent with 77-19-10UCA.

2.

3. Refer to TMF 01/05.08.

G. Practices and Rehearsals

1. Initiate practice sessions for persons involved in the various parts of the execution event.

2. Not all of the persons involved will practice together. Individual teams will practice as units, with inter-team practices scheduled, as necessary.

TMF 01/02.05 Thirteen to Seven to Days Prior to Execution

A. Inmate Property/Accounts

All paperwork on disposition of property and accounts should be completed at least seven days prior to the execution.

B. Disposition of Body
All paperwork should be completed at least seven days prior to the execution.

C. Food Services

1. At least seven days prior to execution, contact the condemned inmate to arrange last meal. TMF 01/05.18.

2. Determine with the Warden, Draper Site Security Deputy Warden, and Public Affairs Director what beverage and food service will be needed at the various locations where staff will be working.

D. Purchase of Substances to Be Used in Lethal Injection

1. Purchase substances to be used in the execution.

2. Refer to TMF 01/05.11.

E. Support Services

Finalize all arrangements involving the Support Services assistance with the Support Services Director.

F. Finalize all arrangements involving the Medical Section assistance with the Correctional Medical Administrator.

G. Allied Agencies

Finalize arrangements with allied agencies assisting with the execution.

TMF 01/02.06 Six to Three Days Prior to Execution

A. Witnesses

1. All witness agreements should be signed.

a. Copies shall be provided to the:

(1) Command Post Director; and

(2) Auditor-in-Charge.

b. Persons refusing to sign agreements shall not be permitted to attend.

2. Exceptions to the time requirements will permit delayed signing of agreements for witnesses coming in from out-of-state.

B. Brief Allied Agencies

1. Members of allied agencies who have not participated in practice sessions or have not otherwise been briefed previously, shall be briefed and their post or responsibilities explained.

2. Briefings will include a detailed review of the individual's post order.

C. Inmate Property and Accounts

1. Complete all unfinished paperwork and arrangements.

2. If the condemned fails to cooperate in these arrangements, he shall be notified

that the property and money will be disposed of according to state law, and Department policy.

D. Executioners

The Warden shall:

1.

2. ensure completion of all arrangements necessary for security of executioners and protection of their identities.

E. Equipment Check/Inventory

1.

2. Refer to TMF 01/05.10(Firing Squad) and 01/10.09 (Lethal Injection).

TMF 01/02.07

A. Observation Period

1.

2.

3. Refer to TMF 01/05.12.

B. Meeting of Execution Planning Team

The Team shall meet to examine preparation for the execution. The checklists shall be reviewed and immediate assignments made to bring all items current with the schedule of events.

Refer to TMF 01/02 pre-execution checklist
Refer to TMF 01/03 execution checklist
Refer to TMF 01/04 post execution procedure

C. Review of Procedures

Conduct final review of procedures.

D. Arrangements for Pickup of Executioners

1.

2.

E. Food Services

1. Verify last meal preparation.

2. Verify beverage/food preparations for working teams.

F. Communications

1. Verify installation of and test communications equipment for:

a.

b.

c. Information Center.

2. Refer to TMF 01/05.10.

G. Contact Support Agencies

1. Contact:

a. the Attorney General's Office;

b. the State Medical Examiner's Office;

c. allied law enforcement agencies; and

d. the Governor's Office.

2. Verify that each agency fully understands its role and is prepared to complete tasks.

H. Equipment Check

1. Complete pre-execution inventory and equipment check.

2. All systems should be tested.

TMF 01/03.00 EXECUTION CHECKLIST

TMF 01/03.01 General Provisions
TMF 01/03.02
TMF 01/03.03
TMF 01/03.04
TMF 01/03.05
TMF 01/03.06

TMF 01/03.00 EXECUTION CHECKLIST

TMF 01/03.01 General Provisions

A. Purpose of Chapter

1. The purpose of this chapter is to provide a checklist of procedures and events which should occur

2. Full detail will not be provided for each procedure or event in this chapter. For detail, reference will be made to Chapter TMF 01/05 and other chapters where such detail may be found.

B. Policy

1. It is the policy of the Department that the count-down to the execution be completed in a systematic manner to ensure that all procedures and events which are necessary to carry out the execution are completed in a carefully coordinated manner.

2. The execution shall be carried out in a manner consistent with state law.

TMF 01/03.02

A.

1.

2.

3. Refer to TMF 01/05.12.

B.

1.

2. Refer to TMF 01/05.12.

C. Inmate Communication

1.

2.

3.

4. Refer to TMF 01/05.12.

D. Food Services

1. The Warden/designee shall contact the condemned to make arrangements for the final three meals.

2. The final meal shall be served.

3. Refer to TMF 01/05.18.

E.

1.

a.

b.

c.

d.

2. Refer to TMF 01/03.03 and TMF 01/05.08.

F. Equipment Check

1.

2. Refer to TMF 01/05.10 and TMF 01/05.11.

TMF 01/03.03

A. Final Briefing

1.

2. The final briefing shall be attended by the Executive Director/designee, DIO Director, Warden, special teams and other persons specified by the Executive Director or Warden. The Warden shall conduct the meeting, with the Executive Director/designee and DIO Director providing policy decisions, as needed.

3. During the briefing, participants shall:

a. identify problems, develop solutions and specify time lines and approve modified policy changes;

b. provide status reports;

c. coordinate support services involvement; and

d. conduct final review of count down procedures.

B. Food Services

1. The condemned shall be fed at specified times

2.

3. Refer to TMF 01/05.18

C. Visits

1.

2.

D. Restricting Access to Prison Property

1.

a.

b.

c.

d.

e.

2.

a.

b.

3.

E.

1.

2.

3.

4.

TMF 01/03.04

A.

1.

a.

b.

c.

2.

a.

b.

c.

3.

a.

b.

c.

4.

a.

b.

B.

1.

2.

TMF 01/03.05

A. Pre-Execution Procedures

1. The Warden shall ensure that all count-down procedures for all required activities and actions are completed.

2. Immediate action to complete any unfinished required procedures shall be initiated.

B. Execution Site Teams Assemble

1.

2. The Tie-Down Teams and their back-ups will be positioned to await escort of the condemned to the execution chamber.

C. Contact with the Attorney General's Office

1.

a.

b.

(2)

2.

3.

a.

b.

4.

A. Communications with Attorney General's Office

Refer to TMF 01/03.05,C, above.

B. Final Sequence of Events: Preparation

1. Bringing Condemned Inmate to Execution Chamber

The condemned inmate shall be:

a. removed from the observation cell by the Tie-Down Team;

b. dressed in a clean jump suit (the color of the jump suit will be at the discretion of the Warden);

c.

d. escorted to the execution chamber.

2. Tie-Down Procedures

the condemned shall be tied down as explained in TMF 01/05.13(lethal injection) or TMF 01/05.14(firing squad).

3. Prepare Condemned Inmate for Execution

The condemned shall be readied for execution:

a. if lethal injection, by completing the I.V. set-up procedure (See TMF 01/05.15); or

b. if firing squad, by completing the firing squad set-up procedures (See TMF 01/05.16).

4. Admit Witnesses

a. Witnesses shall be admitted and escorted to assigned viewing areas.

b. The government witnesses shall enter first and shall be escorted to the government witness area. The escort shall remain with the witnesses.

c. Following the government witnesses, the authorized witnesses invited by the condemned, and the victim's witnesses shall be admitted and escorted to the designated witness area.

(1) If any of the condemned inmate's invited witnesses, or the victim's witnesses wish to be on-site but not actually witness the execution, accommodations may be made for them.

(2) The escort officers shall remain with the condemned inmate's witnesses and the victim's witnesses.

d. The last witnesses to be admitted shall be the news media representatives.

(1) The members of the news media selected to witness the execution shall be escorted to the designated witness room. They shall be separate from the condemned inmate's witnesses and the victim's witnesses. Escort officers shall remain with the news media witnesses and ensure their separation from the other visitors while at the execution site.

(2) The two pool photographers shall be escorted to a designated site, away from, and out of sight of, the execution chamber. They shall

be secured inside the designated site until after the execution and until such time that they are allowed to film the cleaned up execution chamber.

C. Final Sequence of Events: Execution

1. Staff Witness

a. Staff participating in the preparation for the execution shall exit the execution site.

b. Staff members remaining to participate in and observe the execution shall include the:

(1) Executive Director/designee;

(2) Executive Director's back-up;

(3) DIO Director;

(4) Warden;

(5) Executioners;

(6) Escort Officers; and

(7) other staff as designated by the Executive Director/designee, DIO Director, or Warden.

2. Count-Down

a. At the designated hour mandated for the execution, when everything is ready, the phone communication shall be terminated and the Executive Director/designee shall instruct the Warden to proceed with the execution.

b. The Warden and DIO Director shall pull open the curtains covering the witness room windows.

c. The Warden shall ask the condemned inmate if he has any last words or wishes to make a statement.

(1) The statement should not exceed two minutes.

(2) If the inmate uses foul language, the Warden should immediately proceed with the next step in the execution procedure.

(3) If the statement exceeds two minutes, the execution shall proceed without waiting for the conclusion of his remarks.

(4) Audio recording equipment may be used by the Department for the purpose of recording the defendant's last words. The Department shall permanently destroy the recording made under this subsection not later than 24 hours after the completion of the execution.

d.

e. The Executive Director/designee shall instruct the executioners in the case of death by injection, or the firing squad leader in the case of a firing squad execution to proceed with the execution:

(1) upon receiving the Warden's signal to proceed;

(2) after verifying the earliest legal execution time has passed; and

(3) if no instruction to halt has been received from the Attorney General's Office.

f. Following the instruction from the Executive Director/designee to execute the condemned inmate, the executioners shall immediately proceed with the execution as required in TMF 01/05.15(if by lethal injection) or TMF 01/05.16(if by firing squad).

g. If the execution is ordered delayed

the Executive Director shall instruct the executioners to step away from the execution equipment and shall notify them that the execution has been stayed or delayed. The procedures set forth under TMF 01/06 shall then be initiated.

TMF 01/04.00 POST-EXECUTION PROCEDURES

TMF 01/04.01 General Provisions
TMF 01/04.02 Certification of Death
TMF 01/04.03 Removing Witnesses from Execution Chamber
TMF 01/04.04 Removal of Executed Inmate
TMF 01/04.05 Removing Executioners from the Execution Area
TMF 01/04.06 Site Clean-Up
TMF 01/04.07 News Media Re-Entry to Execution Site
TMF 01/04.08 Returning to Standard Operation
TMF 01/04.09 Audit of Execution
TMF 01/04.10 Post-Execution Countdown Schedule

TMF 01/04.00 POST-EXECUTION PROCEDURES

TMF 01/04.01 General Provisions

A. Purpose of Chapter

The purpose of this chapter is:

1. to provide the procedures to be followed following the death by execution of the condemned inmate;

2. to identify the responsibilities for tasks to be completed; and

3. to provide for the transfer of the body of the condemned from the custody of the Department.

B. Policy

It is the policy of the Department that:

1. the witnesses to the execution shall be removed from the execution chamber for the news media witnesses who shall be removed to a secondary location until permitted to return for a filming opportunity in the execution chamber;

2. the condemned inmate shall be examined by a licensed physician following the administering of the fatal drugs or the first volley by the firing squad to ensure that death has occurred;

3. the physician, when satisfied that death has occurred, shall certify the condemned inmate dead;

4. following the certification of death, the body of the condemned shall be surrendered to the State Medical Examiner;

5. after removal of the body, the chamber shall be restored and the news media permitted to return to photograph the chamber;

6. after the chamber has been photographed, the news media shall be returned to the designated area to brief the other assembled members of the news media;

7.

8. the entire execution process will be reviewed and evaluated by the AuditBureau to permit a post-execution examination of the competence, efficiency and effectiveness of the execution procedures and staff (see TMF 01/20).

TMF 01/04.02 Certification of Death

A. After the drugs have been administered/or the execution completed by firing squad:

1. the Warden shall wait a maximum of three minutes;

2. the Warden shall then tell the DIO Director/designee to summon the attending physician to the condemned; and

3. the physician shall take the condemned's vital signs.

B. If there are signs of life, the physician shall wait beside the condemned and check the vital signs every 60 seconds until vital signs cease.

C. If execution is by firing squad, and if after a maximum of ten minutes from the first volley, there are still signs of life, the physician will inform the Warden. The Warden will then initiate the steps in TMF 01/05.16.

D. When no vital signs are detected, the physician shall certify death in keeping with standard medical practices.

TMF 01/04.03 Removing Witnesses from Execution Chamber

2. The Medical Examiner, or his designee, may issue the death certificate for deaths that occur at the prison. (UCA 26-4-7, 26-4-10)

TMF 01/04.05 Removing Executioners from the Execution Area

A.

B.

C.

TMF 01/04.06 Site Clean-Up

A. The injection team shall (if execution was by lethal injection):

1. use universal precautions and protective equipment to protect for blood or other potentially infectious materials;

2.

3.

4.

5.

B. The Tie-Down Team shall be responsible for:

1. using universal precautions and protective equipment to protect against blood and other potentially infectious material; and

A. After the certification of death by the physician, the curtains shall be closed by the Warden and DIO Director/designee and the witnesses shall be escorted from the witness viewing rooms

1.

2.

3.

4.

5.

B. The news media shall be escorted to an alternate location in the execution building until they can be returned for the filming opportunity after the execution chamber has been cleaned up.

C. The condemned inmate's witnesses, government witnesses, and the victim's witnesses shall be escorted to waiting transportation vehicles

D.

TMF 01/04.04 Removal of Executed Inmate

A. After the witnesses have been removed:

1. if the execution is by lethal injection, the IV should be cut by the executioners in order for the catheters to remain in the executed inmate's body; and

2.

B. The State Medical Examiner/designee shall be escorted into the death chamber

1. The State Medical Examiner has jurisdiction over all deaths that occur at the Utah State Prison. (UCA 26-4-7)

2. cleaning up the execution site, using universal precautions where appropriate.

TMF 01/04.07 News Media Re-Entry to Execution Site

A. After the site is restored and cleaned, the news media witnesses and pool photographers shall be escorted to the execution site.

B. The photographers shall be permitted to tape/photograph the site and observation cell (if approved by the Warden) as required in TMF 01/08.

C.

TMF 01/04.08 Returning to Standard Operation

A.

1.

2.

B.

C.

TMF 01/04.09 Review of Execution

Refer to TMF 01/20.

TMF 01/04.10 Post-Execution Countdown Schedule

See Exhibit 04-1 for the proposed schedule for the post-execution period.
(Sample for Lethal Injection)

Execution

_____
Date

0005 DIRECTOR/DESIGNEE GIVES WARDEN OK TO BEGIN EXECUTION
0005 TO 0006 CURTAINS PULLED
0006 TO 0008 LAST STATEMENT BY CONDEMNED
0008 SIGNAL BY WARDEN TO BEGIN EXECUTION
0023 SIGNAL BY EXECUTIONER THAT DRUGS HAVE BEEN ADMINISTERED
0024 DOCTOR BROUGHT INTO EXECUTION CHAMBER
0027 DOCTOR PRONOUNCES DEATH AND DEATH WARRANT SIGNED
0028 CURTAINS CLOSED
0029
0030
0031
0034 TIE DOWN TEAM/MEDICAL EXAMINER INTO DEATH CHAMBER TO REMOVE BODY
0036
0037

0038 CLEAN UP CREW INTO DEATH CHAMBER
0039
0040

0040 WARDEN GIVES DIRECTIVE FOR MEDIA TO RETURN TO EXECUTION CHAMBER
0100 MEDIA RETURNED TO STAGING AREA

(Sample for Firing Squad)

Execution Time Line

_____
Date

0005 DIRECTOR/DESIGNEE GIVES WARDEN OK TO BEGIN EXECUTION
0005 TO 0006 CURTAINS PULLED
0006 TO 0008 LAST STATEMENT BY CONDEMNED
0008 SIGNAL BY DIRECTOR/DESIGNESS TO BEGIN EXECUTION
0011 DOCTOR BROUGHT INTO EXECUTION CHAMBER
0014 DOCTOR PRONOUNCES DEATH AND DEATH WARRANT SIGNED
0015 CURTAINS CLOSED
0017
0018
0019
0021 TIE DOWN TEAM/MEDICAL EXAMINER INTO DEATH CHAMBER TO REMOVE BODY
0023
0025

0026 CLEAN UP CREW INTO DEATH CHAMBER
0031 WARDEN GIVES DIRECTIVE FOR MEDIA TO RETURN TO EXECUTION CHAMBER
0050 MEDIA RETURNED TO STAGING AREA

TMF 01/05.00 EXECUTION PROCEDURES

TMF 01/05.00 EXECUTION PROCEDURES

TMF 01/05.01 General Provisions

A. Purpose of Chapter

1. This chapter provides the procedures which are used when the Department exercises its statutory responsibility to carry out an execution.

2. The topics include those procedures which are employed:

a. immediately prior to receiving the death warrant;

b. from receiving the death warrant to and during the execution;

c. immediately following the execution; and

d. during the debriefing and audit phases of the execution.

B. Policies

1. It is the policy of the Department that the procedures employed in preparing for and carrying out an execution be comprehensive and clearly defined.

2. The procedures shall be developed consistent with state and federal law.

TMF 01/05.02 Death Warrant

A. Judgement of Death

1. When judgment of death is rendered, a warrant signed by the judge and attested by the clerk under the seal of the court, shall be drawn and delivered to the sheriff of the county where the conviction is made. 77-19-6 UCA

2. The Sheriff shall deliver the warrant and a certified copy of the judgment to the UDC Executive Director/designee at

the time of delivering the defendant to the custody of the Department. 77-19-6 UCA

3. The warrant states the conviction and judgment, the method of execution, and the appointed day the judgement is to be executed. The Department of Corrections shall determine the hour, within the appointed day, at which the judgement is to be executed.

B. Return Upon Death Warrant

1. After the execution, the UDC Executive Director/designee shall make a return upon the death warrant showing the time, place and manner in which it was executed. 77-19-12 UCA

   a. The "Certificate of Execution":

      (1) shall be signed by the Warden and the physician; and

      (2) shall include the full names and official titles of the official witnesses.

   b. The "Certificate of Execution" shall be submitted for review to the Executive Director/designee.

   c. Following review by the Executive Director/designee, the "Certificate of Execution" shall be returned to the Warden.

2. The "Certificate of Execution" shall be directed by registered mail to the clerk of the court of the county from which the individual executed was sentenced.

3. A return receipt shall be requested from the recipient.

4. A copy of the certificate shall be placed in the deceased inmate's file.

A. Statutory Requirements

1. The Executive Director/designee shall ensure that the method of judgment of death specified in the warrant is carried out at a secure correctional facility operated by the department at an hour determined by the department on the date specified in the warrant. 77-19-10 (1) UCA

2. When the judgment of death is to be carried out by lethal intravenous injection, the executive director of the department or his designee shall select two or more persons trained in accordance with accepted medical practices to administer intravenous injections, who shall each administer a continuous intravenous injection, one of which shall be a lethal quantity of sodium thiopental or other equally or more effective substance sufficient to cause death. 77-19-10 (2) UCA

B. Selection of Execution Team

1. If the judgment of death is to be carried out by intravenous lethal injection, a minimum of two persons, each trained to administer intravenous injections shall be selected for the IV team.

2. Method of Selection

a. The DIO Director/designee and the Warden of the Utah State Prison, Draper site, shall be members of the execution team by virtue of their official position.

b. The Executive Director/designee, DIO Director/designee and the

Warden shall select a minimum of four (4) additional members, other than the DIO Director/designee and Warden, for the execution team.

1. Of the four (4) additional members, a minimum of two (2) execution team members will be on the IV team.

2. No member of the execution team, other than the DIO Director/designee and Warden, shall be required to serve as a member of the execution team without consent.

3. The Executive Director/designee, DIO Director/designee, and Warden will designate one execution team member as the execution team leader.

   a. The execution team leader shall not be the DIO Director/designee or the Warden; and

   b. The execution team leader shall not be a member of the IV team.

4. The Executive Director/designee, DIO Director/designee, and Warden shall review the qualifications of the IV team members according to requirements outlined in subsection (3)(a through d) and other relevant information as to appropriate training and skills in administering intravenous injections. One IV team member will be designated as the IV team leader.

c. Following the examination and evaluation of candidates, the Executive Director/designee, DIO Director/designee and Warden, shall

select the execution team members.

d. All execution team members shall read and understand the execution procedures. The Warden shall conduct a review of the execution procedures annually.

3. IV Team Qualifications

a. At least two (2) members of the execution team shall be designated as the IV team for an execution by lethal injection.

b. Each member of the IV team shall be a:

1. Phlebotomist;

2. Emergency Medical Technician;

3. Paramedic; or

4. Military Corpsman.

c. Each member of the IV team shall:

1. Have at least one (1) year of professional experience in his specialty;

2. Remain certified in his specialty or profession; and

3. Fulfill all continuing education requirements in his specialty or profession.

d. Prior to participating in an execution, the members of the IV team shall have participated in at least three (3) complete execution practices.

4. Securing Services

a. The Warden/designee shall contact those chosen for the execution team to notify them of their selection and verify their willingness and availability to perform the duties of execution by lethal injection.

1. If any person declines participation, the Executive Director/designee, DIO Director/designee and Warden will select a replacement according to the processes outlined in this section.

2. If all of the execution team members agree to participate, their individual roles as execution team members shall be explained to them.

b.

TMF 01/05.04 Selection of Executioners by Firing Squad

A. Statutory Requirements

1. "The Executive Director of Corrections/ designee shall ensure that the method of judgment of death specified in the warrant is carried out at a secure correctional facility operated by the Department of Corrections." 77-19-10(1) UCA

2. "If the judgment of death is to be carried out by firing squad, the Executive Director of Corrections or his designee shall select a five-person firing squad of peace officers."77-19-10 (3) UCA

B. Selection of Executioners

1. A five-person execution team, plus twoalternates and a team leader shall be chosen for the firing squad.

2. The alternate(s) shall be selected to replace any member(s) of the firing squad who are unable to discharge their required functions.

3. Persons selected for the firing squad shall be POST certified peace officers.

4. Selected peace officers will be required to demonstrate proficiency with weapons designated to carry out the execution.

   a. Under conditions substantially similar to those of the execution chamber, proficiency shall be exhibited by:

      1. Firing each weapon.

      2. At a minimum of 21 feet, accurately hitting the target of the same dimension as that which will be attached to the condemned.

   b. During the proficiency test, failure to accurately hit the specified target with one round from each weapon fired shall disqualify the officer.

5.

C. Method of Selection

1. The Executive Director/designee, DIO Director and Warden shall be responsible for the selection process.

2.

3. The final choice of firing squad members shall be the responsibility of the Executive Director/designee, DIO Director and Warden.

4. The Executive Director/designee, DIO Director/designee and Warden shall review the qualifications of the firing squad, including required proficiency as outlined in section (B4) and other relevant information.

D. Securing Services

1. The Executive Director and/orWarden shall contact those chosen for the firing squad, alternates and team leader to notify them of their selection and to verify their willingness and availability to perform the execution duties.

   a. If any person rescinds his original offer to participate, the selection team shall meet to select a replacement.

   b. If all of the selectees agree, their individual roles shall be explained to them.

2.

TMF 01/05.05 Designation of Persons Required, Permitted or Prohibited from Witnessing the Execution

A. The Utah Code limits and identifies those persons who may attend and witness the execution. (See TMF 01/07.03.)

B. The Warden shall designate the required personnel to carry out the statutory requirements of an execution. Staff should include:

1. Deputy Warden;

2. Observation Officers

3. Tie-down Officers,

4. one Team Foreman for the escort/Tie-Down Team;

5. executioners (reference TMF 01/05.03 & .04);

6. Clean-up Officers (number to be determined by the Warden/designee), assigned to clean up the execution chamber immediately following the execution;

7. Guide Officers (number to be determined by the Warden/designee);

8.

9.

C. The Warden/designee shall designate the appropriate resources necessary to carry out the requirements of an execution. The designated individuals shall be responsible for:

1. advising the Warden concerning any medical supplies, etc.;

2. the preparation and supervision of meals prepared during the observation period, and for the condemned inmate's last meal;

3. ordering, verifying, picking-up the drugs, equipment, etc., necessary to carry out an execution by lethal injection; and

4. pronouncing the death of the condemned inmate.

TMF 01/05.06 Disposition of Condemned Inmate's Property

A. Contact with Condemned Inmate

1. At least 30 days prior to the scheduled execution the condemned inmate should be contacted to discuss arrangements for disposing of his property.

2. At least 14 days prior to the execution property-disposition arrangements should be finalized.

3. At least seven days prior to the execution all paperwork required for final disposition should be completed.

4. If the condemned is uncooperative, doesn't wish to make specific property-disposition arrangements, or for any other reason has not made arrangements for disposition, he shall be notified the property will be disposed of as required under 64-13-15 (1) UCA.

B. Options for Disposing of Property

1. Property may be released to an authorized visitor (family, friend or attorney). The release would follow the normal property release procedures.

2. Property may be mailed through the U.S. Postal Service. The prison's Mail Unit shall process the mailing consistent with standard mail procedures. Indigent status does not cover property-release postage.

3. Property may be donated to a charitable organization.

4. If the condemned fails to designate a property-disposition option:

> "if property is not claimed within one year of death...it becomes property of the state and may be used for correctional purposes or donated to a charity within the state." 64-13-15 (1) UCA

C. Release Procedure

1. Following a decision to release the condemned's property, the property shall be:

   a. inventoried by staff; and

   b. transferred to the property room.

2. The release will then follow according to the appropriate release procedures. Refer to FDr14, "Inmate Property" and FDr03, "Inmate Mail."

TMF 01/05.07 Disposition of Money in Inmate Account

A. Contact with Condemned Inmate

Follow the time-table for contact with the condemned outlined for property under TMF 01/05.06.

B. Options for Disposing of Inmate Accounts

1. The condemned shall be required to complete a money transfer form releasing the money in his account to his next of kin or other person or organization of his choice.

2. If the condemned refuses or otherwise fails to complete the necessary forms, the funds shall be disposed of consistent with state law.

TMF 01/05.08 Disposition of the Body of the Condemned

A. Release to Medical Examiner

1. After the executed inmate is pronounced dead, the body shall be released from the restraints and removed from the execution chamber.

2. The body shall be immediately surrendered to the State Medical Examiner/designee.

TMF 01/05.09 Equipment Check/Inventory: Lethal Injection

A. Responsibility

1. The IV team shall conduct a check of equipment and materials necessary to conduct the execution.

2.

B. Inventory

1.

2.

3.

a.

b.

4.

C. Bloodborne Pathogen Precaution

1. As a precaution, all persons who may come in contact with the condemned's body fluids shall be issued rubber

gloves and bloodborne pathogen protection supplies and equipment.

TMF 01/05.10 Equipment Check/Inventory: Firing Squad

A. The Warden shall ensurean equipment check of appliances necessary to carry out an execution.

B.

1.

2.

3.

4.

5.

6.

7.

C. The execution team leader shall be responsible to arrange for:

1. .30-caliber rifles;

2. live rounds of ammunition;

3. blank rounds of ammunition;

4. practice sessions and dry fire;

5. ensuring equipment is clean and operable; and

6. back-up equipment for items 1, 2, 3, above.

D. prior to the execution:

1. the executioners shall be escorted into the execution chamber by the DIO Director/designee; and

2.

E. Bloodborne Pathogens Precaution

As a precaution, all persons who may come in contact with the condemned's body fluids shall be issued rubber gloves and bloodborne pathogen protection supplies and equipment.

TMF 01/05.11 Procurement, Storage and Accountability of Chemicals for Lethal Injection

A. Purchase

1. the Warden shall provide to the pharmacist for his official records a memorandum specifying:

a. The drugs which must be obtained;

b. A copy of the judgment of death; and

c. A copy of the state statute. 77-19-10(2) UCA

2. the pharmacist shall order the drugs from the vendor. Upon receiving the drugs, the pharmacist shall:

a.

b. Immediately notify the Warden that the drugs have been received;

c.

d.

e.

1.

2.

3.

4.

f.

3. Storage and Handling of Drugs

a.

b. See the next two pages for the Equipment and Materials Checklist.

Quantity	Item	Code
	Sodium Thiopental (Pentathal), 500 mgm., w/diluent	A
	Pancuronium Bromide (Paravulon), 50 mgm. Ampules	A
	Potassium Chloride, 240 miliequiv. Ampules	A
	Valium injection, 10 mgm	A
	Syringe, 60 cc Lur Lock	
	Syringe, 10 cc Lur Lock	
	Syringe, 5 cc Lur Lock	
	Needle, 18 Ga., 1 ½	
	Needle, 25 Ga., 1 ¼	
	Angiocath, 14 Ga., 2 ¼"	
	Angiocath, 18 Ga., 1 ¼"	
	Angiocath, 16 Ga., 1 ¼"	
	Normal saline, IV bad, 1000C	
	Lidocaine HCL, 2% w/Epinephrine	
	Lidocaine HCL, 2% w/o Epinephrine 2	
	Solution injection set, 70" long with	
	Y-injection site: Travenol Code: #2C0005S	
	Extension set, 35" long; Travenol Code #2C0066	
	Stethoscopes	
	Boxes of alcohol preps	
	Rolls of Kling	
	Adhesive tape, 1"	
	Adhesive tape, 2"	
	Scissors, bandage, Pr.	
	Tourniquet	
	Hemostat, sterile	
	Flashlight, w/batteries	A
	Batteries, flashlight, (spares)	A
	Ace wraps 3"	
	Needle holders	
	10 packs sterile gauze	
	Sharp containers	

	BIO-Hazardous trash bags	
	Extra large impervious gowns	
	IV hangars	
	Mayo stand	
	Terry cloth towels	
	Goose neck light	
	Blood spill kits	
	Trash containers	
	Electronic Heart Monitor (EKG)	

TMF 01/05.12 Observation Period and Related Activities

A. Access

1.

2.

3.

B. Preparation of the Observation Cell

1.

a.

b.

c.

2. Stocking the Cell

a. The observation cell shall be outfitted with the following items:

(1) mattress (1);

(2) pillow (1);

(3) pillow case (1);

(4) sheets (2);

(5) blankets (2);

(6) towel (1);

(7) soap, small (1);

(8) toilet paper, roll (1);

(9) jump suit (color to be determined by the Warden) (1);

(10) socks (1 pr.);

(11) shower thongs (1 pr.); and

(12) pocket comb, no metal (1).

b. If requested, the cell will also have the following items purchased new

(1) Bible (1);

(2) magazine

(3) newspaper
; and

(4) photographs
.

c. The following items may be given on request, as needed,

(1) toothbrush (1);

(2) toothpaste

(3)

d. If the condemned inmate receives mail the officer shall allow the condemned inmate adequate time to read the mail

f.

g. Additional property shall be approved by the warden.

3. Test Equipment

a.

b.

C.

1.

2.

3.

4.

5.

6.

a

b.

D. Securing Condemned Inmate's Property/Cell

1.

2.

3.

b.

(1)

(2)

(3)

(4)

c.

(1)

(2)

(3)

(4)

4. Personal property shall be separated from prison property, and the personal property put into a suitable container and sealed. Each search team member shall initial the seal.

5. The designated property officer shall sign for and assume responsibility for the inventoried property.

6.

a.

b.

7.

8. The personal property shall be taken to the DIO property room for storage.

E. Observation Function

1.

a.

b.

c.

d.

e.

f.

g.

2.

a.

b.

3.

4.

5.

F. Activities During the Observation Period

1.

2. Unless previously served, meal service, including the last meal, shall be served during the observation period.

3.

4.

a.

b.

c.

TMF 01/05.13 Tie-Down Procedures: Lethal Injection

A. Transfer of Condemned Inmate to Execution Site

1. The condemned inmate shall be escorted from the observation cell to the execution chamber by the Tie-Down Team.

2.

a.

b.

c.

d.

B. Positioning of Tie-down Team

1.

2.

3.

4.

5.

C. Securing Inmate to Gurney

1.

2.

a.

b.

c.

d.

e.

f.

g.

3.

4.

5. Upon completion of the execution and as directed by the Warden, the Tie-Down Team shall enter the execution chamber and remove the straps in the reverse order as outlined above.

TMF 01/05.14 Tie-Down Procedures: Firing Squad

A. Bringing Condemned Inmate to Execution Chamber

The condemned inmate should be escorted from the observation cell to the execution chamber by the Tie-Down Team

B. Positioning the Tie-Down Team

1.

2.

3.

4.

C. Securing the Inmate to the Chair

1.

2.

a.

b.

3.

4.

5. Upon completion of the execution and as directed by the Warden, the Tie-Down Team shall re-enter the execution chamber and remove the straps in reverse order as outlined above.

TMF 01/05.15 Lethal Injection Protocol

A.

1.

2.

B. Preparation of Syringes

1.

a.

b.

c.

2. The execution team leader shall providethe drug box to the IV team leader.

a. The IV team leader shall prepare each chemical in accordance with the manufacturer's instructions and draw them into the two (2) sets of syringes.

b. The second member of the IV team and the execution team leader shall observe preparation of the chemicals and verify that the instructions and procedures have been carried out correctly.

c.

3. The syringes containing the chemicals shall be prepared and loaded in the following order:

a. Two 60-cc syringes, each containing 240 milliequivalents of Potassium Chloride in 50-cc and label syringes "Syringe #3.

b. Two 60-cc syringes, each containing fifty (50) milligrams of Pancuronium Bromide in 50-cc and

label syringes "Syringe #2".

c. Two 60-cc syringes, each containing three (3) gm of Sodium Thiopental in 50-cc and label syringes "Syringe #1".

d. The secondary syringes containing each of the three chemicals are to serve the following purposes.

1. Secondary syringe of Sodium Thiopental is prepared in the event the condemned has not lost consciousness sixty (60) seconds after the first administration of the chemical.

2. Secondary syringes containing Potassium Chloride and Pancuronium Bromide are prepared in the event the condemned has not been pronounced dead after the first administration of the chemicals.

4. Any syringes that are loaded with lethal injection chemicals that are not used during the execution shall:

a. Be returned to the Warden by the execution team leader;

b. Be destroyed by the Warden,

5. Any unused chemicals that were not mixed in preparation of the lethal injection shall:

a. Be returned to the Warden by the IV team leader;

b. Be destroyed by the Warden,

C.

D.

E. The IV team leader:

1. Shall, along with the second IV team member, verify two (2) labeled sets of each of the three (3) chemicals are present, filled, and clearly labeled;

2. Provide the two (2) labeled sets of each of the three (3) chemicals contained in the drug box to the execution team leader who will verify, along with another execution team member, selected by the execution team leader, the appropriate number of syringes have been surrendered and are clearly labeled; and

3. Prepare the IV set-up.

F. IV Set-up Procedure by IV Team

1. The connector of Administration Set (McGaw V1417 or equivalent) shall be inserted into the bag of Normal Saline IV solution.

2. The Flo Trol clamp located above the "Y" site shall control the flow of solution.

3. A 35-inch Extension Set (Travenol 2C0066 or equivalent) shall be connected to the needle adapter of the Administration Set.

4. The set-up for administration into the back-up IV site may require additional Extension Sets due to the potential of additional distance.

5. All connections should then be taped to ensure they do not come apart during the procedure.

6. The tubing shall be cleared of air by removing the protector from the needle adapter and opening the Flo Trol clamp letting the tube fill with solution.

7. The Flo Trol clamp shall then be closed and the protective cap over the needle adapter replaced.

8. Steps 1 through 7 shall be repeated for the second set-up.

G. Injection Procedure by IV Team

1. The Warden shall order the condemned person escorted to the execution chamber and strapped to the gurney.

2. The IV team shall run the IV lines to the condemned person by the following:

   a. Site and insert one (1) primary IV line; and

   b. Site and insert one (1) back-up IV line.

3. The IV team members shall determine the location of the IV sites on the body of the condemned person.

4.

   a.

   b.

   c.

   d.

H. IV Placement Process by IV Team

1. The angiocath shall be inserted into the vein of the primary IV site.

2. To best ensure that a needle is inserted properly into a vein, the IV team members shall look for the presence of blood in the valve of the sited needle.

3. The inner needle is then withdrawn and the needle adapter is placed on the angiocath.

   a.

   b.

4. The flow of normal saline shall be started and administered at a slow rate to keep open.

5. Step 1 through 3 shall be repeated for the back-up IV site.

6. The Administration Sets shall be running at a slow rate of flow, to keep open and ready for the insertion of syringes containing the injection chemicals.

7. Both set-ups shall be observed by the IV team members to ensure they are both patent and functioning properly.

8. No further action is necessary at this time.

I. Lethal Injection Procedure

1. The execution team shall:

a. Securely connect the electrodes of the cardiac monitor to the condemned person; and

b. Ensure the equipment is functioning properly.

2. At the designated hour mandated for the execution, when everything is ready:

a. The DIO Director/designee and Warden shall pull open the curtains covering the witness room windows.

b. The Warden shall ask the condemned inmate if he has any last words or wishes to make a statement.

1. The statement should not exceed two minutes.

2. If the inmate uses foul language, the Warden should immediately proceed with the next step in the execution.

3. If the statement exceeds two minutes, the execution shall proceed without waiting for the conclusion of his remarks.

4. The Department, for the purpose of recording the condemned inmate's last words, may use audio recording equipment.

a. The Department shall permanently destroy the recording made under this subsection not later than 24 hours after the completion of the execution.

b. No form of duplication of the audio shall be permitted.

c. The Warden, witnessed by the DIO Director/designee, shall

destroy any audio recording.

c. At the conclusion of the remarks, or when the Warden determines it is time to proceed, a prearranged signal shall then be given by the Warden to the Executive Director/designee.

d. The Executive Director/designee shall order the execution team leader to begin the administration of the chemicals providing:

1. The earliest legal execution time has been verified and has passed; and

2. No instruction to halt has been received from the Attorney General's Office.

e. Following the instruction from the Executive Director/designee to execute the condemned inmate, the execution team leader shall immediately proceed with the execution.

f.

1.

2.

3.

3. Upon the Executive Director/designee's order to proceed, the execution team leader shall begin the following

sequence:

a. The flow of the normal saline into the arm shall be cut off using the Flo Trol clamp.

b. The clamp should be moved as close to the "Y" site as possible.

c. The 18 ga needle of Syringe #1 (three (3) gm of Sodium Thiopental) shall be inserted into the "Y" site and the injection shall commence.

1. A steady, even flow of the injection shall be maintained with only a minimum amount of force applied to the syringe plunger.

2. When the entire contents of the syringe have been injected, syringe #1 shall be removed from the "Y" site.

d. The Flo Trol clamp should then be opened fully and allowed to run for 15 seconds.

e. The Flo Trol clamps shall then be closed.

f. A period of sixty (60) seconds shall pass after the administration of the Sodium Thiopental and closure of the Flo Trol clamp.

1. After the passage of sixty (60) seconds:

a. If it appears to the Warden based on his visual inspection that the condemned person is not unconscious:

i. The Warden shall notify the Executive Director/designee;

ii. The Executive Director/designee

will order the execution team to switch to the back-up IV site;

iii. The Executive Director/designee shall order that the back-up IV site be used with a new flow of Sodium Thiopental (secondary syringe labeled Syringe #1); and

iv. The Executive Director/designee shall order the remaining sequence of chemicals to be injected through the back-up IV site.

2. If it appears to the Warden based on his visual inspection that the condemned person is unconscious after the first injection of Sodium Thiopental, the Warden shall notify the Executive Director/designee who will then order the execution team to continue to the next step in the sequence.

g. The 18 ga needle of Syringe #2 (fifty (50) milligrams of Pancuronium Bromide) shall be inserted into the "Y" site and the injection shall commence;

1. A steady, even flow of the injection shall be maintained with only the minimum amount of force applied to the syringe plunger.

2. When the entire contents of the syringe have been injected, Syringe #2 shall be

removed from the "Y" site.

h. After syringe #2 has been given, the Flo Trol clamp should be opened fully for 15 seconds.

i. The Flo Trol clamp shall then be closed.

j. The 18 ga needle of Syringe #3 (240 milliequivalents of Potassium Chloride) shall be inserted into the "Y" site and the injection shall commence;

1. A steady, even flow of the injection shall be maintained with only the minimum amount of force applied to the syringe plunger.

2. When the entire contents of the syringe have been injected, Syringe #3 shall be removed from the "Y" site.

k. The Flo Trol clamp shall then be opened fully and allowed to run for 15 seconds.

l. The Flo Trol clamp shall then be closed.

m. An execution team member designated by the execution team leader shall start a stopwatch once the lethal injections are complete.

n. The execution team leader shall:

1. Observe the heart monitor; and

2. Advise the attending physician electrical activity of the heart has ceased as indicated by a flat line on the heart monitor.

o. The Warden shall notify the Executive Director/designee if it appears an additional set of lethal chemicals needs to be administered

due to the following conditions:

1. Heart monitor does not indicate a flat line after ten (10) minutes; or

2. The attending physician is not able to declare the time of death after ten (10) minutes.

p. In the event death has not occurred;

1. The Executive Director/designee will order the process established in subsection (2)(f) of this section and subsequent sections to continue with the secondary set of syringes until death has occurred.

q. During the execution by lethal injection, the DIO Director/designee and Warden shall:

1. Watch the primary IV site for failure, leakage, the catheter coming out of a vein, or any other problem.

2. In the event that an IV fails, leaks, if the catheter comes out of the vein, or any other problem arises, the execution team shall be ordered to switch to the back-up IV.

3. In the event the execution team is ordered to switch to the back-up IV, the DIO Director/Warden shall watch the back-up IV site for failure, leakage, the catheter coming out of a vein, or any other problem.

J. Post Lethal Injection Steps

1. When the physician declares death, the Executive Director/designee, DIO

Director/designee and Warden shall be informed.

2. The DIO Director and Warden shall close the viewing room curtains.

3. The Executive Director/designee shall make appropriate contact with the Governor and Attorney General informing them of the completion of the execution.

K. Disposal of BIO-Hazardous Contaminated Items

1. The execution team leader shall place items that have been contaminated with blood or other potentially infectious materials (OPIM) that have the potential to puncture into a puncture proof container (sharps container).

2. The execution team leader shall place other types of blood or other potentially infectious materials in trash containers lined with a red BIO-Hazardous waste bag.

3. The Correctional Medical Administrator shall ensure that the contaminated waste is disposed of in the proper Dumpster.

TMF 01/05.16 Execution by Firing Squad

A.

B.

1. Refer to TMF 01/05.10.

2. The team leader shall load the weapons and prepare to issue them to the members of the firing squad.

3. Two rounds shall be loaded in each weapon.

4. Care shall be taken to preclude any knowledge by the members of the firing

squad of who is issued the weapon with two blank cartridges.

C. The Warden shall direct that an aiming point or target be placed over the condemned inmate's heart.

D. Upon completion of "C", above, the Warden shall direct the person who placed the target to exit the execution chamber.

E. After the target is in place and all witnesses are secured, the Warden shall direct that the viewing room curtains be opened.

F. After all preliminaries are completed, the Warden, at the conclusion of the condemned inmate's last words (which shall not exceed two minutes and cease at any point should the condemned use foul language), shall place the hood over the condemned's head.

(1) Audio recording equipment may be used by the Department for the purpose of recording the defendant's last words.

(2) The Department shall permanently destroy the recording made under this subsection not later than 24 hours after the completion of the execution.

(3) No form of duplication of the audio shall be permitted.

(4) The Warden, witnessed by the DIO Director/designee, shall destroy any audio recording.

G. The DIO Director/designee, Warden, and any other observers shall exit the execution chamber.

H. When the Warden enters the executioners' room and secures the door, if no stay or delay in the execution has been ordered, the Executive Director/designee shall immediately order the firing squad team leader to begin the cadence for the executioners to fire.

I. A designated execution team member shall start a stopwatch once the first volley has been fired.

J. If the condemned inmate appears to be unconscious, upon the order of the Executive Director, the Warden and DIO Director shall re-enter the execution chamber after the first volley.

1. The Warden shall wait a maximum of three minutes after the first volley and then call for the physician to check the vital signs of the condemned.

a. If there are signs of life, the physician shall wait beside the condemned and check the vital signs every 60 seconds.

b. When no vital signs are detected, the physician shall certify death in keeping with standard medical practices.

c. After death is certified, the Warden shall direct that the viewing room curtains be closed.

2. If, after a maximum of ten minutes from the first volley, the inmate is unconscious but alive, the Warden shall direct the physician to make a final check of the condemned's vital signs.

a. If on final check, vital signs are detected, the Warden shall order the physician to exit the execution chamber.

b. The Warden and DIO Director shall re-enter the executioner's room.

d. The Executive Director/designee shall order the firing squad team leader to make the weapons ready to fire.

e. The Executive Director/designee shall immediately order the firing squad team leader to begin the

cadence for the firing squad to fire a second volley.

f. After the firing of the second volley, the Warden and DIO Director shall re-enter the execution chamber and proceed with paragraph "J,1", above.

K. If, after the first volley is fired, the condemned is obviously conscious, the Executive Director/designee shall instruct the firing squad team leader to immediately prepare the weapons to fire again.

1. The firing squad team leader shall ready the weapons in a controlled and safe manner.

2. The firing squad team leader shall ensure the executioners do not see which weapon contains the blank cartridges.

3. When the weapons are ready, if the condemned is still obviously conscious, the Warden shall ensure no staff members are in the execution chamber.

4. Upon notice from the Warden that the execution chamber is clear, the Executive Director shall immediately order the firing squad team leader to begin the cadence for the executioners to fire a second volley.

5. After the second volley, continue with "J", above.

L. The Executive Director shall make notification of the condemned's death to the Governor and the Attorney General.

TMF 01/05.17 Pre-Execution Rehearsals and Practices

A. A minimum of three rehearsals and practices shall be conducted to carry out an execution in a timely fashion maintaining the necessary

security. Practice/rehearsal shall be provided for but will not be limited to:

1. briefing;

2. removing the condemned inmate from the observation cell;

3.

4. escort to execution chamber;

5. tie-down procedures completed;

6. approximate time for IV injection procedure (execution time approximate);

7. clearing and escorting witnesses to/from execution site;

8. security curtains opened and closed;

9. condemned inmate's body removed from execution table/chair;

10.

11. clean-up;

12. debriefing outlined;

13. firing of weapons; and

14. ensure sufficient precautions are taken to minimize the risk of bio-hazardous exposure.

B. Planning backward from the execution shall be used to develop realistic time lines for each function involved in the execution.

C.

1. Discrepancies, concerns or proposed modifications due to system problems

shall be immediately reported to the Warden.

2.

TMF 01/05.18 Support Services Functions

A. Food Services

1. Observation Period Meal Service

a.

b. The Food Services Director/designee shall confirm the condemned's choice of a last meal. The confirmation should be made 48-24 hours prior to the execution.

c.

d.

e. Alcoholic beverages shall not be served nor used for cooking.

2. Beverage and Food Service for Staff

a. Because of the length of time many persons will be required to remain on site without being able to leave, it may be necessary to serve food and beverages to those assigned to the execution.

b.

c. Food and beverage services may be provided to:

(1) the command post;

(2) the Information Center;

(3) the food preparation area of the building in which the execution will occur;

(4) to the Draper site Security Deputy Warden for delivery to perimeter posts; and

(5) other sites as needed.

d.

B. Medical Staff

1. Receipt of Death Warrant

Upon receipt of the death warrant the Correctional Medical Administrator shall:

a. review the medical procedures, post orders and equipment checklist and make recommendations in writing to the Warden concerning any back-up or duplication of any medical

paraphernalia that may be necessary to carry out an execution; and

b. shall confer with the Chief Physician and assign all execution-related tasks to be completed.

2. Thirteen to Seven Days

a. At least thirteen days prior to the execution the Warden shall provide to the pharmacist, for his official record, authorization to purchase drugs. Authorization shall be in the form of a memorandum including:

(1) the names of the drugs which shall be obtained;

(2) a copy of the judgement of death; and

(3) a copy of the state statute (77-19-10 (2) UCA).

b. At least seven days prior to the execution the pharmacist shall order the drugs from the vendor (refer to chapter TMF 01/05.11).

(1) If the state's prime vendor cannot deliver the drugs, the pharmacists shall make arrangements with other vendors or hospitals to obtain the drugs.

(2) If the drugs cannot be delivered to the prison by the primary vendor or their delivery service to the prison, the pharmacist shall notify the Correctional Medical Administrator.

(2) The Correctional Medical Administrator shall make arrangements with the Draper site Security Deputy Warden to have an officer accompany them

to the location where the other drugs may be obtained.

c.

3.

4.

5.

a.

b.

c.

6.

a.

(1) the sodium pentothal syringes shall be prepared by the pharmacist at the direction of the Warden when it appears the execution shall be carried out;

(2) a medical-response team shall be on standby to provide any medical attention which may be needed during the time of the scheduled execution;

(3) a USP emergency equipment kit and a back-up kit shall be made available at the execution site; and

(4) the Correctional Medical Administrator (CMA)/designee and a USP Medical staff with skills in intravenous injections, I.V. set-up, cut-down, etc., shall be available at the execution site to provide medical assistance in the execution chamber, if necessary.

b. Equipment and lethal drugs shall be gathered up by the CMA/designee following the execution.

(1) The CMA/designee shall be responsible for the disposal of the medical equipment used for lethal injection in accordance with TMF 01/05.15.

(2)

C. Maintenance Staff

1. Receipt of Death Warrant

a. Upon receipt of the death warrant the Deputy Warden Support Services shall:

(1) review the maintenance procedures and the equipment checklist and make recommendations in writing for changes, additional equipment, etc. as is viewed essential

and provide such recommendations to the Warden prior to the scheduled execution date; and

(2) confer with the Maintenance Director and assign all execution related tasks to be completed.

b. The Maintenance Director shall then prepare a task completion calendar which shall be presented to the Deputy Warden Support Services for approval, including:

(1) a review of the maintenance procedure and the equipment checklist;

(2) recommendations to the Warden in writing of changes, additional equipment, etc. as is viewed essential prior to the scheduled execution date;

(3) identification of strategies to ensure that all systems, equipment, and mechanisms associated with the execution facility are functional and are readily repairable given an unexpected malfunction;

(4) identification of emergency equipment, materials, and substances necessary to ensure that system, equipment, and/or mechanism malfunctions are expeditiously remedied;

(5) establishment of inspection checklist and time frames for:

(a) the facility designated for the execution;

(b) the observation cell; and

(c) emergency backup systems;

(6) ensuring that all maintenance service/repair trucks are in good operational condition and supplied with equipment, tools, and supplies necessary to correct all execution related emergencies; and

(7) identification of maintenance personnel necessary to address all execution day maintenance emergencies.

2.

The Maintenance Director shall:

a. complete a pre-inventory check of the necessary equipment; and

b. complete a written report to the Deputy Warden Support Services of equipment, etc. requiring repair, replacement or duplications, including recommendations to correct problems and time frame necessary to make necessary corrections.

3.

The Deputy Warden Support Services shall direct the Maintenance Director to:

a.

c. conduct an inspection of the following equipment:

(1) execution chamber;

(2) observation cell; and

(3) emergency back-up systems and equipment.

4.

a.

(1)

(2)

(3)

b. A pre-inventory check shall be completed to ensure equipment is operational and in proper working order.

5.

a.

(1)

(2)

(a)

(b)

(c)

(3) emergency back-up systems and equipment.

b. Emergency equipment shall be checked to ensure readiness for the execution.

6.

a. Complete the procedures as outlined in 5, above.

b.

c.

d.

(1)

(2)

(3)

(4)

(5)

(6)

TMF 01/07.00 WITNESSES

TMF 01/07.01 General Provisions
TMF 01/07.02 News Media Witnesses
TMF 01/07.03 Designation of Persons Required, Permitted or Prohibited from Witnessing
TMF 01/07.04 Witness Agreement

TMF 01/07.00 WITNESSES

TMF 01/07.01 General Provisions

A. Purpose of Chapter

The purpose of this chapter is to:

1. identify the types and number of witnesses permitted to attend the execution; and

2. to provide legal requirements concerning the witnessing of the execution.

B. Policy

It is the policy of the Department that:

1. procedures for selecting witnesses to the execution shall conform with 77-19-11 UCA;

2. witnesses shall enter into written agreements before being approved for attendance; and

3. witnesses shall be subject to search prior to being admitted.

TMF 01/07.02 News Media Witnesses

A. Members of the news media shall be permitted to witness the execution.

B. Selection shall be at the discretion of the Executive Director/designee.

C. Refer to TMF 01/08 for news media selection procedures.

TMF 01/07.03 Designation of Persons Required, Permitted or Prohibited from Witnessing

A. The Utah Code limits and identifies those persons who may attend and witness the execution.

1. The Executive Director of Corrections or his designee shall:

   a. cause a physician to attend the execution, 77-19-10 (5) UCA; and

   b. permit the attendance at the execution of members of the press and broadcast news media named by the Executive Director of the Department/or his designee, 77-19-11 (4) UCA.

2. At the discretion of the Executive Director of the Department of Corrections/designee, the following may attend the execution:

   a. the prosecuting attorney, or his designated deputy, of the county in which the defendant committed the offense for which he is being executed, 77-19-11 (2)(a) UCA;

   b. no more than two law enforcement officials from the county in which the defendant committed the offense for which he is being executed, 77-19-11 (2)(b) UCA;

   c. the Attorney General or his designee, 77-19-11 (2)(c) UCA;

   d. religious representatives, friends, or relatives designated by the defendant, not exceeding a total of five persons, 77-19-11 (2)(d) UCA; and

   e. unless approved by the Executive Director, no more than five close relatives of the deceased victim, as selected by the Executive Director, but giving priority in the order listed in TMF 01/01.04.

3. The persons enumerated in Subsection (2) may not be required to attend, nor may any of them attend as a matter of right, 77-19-11 (3) UCA.

4. The following persons may also attend the execution:

   a. staff as determined necessary for the execution by the Executive Director of the Department of Corrections/designee; and

   b. no more than three correctional officials from other states that are preparing for executions, but no more than two correctional officials may be from any one state, as designated by the Executive Director of the Department of Corrections or his designee, 77-19-11 (7)(a) UCA.

5. Other necessary staff designated by the Executive Director of the Department of Corrections/designee shall be permitted to the execution.

   a. The "necessary staff" shall include those persons identified in the post orders and procedures in TMF 01.

   b. "Necessary staff" shall not be limited to members of the Utah Department of Corrections but may include members of allied agencies assisting with the execution.

6. The Department is empowered and directed by 77-19-11 (8) UCA to adopt rules governing the attendance of persons at the execution.

7. No person under the age of 18 may attend the execution.

B. For those persons who shall carry out the execution or serve in support roles in the execution area, refer to TMF 01/05.05 B, C.

TMF 01/07.04 Witness Agreement

(See following page for Witness Agreement.)

Rules of Conduct for Witnesses Observing an Execution at the Utah State Prison

1. That you will not bring onto prison property anything constituting legal or illegal contraband under any applicable statute, rule, or policy including any firearm, dangerous weapon, implement of escape, explosive, spirituous of fermented liquor, medicine, poison, or any other item creating a threat to the safety, security, or management of the prison;

2. That you agree to submit to a reasonable search for contraband and other searches as considered necessary by the Department for entry to Department prison and staging area property;

3. That you conduct yourself in a lawful and orderly manner;

4. That you comply with all lawful directives of correctional personnel while on Department property;

5. That you will not bring to the execution site any photographic or recording equipment; and

6. That you understand that the Department of Corrections will not provide mental health services to witnesses.

7. That you understand the Department of Corrections is required to record/report the names of all witnesses in attendance as well as provide the information to media representatives.

I have read the above rules and agree to abide by them. I understand that my failure to comply with the rules will result in my immediate removal from Department of Corrections property and that I may be subject to criminal prosecution.

_____ _____

Signature of Witness Date

_____ _____

UDC Representative Date

TMF 01/08.00 NEWS MEDIA PROCEDURES

TMF 01/08.01 General Provisions
TMF 01/08.02 News Media Selection
TMF 01/08.03 Alternate Coverage/Accommodations
TMF 01/08.04 News Media Attendance at the Execution
TMF 01/08.05 Limitations on Coverage
TMF 01/08.06 News Media Briefing
TMF 01/08.07 News Media Support and Equipment
TMF 01/08.08 Media Representative Agreement

TMF 01/08.00 NEWS MEDIA PROCEDURES

TMF 01/08.01 General Provisions

A. Purpose of Chapter

The purpose of this chapter is:

1. to provide the policies, procedures and requirements for providing access to the execution and information relating to the execution to the news media;

2. to provide the procedure for:

   a. releasing background information;

   b. releasing information during the execution;

   c. coverage of the execution; and

3. to provide requirements for safeguarding the institution and protected information.

B. Policy

1. It shall be the policy of the Department to permit press access to the execution and information concerning the execution consistent with the requirements of the constitutions and laws of the United States and state of Utah.

2. The Department is generally required to provide no more access to the news media, to the inmates and facilities it supervises and controls than that available to the general public.

3. The Department and the Utah Code recognize the need for the public to be informed concerning executions conducted by the Department of Corrections.

   a. The Department will participate and cooperate with the news media to inform the public concerning the execution.

   b. Information should be provided in a timely manner.

4. If the condemned is willing, the Department may allow an opportunity forthe condemned to speak with the news media. If allowed, the interview may:

   a. include those members of the news media selected to witness the execution;

   b. include additional members of the news media authorized by the Department, but not including more than one reporter from the same agency; and

   c. be held at a time and location determined by the Department.

5. During exigent circumstances, communication may be temporarily suspended until the situation has been stabilized. Exigent circumstances shall include, but not be limited to:

   a. riots;

   b. hostage situations;

   c. fires or other disasters; or

   d. other inmate disorders.

6. Refer to Chapter AGr05,"Media Relations" for general news media access to information, inmates and facilities.

TMF 01/08.02 News Media Selection

A. Number in Attendance

The Department shall permit members of the press and broadcast news media to witness the execution.

B. Authority to Select

The Executive Director/designee shall be responsible for selecting the members of the

news media who will be permitted to witness the execution. 77-19-11(4) UCA

C. Selection Process

1. After the court sets a date for the execution of the death penalty, news directors or editors may submit a written list of news media witnesses (one per organization) and other news personnel needed at the execution, to the attention of the Executive Director at least 30 days prior to the execution. When administrative convenience or fairness to the news media dictates, the Department in its discretion may extend the request deadline.

2. Requests for consideration may be granted by the Executive Director/designee provided they contain the following:

   a. a statement setting forth facts showing that the requesting individual falls within the definition of "member of the press and broadcast news media" set forth in these regulations;

   b. an agreement to act as a pool representative as described in these regulations;

   c. an agreement that the media member will abide by all of the conditions, rules and regulations while in attendance at the execution; and

   d. agreement that they will conduct themselves consistent with existing press standards.

3. Upon receipt of a news director's or editor's request for permission for news media witnesses to attend the execution, the Executive Director/designee may take such steps as he deems necessary to verify the statements made in the request. After verifying the information in the requests, selection

of witnesses shall be made by the Executive Director/designee.

4. The Executive Director/designee shall identify the media members who have been selected to witness the execution. Media members shall be selected on a rotating basis from the following organizations:

   a. Salt Lake daily newspapers;

   b. television stations licensed and broadcasting daily in the State of Utah;

   c. one newspaper of general circulation in the county in which the crime occurred;

   d. one radio station licensed and broadcasting in the State of Utah; and

   e. the remainder from a pool of broadcast, print and wire services news media organizations operating in Utah.

5. In the event that the Executive Director is unable to name a news media witness from each of the above-described organizations, he shall name other qualifying media members to attend.

6. No news media witnesses other than those named to attend the execution as described in this chapter shall be permitted to witness the execution.

D. Pool Photographers

1. Two photographers shall be appointed as pool photographers to photograph/film the execution chamber following clean up.

2. The pool photographers may be selected from agencies other than those

represented among those witnessing the execution.

TMF 01/08.03 Alternate Coverage/Accommodations

A. Additional Media Selected

1. The Executive Director may designate additional members of the press and broadcast news media who request and receive permission to be allowed at a location designated by the Executive Director on prison property during the execution.

2. The additional media selected shall be from both the print and broadcast media.

B. Alternate Location

1. The alternate location shall be a press briefing area.

2. Media members must contact the Department's Public Affairs Director at least 14 days prior to the execution date to make any special arrangements for hook ups or other necessary arrangements. Any expense incurred shall be borne by the specific news media requiring special equipment or hook ups.

3. No special access nor briefings will be provided to members of the press who are not selected as witnesses nor selected for the alternate site.

4. The alternate site shall be made available to the selected members of the news media at 1700 hours the day prior to the scheduled execution date.

C. Briefing Media at the Alternate Site

1. The Public Affairs Director shall arrange for:

a. pre-execution briefings;

b. distribution of media briefing packages;

c. briefings throughout the execution event; and

d. post-execution briefings by the news media who witnessed the execution.

2. The news media witnesses to the execution shall be returned to the media briefing area to answer questions from media members at the alternate site.

TMF 01/08.04 News Media Attendance at the Execution

A. The Warden/designee shall permit the members of the press and broadcast news media, selected by the Executive Director/designee in accordance with these regulations, to witness the execution.

B. Each news media witness attending the execution shall be carefully searched prior to admittance to the execution chamber.

1.

a. Electronic or mechanical recording devices include, but are not limited to, still, moving picture or video cameras, tape recorders or similar devices, broadcasting devices, or artistic paraphernalia, such as notebooks, and drawing pencils or pens, etc.

b. Violation of this prohibition is a class B misdemeanor. 77-19-11(5)

c. Only a small notebook (no larger than 4" x 6") and a pen or pencil issued by the Department shall be permitted.

2. Only the selected members of the news media (witnesses and two pool photographers) shall be allowed to

attend the pre-execution briefing. The group will be escorted into a briefing room.

a.

b.

c.

3.

a.

b.

4. Persons requesting to witness the execution shall be required to sign a statement or release absolving the institution or any of its staff from any

legal recourse resulting from the exercise of search requirements or other provisions of the witness agreement.

C. The Warden/designee shall not exclude any news media witness duly selected in accordance with these regulations from attendance at the execution except as described in these regulations, nor may the Warden/designee cause a selected news media witness to be removed from the execution chamber unless the media member:

1. refuses to submit to a reasonable search as permitted in these regulations;

2. faints, becomes ill or requests to be allowed to leave during the execution;

3. causes a disturbance within the execution chamber; or

4. refuses or fails to abide by the conditions and regulations set forth by the Department.

D. The execution chamber shall be arranged so as to provide space for the attending news media witnesses and the space arranged shall have a view of the execution site, with the exception of:

1. a view of the members of the firing squad, if employed; or

2. if lethal injection is chosen, those directly administering the method of execution, who shall be concealed from the view of the media members so that their identities will remain unknown.

E. The selected news media witnesses shall be transported as a group to the execution location prior to the execution and shall be allowed to remain there throughout the proceeding.

F. The Department shall designate a representative or representatives to remain with the media members throughout the execution proceedings for the purpose of supervising and escorting.

G. News media witnesses shall be admitted to the execution area on the date set for the execution only after:

1. proof of identification have been presented to the Public Affairs Director/designee at the staging area;

2. receiving an orientation by the Public Affairs Director/designee; and

3. signing an agreement to abide by conditions required of news media witnesses to the execution.

H. After the execution has been completed and the site has been restored to an orderly condition, news media witnesses may be permitted to return to the execution chamber for purposes of filming, photographing and recording the site.

1. Re-entry to the site shall be permitted only after the site has been restored to an orderly condition, including:

a. removal of the body of the condemned;

b. evacuation of those involved in administering the execution; and

c. clean up of the execution chamber.

2. Restoring the site to an "orderly condition" prior to the filming opportunity shall not unnecessarily disturb the physical arrangements for the execution.

3. Media members permitted to return to the execution chamber for the filming and recording of the site shall include:

a. the news media witnesses who were selected to witness the execution;

b. one pool television camera man; and

c. one pool newsprint photographer.

4. The film/videotape shall not be used in any news or other broadcast until made available to all agencies participating in the pool. All agencies receiving the film/videotape will be permitted to usethem in news coverage and to retain the film/videotape for file footage.

I. News media representatives shall, after being returned from the execution to the staging area, act as pool representatives for other media representatives covering the event.

1. The pool representatives shall meet at the designated media center and provide an account of the execution and shall freely answer all questions put to them by other media members and shall not be permitted to report their coverage of the execution back to their respective news organizations until after the non-attending media members have had the benefit of the pool representatives' account of the execution.

a. News media members attending the post-execution briefing shall agree to remain in the briefing room and not leave nor communicate with persons outside the briefing room until the briefing is over.

b. The briefing shall end when the attending news media members are through asking questions or after 90 minutes, whichever comes first.

2.

TMF 01/08.05 Limitations on Coverage

A. The Warden, with the concurrence of the Executive Director, may alter these regulations to impose additional conditions, restrictions and limitations on media coverage of the execution when such requirements become necessary for the

preservation of prison security, personal safety or other legitimate interests which may be in jeopardy.

B. If extraordinary circumstances develop, the additional conditions and restrictions shallbe no more restrictive than required to meet the exigent circumstances.

TMF 01/08.06 News Media Briefing

A. Pre-Execution Briefing Packets

1. The Public Affairs Director shall prepare a press briefing packet for reporters approved to witness the execution, or to cover the execution from the news media staging area.

2. The briefing press packet should be provided to news media representatives as they arrive at the staging area.

3. The contents of the press briefing packet shall include, but not be limited to, biographical information on the condemned, the list of official witnesses, pool reporters, family witnesses, execution procedures, sequence of events, and the history of executions in Utah.

4. Updates will generally be communicated and/or distributed to the press on an hourly basis beginning about 1700 hours the day preceding the execution. Briefing updates should include:

a. a summary of activities related to the execution procedures and sequence of events; and

b. a summary of the condemned inmate's activities during his final 24 hours.

B. Death Announcement

1. The Public Affairs Representative/designee shall read a prepared statement to the press, prior to the post-execution press conference, announcing that the execution has been completed.

2. The announcement shall include, but not be limited to:

a. the time of the execution;

b. the time the condemned was pronounced dead; and

c. the condemned's final words.

C. Post-Execution Conference

1. The post-execution conference shall begin immediately following the arrival of the pool reporters from the execution site.

2. The Public Affairs Director shall introduce the members of the press who witnessed the execution and facilitate the post-execution conference.

3. The Executive Director, Deputy Director, Institutional Operations Division Director and/or Warden may appear and answer questions at the press conference.

4. The post-execution conference shall continue for ninety minutes or until the questioning of the reporters who witnessed the execution has been completed; whichever comes first.

D. Travel Routes

1.

2.

E. Media Center

1. The Media Center shall be located in the designated staging area.

2. The Public Affairs Director shall assume responsibility for routine press briefings at the Media Center.

3. Press briefings and the post-execution conference will be held at the Media Center.

4. News media personnel may not access nor occupy any other part of the staging area. The media shall have access only to the designated media center.

5. Members of the news media may not seek, speak to or interview any official visitor while at the staging area.

6.

TMF 01/08.07 News Media Support and Equipment

A. Telephones

1. The Public Affairs Director shall coordinate all telephone needs with the Deputy Warden Support Services at the Utah State Prison.

2. Each news agency requiring dedicated telephone lines, shall submit in writing its telephone needs to the Public Affairs Director 14 days prior to the scheduled execution. Agencies requesting dedicated phone lines will be responsible for the cost of those lines.

3. The Department shall install a reasonable number of telephones, for local use and collect calls only, for news media use at the Media Center. If the Department is unable to install collect-call only telephones, personal cellular phones may be used.

B. Electrical Outlets

Each news agency must communicate its needs for electrical power to the Public Affairs Director 14 days prior to the scheduled execution.

C. Refreshments

The Public Affairs Director may inquire about having a private caterer at the staging area for the media to purchase items.

D. News Media Support Vehicles

1.

2.

TMF 01/08.08 Media Representative Agreement

(See following page for Media Representative agreement.)

Rules of Conduct for Media Representatives Observing an Execution at the Utah State Prison

1. That you will not bring onto prison property anything constituting legal or illegal contraband under any applicable statute, rule, or policy including any firearm, dangerous weapon, implement of escape, explosive, spirituous of fermented liquor, medicine, poison, or any other item creating a threat to the safety, security, or management of the prison;

2. That you agree to submit to a reasonable search for contraband and other searches as considered necessary by the Department for entry to Department prison and staging area property;

3. That you conduct yourself in a lawful and orderly manner;

4. That you comply with all lawful directives of correctional personnel while on Department property;

5. That you will not bring to the execution site any photographic or recording equipment;

6. That you understand that the Department of Corrections will not provide mental health services to witnesses; and

7. That you understand the Department of Corrections is required torecord/report the names of all witnesses in attendance as well as provide the information to media representatives.

I have read the above rules and agree to abide by them. I understand that my failure to comply with the rules will result in my immediate removal from Department of Corrections property and that I may be subject to criminal prosecution.

News Organization_____

_____ _____
Signature of News Media Witness Date

_____ _____
News Agency Editor/Producer Date

TMF 01/20.00 REVIEWAND DOCUMENTATION

TMF 01/20.01 General Provisions
TMF 01/20.02 Review Assignment
TMF 01/20.03 Documentation of Execution
TMF 01/20.04 Retention and Safeguarding Documentation
TMF 01/20.05 UDC Employee Questionnaire

TMF 01/20.00 REVIEW AND DOCUMENTATION

TMF 01/20.01 General Provisions

A. Purpose of Chapter

The purpose of this chapter is to provide the policies, procedures and requirements for reviewingthe execution process.

B. Policy

1. It shall be the policy of the Department that of the execution process shall be performed as ordered by the Executive Director.

2. Auditors assigned to perform thesereviewsshall beallowed access to designated aspects of the executionpreparation.

3. Auditors participating in the reviewof the execution are not to be involved in the execution preparationprocess, but shall act as observers only and, at all times, act in such a way that they create the least disruption possible in that process.

5. Appropriate documentation of the execution shall be created, collected, safeguarded, and retained to provide an adequate review trail and a proper historical record.

6. Documentation shall be protected in accordance with 64-13-25(2) UCA.

TMF 01/20.02 ReviewAssignment

Authority to Conduct a Review

1. The Executive Director shall be responsible for determining if a reviewis to take place in each execution.

2. The Auditor(s) selected for the execution review shall, upon direction

from the Executive Director, prepare a questionnaire to be completed by staff involved in the execution process. The survey shall be approved by the Executive Director and all responses shall be confidential. Only the Executive Director may grant release of the survey responses.

TMF 01/20.03 Documentation of Execution

Documentation to be Retained

Documentation which shall be retained shall include:

1. the warrant and all other legal papers;

2. correspondence, both official and unofficial, which is received by the Department of Corrections;

3. minutes of meetings held for purposes of planning or disseminating information;

4. inter-agency written communication;

5. intra-departmental written communication;

6. logs, journals, chronological notes, etc., of key locations; and

7. a newspaper file.

TMF 01/20.04 Retention and Safeguarding Documentation

A. Execution File

1. An execution file shall be established for each condemned person. The file shall be organized into sections which should include:

a. legal documents;

b. official correspondence;

c. unofficial correspondence;

d. intra-departmental written communication;

e. chronological notes, logs, etc.; and

f. meeting minutes.

2. Each section of the execution file shall have material filed in chronological order.

3. All working documents which cannot be filed during the execution process or immediately after, shall be copied and a copy shall be placed in the execution file.

4. All intra-departmental communication shall have a courtesy copy to the execution file.

B. Execution File Maintenance

1.

2.

C. Access to Execution File

Only those individuals authorized by the Executive Director of Corrections, DIO Director, or Warden, shall have access to the execution file.

D. Long-Term Storage

To ensure that all documents concerning an execution shall be retained to provide a reviewtrail and an adequate historical record, the execution file shall be stored in accordance with the archive's plan of the Department.

TMF 01/20.05 UDC EMPLOYEE QUESTIONNAIRE

_____
Name of the Condemned

INSTRUCTIONS:

Please complete this questionnaire as soon after the execution as possible. Answer each question completely and accurately. Add as many pages as necessary if answers need more space.

Complete and return this questionnaire to the AuditBureau at Utah Department of Corrections, 14717 S. Minuteman Drive, Draper, 84020, by _____.

Thank you.

FULL NAME:_____

TITLE:_____

LOCATION:_____

FUNCTION DURING THE EXECUTION:_____

1. Were you provided adequate direction for your area of responsibility?

   If you answered "No," please explain what direction would havebeen beneficial to you.

   _____
   _____
   _____

2. Were you adequately trained or briefed in your area of responsibility?

   Yes___No___

   If you answered "No," please explain what training or briefing would have been beneficial to you.

   _____
   _____
   _____
   _____

3. Did you observe anything that you thought was not adequately addressed?

   Yes___No__

   If you answered "Yes," please explain.

   _____
   _____
   _____
   _____
   _____

4. Please make any additional comments or suggestions.

THANK YOU!

TMF 01/21.00 TRAINING AND BRIEFING

TMF 01/21.01 General Provisions
TMF 01/21.02 Training and Briefing Components

TMF 01/21.00 TRAINING AND BRIEFING

TMF 01/21.01 General Provisions

A. Purpose of Chapter

The purpose of this chapter is to provide the policy and procedure concerning briefing and training of staff, members of allied agencies and others involved in an execution.

B. Policy

It is the policy of the Department that staff and others involved in carrying out an execution:

1. receive comprehensive briefings covering:

   a. their duties and responsibilities;

   b. the specifics of post orders covering assigned positions;

   c. communication and chain of command;

   d. overview of functions and activities during the execution;

2. are provided copies of post orders outlining the duties and responsibilities of assigned positions;

3. receive the level of briefing and training necessary based on the requirements of assigned duties;

4. rehearse and practice functions which involve:

   a. difficult timing;

   b. a high degree of skill;

   c. procedures of a highly critical nature; and/or

   d. moderately difficult or complex interaction with others; and

5. receive instructions concerning back-up systems to provide:

   a. problem-resolution assistance;

   b. policy decisions;

   c. crisis management assistance; and

   d. information requests.

TMF 01/21.02 Training and Briefing Components

A. General

Training and briefing shall include, but not be limited to:

1. issuing all members or other participants a post order for their assigned positions;

2. providing an orientation or briefing covering assigned duties and general operational information;

3. if necessary, detailed training covering legal, operational or technical aspects of assigned position;

4. if necessary, rehearsal of job functions; and

5. key positions in Manual TMF 01.

B. Post Orders

1. Each member or other participant shall be issued the post order or instructions for his assigned position.

2. The post order shall include, but not be limited to:

   a. the position title;

   b. location(s) of assignment;

   c. title of supervisor;

d. supervisory role, if any;

e. duties and responsibilities--general and specific; and

f. emergency role.

3. When appropriate, one or more chapters of TMF 01 may be issued with a post order.

4. All post orders (and any accompanying manual material) shall be returned at the completion of the execution event.

C. Briefing/Orientation

1. Most assignments will be very specialized, involving a narrow range of duties. For such positions, briefing/orientation sessions will be all the training required in addition to the general training skills and experience of the persons assigned.

2. Orientation sessions shall include but not be limited to:

a. an overview of the execution process and operational components;

b. location of assigned post;

c. chain of command and organizational information;

d. an overview of the countdown of activities and procedures leading to the execution;

e. an explanation of support and crisis intervention systems;

f. interaction with the news media;

g. a review of the specific post order requirements, duties and other elements; and

h. a question-and-answer period.

D. Training/Rehearsal

1. For assignments requiring more technical or complex functions, critical timing or interaction elements, or duties of a particularly difficult nature, more comprehensive training shall be required.

2. Team leaders shall be responsible for training and scheduling rehearsals as needed for team members.

AFFIDAVIT OF JOSEPH CUMMINGS, III

I, Joseph Cummings, III, do declare as follows:

1. I am currently employed as an Investigator with the Eastern District Federal Public Defender Office of Arkansas. I was assigned to complete a work request pertaining to the Lethal Injection Litigation that is currently being litigated by our office. One of the work requests I received requested that I contact various pharmaceutical companies to obtain information about the products sevoflurane and isoflurane. First, was to verify if sevoflurane and/or isoflurane are available for purchase to Department of Correction Agencies. Second, to establish whether the company has any objections to the use of their products by Department of Correction Agencies for use in executions; and if the company has any provisions set forth in their distribution contracts to prevent their products from being obtained by Department of Correction Agencies for use in executions.

2. On July 18, 2016, I contacted Piramal Healthcare. Piramal Healthcare is located at 3950 Schelden Circle in Bethlehem, Pennsylvania. I spoke to Ester Kessler by telephone to discuss the issues stated above. Ms. Kessler is a Sales Representative for Piramal Healthcare. Ms. Kessler stated if the Arkansas Department of Correction was a member of the Federal Supply Schedule or Managed Healthcare Associates, the Arkansas Department of Correction would have access to their products, isoflurane and sevoflurane, through multiple wholesale companies at a discounted price for purchase. Ms. Kessler stated the products, isoflurane and sevoflurane, would be available for direct purchase from the manufacturer if the Arkansas

Department of Correction was not a member of the Federal Supply Schedule or Managed Healthcare Associates.

3. I declare under penalty of perjury under the laws of the United States of America that the above information is true and correct to the best of my knowledge.

FURTHER AFFIANT SAYETH NOT.

Joseph I. Cummings, III
Capital Habeas Unit Investigator
Federal Public Defender Office-Eastern District

ACKNOWLEDGMENT

STATE OF ARKANSAS)
)
COUNTY OF PULASKI)

Subscribed and sworn to before me, a Notary Public, on this 20th day of July, 2016.

Notary Public

My Commission Expires:

CYNTHIA L. WESTLAKE
PULASKI COUNTY
NOTARY PUBLIC - ARKANSAS
My Commission Expires May 31, 2017
Commission No. 12361103

Nitrogen Induced Hypoxia as a Form of Capital Punishment

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East Central University

Executive Summary

At the request of Oklahoma State Representative Mike Christian, the authors of this study researched the question of whether hypoxia induced by nitrogen gas inhalation could serve as a viable alternative to the current methods of capital punishment authorized under Oklahoma law. As per the above, this study does not express an opinion on the wider question of whether Oklahoma should continue to administer capital punishment in general. The scope of this study is limited to the assumption that capital punishment will continue to be administered in Oklahoma, and given that assumption, analyzing whether hypoxia via nitrogen gas inhalation would be an effective and humane alternative to the current methods of capital punishment practiced in Oklahoma law.

This study was conducted by reviewing the scientific, technical, and safety literature related to nitrogen inhalation.

The study found that:

1. An execution protocol that induced hypoxia via nitrogen inhalation would be a humane method to carry out a death sentence.
2. Death sentence protocols carried out using nitrogen inhalation would not require the assistance of licensed medical professionals.
3. Death sentences carried out by nitrogen inhalation would be simple to administer.
4. Nitrogen is readily available for purchase and sourcing would not pose a difficulty.
5. Death sentences carried out by nitrogen inhalation would not depend upon the cooperation of the offender being executed.

Accordingly, it is the recommendation of this study that hypoxia induced by the inhalation of nitrogen be offered as an alternative method of administering capital punishment in the State of Oklahoma.

The views expressed in this study are solely those of its authors and do not necessarily reflect those of the university at which we are affiliated.

Introduction

Nitrogen is an inert gas that at room temperature is colorless, odorless, and tasteless. It is the most common gas in the earth's atmosphere, comprising 78.09% of the air that humans breathe on a regular basis.

When combined with the normal 20.95% oxygen found in the atmosphere, nitrogen is completely safe for humans to inhale. However, an environment overly enriched in nitrogen will lack the appropriate level of oxygen necessary for human survival and will thus lead to hypoxia and rapid death. (U.S. Chemical Safety and Hazard Investigation Board, 2003, p.1).

Nitrogen hypoxia has been suggested as a means of administering capital punishment in the popular media on previous occasions. For example, in1995 the National Review featured an article by Stuart Creque titled *Killing With Kindness: Capital Punishment by Nitrogen Asphyxiation (1995).* Creque's article was written in response to a 9th Circuit U.S. District Court decision that California's gas chamber was an unconstitutionally cruel and unusual punishment. The article suggested nitrogen could provide a simple and painless alternative to the gas chamber that would require no elaborate medical procedures to administer.

The idea of administering capital punishment via nitrogen hypoxia resurfaced more recently in a Tom McNichol Slate magazine article titled *Death by Nitrogen (2014).* The article was inspired by the stay of execution issued by the U.S. Supreme Court for a Missouri man facing execution via lethal injection. Again, the author suggested nitrogen induced hypoxia as a painless alternative to traditional methods of execution, adding that it offered the additional benefits of requiring no medical training to administer and lacked any of the supply issues that exist with lethal injection.

The capital punishment protocols cited that utilize nitrogen to administer a death sentence do not actually rely on the nitrogen itself to bring about death. Nitrogen simply displaces the oxygen normally found in air and it is the resulting lack of oxygen which causes death. Without oxygen present, inhalation of only 1-2 breaths of pure nitrogen will cause a sudden loss of consciousness and, if no oxygen is provided, eventually death. (European Industrial Gases Association, 2009, p. 3).

Since nitrogen has not previously been used for capital punishment there is a lack scientific literature that specifically addresses its performance for that purpose. However, there have been medical experiments which involved human subjects breathing pure nitrogen until they became unconscious. Beyond those experiments, most of the data related to nitrogen induced hypoxia comes from documented suicides in humans and research in high altitude pilot training.

> *Author's Note: in some cases the lay press will inadvertently refer to hypoxia as asphyxiation. This is technically inaccurate in this context, as asphyxia is the inability to breathe in oxygen* ***and*** *the inability to exhale carbon dioxide. Hypoxia is the pathology related to the inability to intake oxygen even though one may still be able to exhale carbon dioxide. As will be seen later, the ability to exhale carbon dioxide is critical to the proposed method of execution, as it prevents the acidosis normally associated with asphyxiation.*

Medical Literature

The adult brain uses about 15 per cent of the heart's output of oxygenated blood (Graham, 1977, p.170). Hypoxia is the condition of having a lower-than-normal amount of oxygen in the blood. Anoxia is an extreme form of hypoxia in which there is a complete absence of oxygen in the blood (Brierley, 1977 p.181). If the supply of oxygen in the blood is reduced

below a critical level it will result in a rapid loss of consciousness and eventually irreversible brain damage will occur (Graham, 1977, p.170).

A complete immediate global loss of oxygen to the brain, (a scenario in which no residual oxygen in the lungs or blood is delivered to the brain), will result in a loss of consciousness in eight to ten seconds, and a loss of any electrical output by the brain will occur a few seconds later. The heart may continue to beat for a few minutes even after the brain no longer functions (Brierley, 1977 p.182).

Ernsting (1961) performed a study on human volunteers that hyperventilated on pure nitrogen gas. The subjects performed the test multiple times, varying the length of time they inhaled the nitrogen. When the subjects inhaled nitrogen for eight-to-ten seconds they reported a dimming of vision. When the period was expanded to fifteen-to-sixteen seconds, the subjects reported some clouding of consciousness and impairment of vision. When the tests were expanded to seventeen-to-twenty seconds, the subjects lost consciousness. There was no reported physical discomfort associated with inhaling the pure nitrogen. (p. 295)

Unlike asphyxiation, hypoxia via the inhalation of nitrogen allows the body to expel the carbon dioxide buildup that is normally associated with the respiratory cycle. This helps prevent a condition known as hypercapnia - an accumulation of carbon dioxide in the blood. The result of this buildup of carbon dioxide is respiratory acidosis - a shifting of the ph levels in the blood to become more acidic. This is the pathology many people associate with suffocating. Some of the symptoms of respiratory acidosis are expected to be present in cases of asphyxiation, but not expected to be present under pure hypoxia are anxiety and headaches, (Merrick Manuel, 2013).

Suicide Data

Perhaps one of the greatest testaments to both the humanity of nitrogen induced hypoxia as well as the ease of administration is its rapidly gaining popularity as a self-selected means of suicide. Suicide by hypoxia using an inert gas is the most widely promoted method of human euthanasia by right-to-die advocates (Howard, M.O. et. al., 2011, P. 61).

The trend toward using an "exit bag" filled with an inert gas such as nitrogen or helium likely started with a publication of *Final Exit: The Practicalities of Self Deliverance and Assisted Suicide for the Dying*. The authors of the publication sought to identify methods of death that were swift, simple, painless, failure-proof, inexpensive, non-disfiguring and did not require a physician's assistance or prescription (Howard, M.O. et. al., 2011. p 61).

This method of suicide is indeed simple. It involves a clear plastic bag fitted over the head, two tanks filling the bag with helium via vinyl tubing, and an elastic band at the bottom of the bag to prevent the bag from slipping off the head. The parts needed to create the bag are inexpensive and available locally without prescription (Howard, M.O. et. al., 2011. p 61-62).

Reports of deaths observed via this method suggest that it is painless. Jim Chastain, Ph.D. President of the Final Exit Network of Florida described the process this way:

> In the several events I have observed the person breathes the odorless, tasteless helium deeply about three or four times and then is unconscious, no gagging or gasping. Death follows in 4-5 minutes. A peaceful process.

Derek Humphrey, current chair of the Final Exit advisory board is quoted as saying:

> In the approximate 300 cases which have been reported to me there has never been mention of choking or gagging. When I witnessed the helium death of a friend of mine it could not have been more peaceful (Final Exit, 2010).

However, it should be noted that deviations from the above protocols have not always been as successful. When masks were placed over the face (instead of using bags of helium over

the head) it has been reported some problems have occurred. This is typically a result of the mask not sealing tightly to the face, resulting in a small amount of oxygen being inhaled by the individual. This extends the time to become unconscious and extends the time to death. This may result in purposeless movements by the decedent (Ogden et al, 2010. p 174-179).

Research on High Altitude Pilot Training

A great deal of research on the effects of hypoxia on human beings comes from aerospace medicine. Pilots that fly at high altitudes are subject to becoming hypoxic if their cabins lose air pressure. Altitude hypoxia has similar effects as the hypoxia one gets from breathing inert gases although it is caused by the inability of the lungs to absorb the oxygen in the air rather than a lack of oxygen in the air.

The Federal Aviation Administration (2003, p. 11) states:

> Hypoxia is a lack of sufficient oxygen in the body cells or tissues caused by an inadequate supply of oxygen, inadequate transportation of oxygen, or inability of the body tissues to use oxygen. A common misconception among many pilots who are inexperienced in high-altitude flight operations and who have not be exposed to physiological training is that it is possible to recognize the symptoms of hypoxia and to take corrective actions before becoming seriously impaired. While this concept may be appealing in theory, it is both misleading and dangerous for an untrained crew member. Symptoms of hypoxia vary from pilot to pilot, but one of the earliest effects of hypoxia is impairment of judgment. Other symptoms can include one or more of the following:
> (1) Behavioral Changes (e.g. a sense of euphoria).
> (2) Poor coordination.
> (3) Discoloration in the fingernails (cyanosis).
> (4) Sweating.
> (5) Increased breathing rate, headache, sleepiness, or fatigue
> (6) Loss or deterioration of vision
> (7) Light-headedness or dizzy sensations and listlessness.
> (8) Tingling or warm sensations.

Indeed, hypoxia has caused several airline accidents which are often fatal. The onset of hypoxia is typically so subtle that it is unnoticeable to the subject. The effects of hypoxia are often difficult to recognize. (Federal Aviation Administration, 2014, Ch. 8-1-2 (A) 5)

Attempts to train pilots to notice hypoxia are conducted using a hyperbaric chamber to simulate high altitudes. Often a trainee will be asked to remove his or her mask and perform simple tasks. At low levels of hypoxia, trainees typically feel little more than euphoria and a sense of confidence. At higher levels of hypoxia, trainees will quickly become unconscious. Time of useful consciousness at altitudes above 43,000 is 5 seconds (Federal Aviation Administration, 2003, p. 13).

Findings

Based on the review of the literature related to hypoxia induced by inert gases, this study makes the following findings:

1. An execution protocol that induced hypoxia via nitrogen inhalation would be a humane method to carry out a death sentence.
2. Death sentence protocols carried out using nitrogen inhalation would not require the assistance of licensed medical professionals.
3. Death sentences carried out by nitrogen inhalation would be simple to administer.
4. Nitrogen is readily available for purchase and sourcing would not pose a difficulty.
5. Death sentences carried out by nitrogen inhalation would not depend upon the cooperation of the offender being executed.
6. Use of nitrogen as a method of execution can assure a quick and painless death of the offender

Finding 1. An execution protocol that induced hypoxia via nitrogen inhalation would be a humane method to carry out a death sentence.

Rationale:

As an inert gas, nitrogen is odorless, colorless, tasteless and undetectable to human beings. It is 78% of the air we breathe on a daily basis, and thus there is little chance that any subject would have an unusual or allergic reaction to the gas itself.

Because the subject is able to expel carbon dioxide, the anxiety normally associated with acidosis in asphyxiation would not be present.

The literature indicates after breathing pure nitrogen, subjects will experience the following: within eight-to-ten seconds the subjects will experience a dimming of vision, at fifteen-to-sixteen seconds they will experience a clouding of consciousness, and at seventeen-to-twenty seconds they will lose consciousness. There is no evidence to indicate any substantial physical discomfort during this process.

There is a possibility that subjects will feel euphoria prior to losing consciousness and a slight possibility they will feel a tingling or warm sensation. After the subjects are unconscious, it should be expected some of the subjects will convulse. Most electrochemical brain activity should cease shortly after loss of consciousness, and the heart rate will begin to increase to varying degrees until it stops beating 3 to 4 minutes later. Observed suicides involving inert gas hypoxia are described as peaceful, so long as caution is taken to eliminate the possibility of the subject inadvertently receiving supplemental oxygen during the process. Inert gas hypoxia is considered such a humane and dignified process to achieve death that it is recommended as a preferred method by right-to-die groups.

Finding 2. Death sentence protocols carried out using nitrogen inhalation would not require the assistance of licensed medical professionals.

Rationale:

The administration of a death sentence via nitrogen hypoxia does not require the use of a complex medical procedure or pharmaceutical products. The process itself, as demonstrated by those who seek euthanasia, requires little more than a hood sufficiently attached to the subject's head and a tank of inert gas to create a hypoxic atmosphere.

While a state execution would likely have a more elaborate mechanism to create hypoxia, nothing in the process would require specialized medical knowledge or the use of regulated pharmaceutical products. Accordingly, except for the pronouncement of death, the assistance of licensed medical professionals would not be required to execute this protocol.

Finding 3. Death sentences carried out by nitrogen inhalation would be simple to administer.

Rationale:

When considering a substitute method of capital punishment it is important to consider more than just what happens if everything goes according to protocol. The likelihood of mishaps must also be considered, as well as the consequences that would flow if those mishaps should occur.

Because the protocol involved in nitrogen induced hypoxia is so simple, mistakes are unlikely to occur. Oxygen and nitrogen monitors may be placed inside the contained environment to insure the proper mixes of gas are being expelled into the bag and inhaled by the subject.

However, the protocol should be careful to prevent the possibility of oxygen entering into the hood, as that can prolong time to unconsciousness and death, as well as increase the possibility of involuntary movements by the subject.

The risks to witnesses are minimal, as any potential leak of the nitrogen would not be harmful in a normally ventilated environment.

Finding 4. Nitrogen is readily available for purchase and sourcing would not pose a difficulty.

Rationale:

Nitrogen is utilized harmlessly in many fields within United States industries. Nitrogen is used in welding, hospital and medical facilities, cooking, and used in the preparation of liquid nitrogen cocktails. Nitrogen is used as a process to extend the life of food products such as potato chips. Nitrogen is used in doctor's offices to remove skin tags as well as other procedures. Accordingly, sources of nitrogen to be used for administering a death sentence should be easy to find and readily available for purchase for such purpose.

Finding 5. Death sentences carried out by nitrogen inhalation would not depend upon the cooperation of the offender being executed.

Rationale:

Some forms of capital punishment require the offender to submit or comply to some degree in order to assure an efficient and humane method of execution. With proper protocol and utilizing such devices as a restraint chair, nitrogen inhalation can be administered despite the presence of a non-compliant offender. The use of nitrogen can be used by non-medical personnel and a delivery system can be designed to ensure the execution is carried out without issue.

Conclusion

As per the above, it is the recommendation of this study that hypoxia induced by the inhalation of nitrogen be offered as an alternative method of administering capital punishment in the State of Oklahoma.

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Appendix D

Death by Nitrogen: Will This New Method of Execution Save the Death Penalty?

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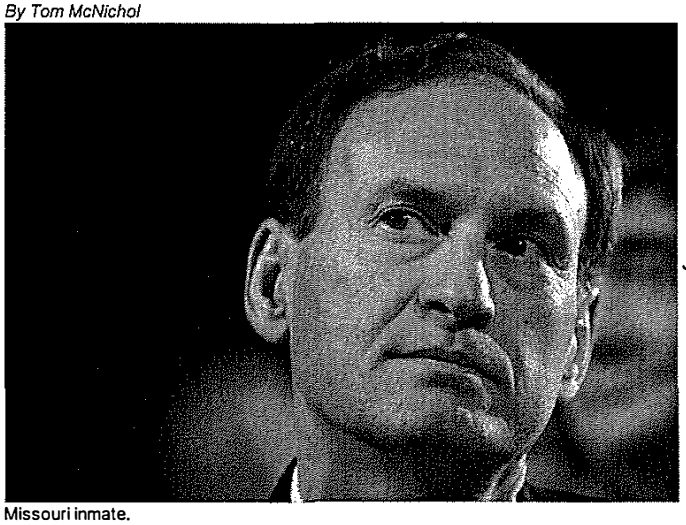
JURISPRUDENCE | THE LAW, LAWYERS, AND THE COURT. | MAY 22 2014 11:47 AM

Death by Nitrogen

If lethal injection falls out of favor, death penalty states could turn to a new method: nitrogen gas.

By Tom McNichol



Justice Samuel Alito issued an order halting the execution of a Missouri inmate.

Photo by Saul Loeb/AFP/Getty Images

On Wednesday night, the Supreme Court stopped an execution by lethal injection. The condemned Missouri man, Russell Bucklew, says he has a medical condition, affecting his veins, that would make the injection cause hemorrhaging—and make him feel like he's choking on his own blood. The court took the unusual step of intervening at the last minutes, when every other court had turned Bucklew down, and also of sending the case back to the lower courts to decide whether to hold a hearing about Bucklew's claim.

The Supreme Court ruled in 2008 that Kentucky's three-drug protocol for carrying out lethal injections was constitutional, but there's no question that the method looks grimly suspect in the wake of Clayton Lockett's apparently painful, botched execution in Oklahoma last month. Not so long ago, though, this was the method that represented progress. Hanging. Firing squad. The guillotine. The electric chair. The gas chamber. Lethal injection. Every age seems to feature a new and improved method of capital punishment, billed as more efficient and humane. The spectacle of Lockett's death, and the Supreme Court's hesitation, shines a spotlight on the latest idea—death by nitrogen.

As long as there's a will to kill criminals, someone will come up with an improved form of capital punishment.

This new proposed method, known as nitrogen asphyxiation, seals the condemned in an airtight chamber pumped full of nitrogen gas, causing death by a lack of oxygen. Nitrogen gas has yet to be put to the test as a method of capital punishment—no country currently uses it for state-sanctioned executions. But people do die accidentally of nitrogen asphyxiation, and usually never know what hit them. (It's even possible that death by nitrogen gas is mildly euphoric. Deep-sea divers exposed to an excess of nitrogen develop a narcosis, colorfully known as "raptures of the deep," similar to drunkenness or nitrous oxide inhalation.)

You can oppose the death penalty and still see the merit in making executions more humane. As Boer Deng and Dahlia Lithwick argued in ***Slate***, opponents of the death penalty inadvertently have made lethal injection *less* safe, by forcing prison officials into using inferior methods and substandard drug providers. As the states struggle to obtain drugs, such as pentobarbital, for lethal injections because of an export ban by the European Union, lethal injection has been turned from a method of execution into a medical experiment.

Proponents say that death by nitrogen, by contrast, adheres to the constitutional prohibition against cruel and unusual punishment. The condemned prisoner would detect no abnormal sensation breathing the odorless, tasteless gas, and would not undergo the painful experience of suffocation, which is caused by a buildup of carbon dioxide in the bloodstream, not by lack of oxygen.

In late April, Louisiana Department of Corrections Secretary James LeBlanc suggested to a state legislative committee that Louisiana should look into using nitrogen gas as a new method of execution, since lethal injection has become so contentious. "It's become almost impossible to execute someone," LeBlanc complained to the Louisiana House Administration of Criminal Justice Committee.

"Nitrogen is the big thing," LeBlanc told the committee. "It's a painless way to go. But more time needs to be spent [studying] that." The committee instructed LeBlanc to do some research on the subject and report back. In the meantime, Louisiana has delayed a pending execution. "I'm not taking anything off the table," says state Rep. Joseph P. Lopinto III, chairman of the state's Administration of Criminal Justice Committee. "If someone says nitrogen gas is the way to go, then we can debate that and do it if need be."

As long as 32 states have capital punishment on the books, there should be a less reliably cruel method of execution than lethal injection. "If we're going to take a life, then we should do it in the most humane, civilized manner as is possible," says Lawrence Gist II, an attorney and professor of business and law at Mount St. Mary's College. "Right now, nitrogen is the best of the available options."

Gist, a death penalty opponent, runs a website dedicated to promoting nitrogen asphyxiation for state-sanctioned executions. Polling suggests the public could get behind the idea. In a recent NBC News poll, 1 in 3 people said that if lethal injections are no longer viable, executions should be stopped altogether. But many others were open to alternative methods of putting prisoners to death. About 20 percent opted for the old version of the gas chamber (which traditionally used hydrogen cyanide to kill), 18 percent for the electric chair, 12 percent for death by firing squad, and 8 percent for hanging.

Nitrogen gas, unlike the lethal drugs that states have relied on, is widely available. The gas is used extensively in industrial settings, from aerospace to oil and gas production "Lethal injection is just fine if you can get the pentobarbital," says Kent Scheidegger, legal director of the Criminal Justice Legal Foundation, a group that favors capital punishment. "But if that's not available, an alternative like nitrogen gas would work."

Top Comment

I always thought that people who voluntarily went to witness a cyanide gas chamber execution were morons. You have to have a special kind of faith in window caulking. More...

-Pete R

Join In

In contrast to lethal injection, no medical expertise would be needed to introduce nitrogen gas into a sealed chamber. The gas chamber itself is technology that has been around since the 1920s. In fact, three states—Arizona, Missouri, and Wyoming—still authorize lethal gas as a method of execution (depending on the choice of the inmate, the date of the execution or sentence or the possibility that lethal injection is held unconstitutional).

The last gas chamber execution in the U.S. was in 1999—the method fell out of favor because hydrogen cyanide is a poison causing suffering that lasts 10 minutes or longer. Lethal injection, of course, was supposed to be painless and better. What if it's not? That's the question the Supreme Court now finally seems to be returning to. The history of capital punishment suggests that as long as there's a will to kill criminals, someone will come up with an improved way. The new tool in the executioner's bag may turn out to be nitrogen, a better way to carry out a gruesome task.

Tom McNichol is a writer in San Francisco.

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alt.suicide.methods

Killing with kindness - capital punishment by nitrogen asphyxiation (too old to reply)

Philbert 9 years ago

http://www.findarticles.com/p/articles/mi_m1282/is_n17_v47/ai_17374449

Capital punishment needn't be cruel or unusual -- especially if you use nitrogen asphyxiation to put people to sleep.

LAST October, Judge Marilyn Hall Patel of the 9th U.S. District Court ruled that execution in California's gas chamber is a form of cruel and unusual punishment, the first ruling ever by a state or federal judge to invalidate a method of execution on Eighth Amendment grounds. She noted that the evidence showed that the condemned man might remain conscious for several minutes, experiencing the emotions of `anxiety, panic, terror,' as well as `exquisitely painful muscle spasms' and `intense visceral pain.'

On its face, Judge Patel's ruling applies only to the gas chamber, but every method of execution in current use involves toxic chemicals or physical trauma to induce death -- and every method can go awry. An ideal hanging snaps the condemned man's neck cleanly; a botched one either strangles him slowly or severs the head entirely from the body. A firing squad that misses its mark leaves the condemned man conscious as he bleeds to death. In the electric chair, according to eyewitness accounts, some condemned men have literally been cooked until their flesh was charred and loosened from the bone; some had sparks and flame emanating from their cranial-cap electrodes.

Besides society's concern for the condemned man's physical suffering, all of these methods implicitly require an executioner to inflict some degree of trauma upon the condemned. Concern for the executioner's conscience drives such customs as loading one of the guns for a firing squad with a blank cartridge, so that each member of the squad can imagine that his will be the non-lethal shot. And with lethal injection, the executioner's use of skills and procedures normally devoted to life-saving poses ethical questions for medical caregivers.

Given these defects, abolitionists will presumably press to have each of these methods declared `cruel and unusual.' The intended result of these efforts is to make the death penalty unconstitutional in practice, even if it remains constitutional in theory.

It is in fact possible to conceive of a method of execution that would cause neither pain nor physical trauma, require no medical procedure (other than pronouncing death), and use no hazardous chemicals. A case of accidental

death suggests such a method.

Early in the Space Shuttle program, a worker at Kennedy Space Center walked into an external fuel tank (a vessel nearly as big inside as a Boeing 737) to inspect it. He was not aware that it had been purged with pure nitrogen gas to prevent oxygen in the air from corroding its interior. Since nitrogen is the major component of ordinary air, pure nitrogen has no distinctive feel, smell, or taste; the worker had no indication that anything was out of the ordinary. After walking a short distance into the tank, he lost consciousness and collapsed. A co-worker, not realizing that his collapse had an external cause, ran in to aid him and succumbed also. By the time other workers realized what was happening, the two men were dead.

More recently, a bizarre accident involving nitrogen killed two people in the Bay Area. They had stolen from a hospital a gas cylinder containing what they thought was laughing gas. However, the cylinder contained not the anaesthetic nitrous oxide but pure nitrogen. When the two men stopped their car to partake of their booty, the nitrogen gas displaced the air in the car, leaving them without oxygen. Had they had any indication of the problem, they could have saved their lives simply by opening the car doors.

These deaths were similar in cause to a relatively common drowning accident known as shallow-water blackout, mentioned specifically in certification classes for recreational scuba diving. When a person is skin diving (that is, without scuba gear), his bottom time is limited by how long he can hold his breath. Occasionally, a skin diver will attempt to lengthen the time he can stay under by hyperventilating before a dive. Unfortunately, this can lead to his losing consciousness underwater, sometimes only a few feet before reaching the surface.

THE connection between nitrogen asphyxiation and shallow-water blackout lies in human respiratory physiology. When you hold your breath, you begin to develop a powerful urge to breathe. This is caused not by the depletion of oxygen from your body, but by the buildup of carbon dioxide in your bloodstream, which changes the pH of the blood. The ambitious skin diver ``blows off' most of the carbon dioxide in his bloodstream when he hyperventilates; as a result, he notices the urge to breathe much later than he normally would, at a point when his blood oxygen is dangerously low. If his blood oxygen falls too low before he reaches the surface, he blacks out and drowns. Because the Kennedy Space Center workers continued to exhale carbon dioxide with each breath, neither of them noticed an unusual urge to breathe, even though they were completely deprived of oxygen.

Nitrogen asphyxiation is a unique way to die. The victim is not racked by a choking sensation or a burning urge to breathe, because as far as his body

knows, he is breathing normally. Carbon dioxide is not building up in his bloodstream, so he never realizes that anything is wrong, nor does he experience any discomfort; he simply passes out when his blood oxygen falls too low.

Nitrogen asphyxiation is therefore a perfect method of execution. It uses a cheap and universally available working medium that requires no special environmental precautions for its storage and disposal. Its first symptom is loss of conscious sensation, a primary goal in a humane execution. It involves no physical trauma, no toxic drugs; the executed man's organs will even be suitable for donation, a factor cited in a recent stay of execution for a Georgia killer.

Assuming that the prisoner's guilt has been sufficiently proved, nitrogen asphyxiation is perhaps the most gentle way to deal with him. A condemned man awaiting death by nitrogen asphyxiation would experience no more pain or suffering than he created in his own mind.

nubbins 9 years ago

```
x-no-archive:yes

Maybe even go out laughing.

- nubbins -
```


Philbert 9 years ago

> *Post by nubbins*
> x-no-archive:yes
> Maybe even go out laughing.
> - nubbins -

```
You're thinking of nitrous oxide aka laughing gas. The article is about
nitrogen.
```

nubbins 9 years ago

```
x-no-archive:yes
```

> *Post by Philbert*
> > *Post by nubbins*
> > Maybe even go out laughing.

> You're thinking of nitrous oxide aka laughing gas. The article is about nitrogen.

You are absolutely correct, sir. I was not paying due attention. Gets me in trouble in class all the time. Who would mind if a doctor diagnosed onychomycosis as cryptorchidism, really? Details, details.

- nubbins -

d*@hotmail.com** 9 years ago

Awesome article. I think you just solved the puzzle for me. Thank you.

Philbert 9 years ago

Google nitrogen suicide for a lot of stuff. Basically people find that euthanising animals works pretty well using nitrogen, plus it's safe to use
unless it's in a very high concentration.

Rabbits don't like nitrogen because they have adaptive traits for living in
holes where nitrogen can build up, unlike other animals and humans.

On 4/6/06 3:25 PM, in article

> *Post by d***@hotmail.com*
> Awesome article. I think you just solved the puzzle for me. Thank you.

slunky 9 years ago

Thanks for finding an article on it. I've been saying it for weeks, and was starting to wonder if I had just imagined it or what.

--
-slunky

Cesar 9 years ago

Thanks for the great post and it was interesting and informative. I have concern that when the death penalty is ruled out as cruel and inhumane, it leaves the potential that the prisoners on death row could at some point get release and re-enter society. When prisons become too full, it can be ruled that a certain amount of prisoners be released early. In the years to come, laws could change and see a prisoner sentenced to death instead getting a life sentence of 20 years then getting out. Of course, it would help those that were wrongly convicted in the first place.

Jimmy 9 years ago

HAZARDS OF INERT GASES AND OXYGEN DEPLETION

IGC Document 44/09/E

Revision of IGC Doc 44/00/E

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IGC Doc 44/09/E

HAZARDS OF INERT GASES AND OXYGEN DEPLETION

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Table of Contents

1 Introduction

EIGA is very concerned about the accidents that industrial gas companies and users of inert gases continue to report each year, where the direct cause has been lack of oxygen resulting in asphyxiation. EIGA identified that existing information on the hazards of inert gases was not sufficiently directed at the users who were most at risk. This document sets out the essential information that is necessary to prevent asphyxiation accidents involving inert gases.

2 Scope and purpose

It is intended that this document is used as a training package suitable for supervisors, line managers, direct workers and users wherever inert gases are produced, stored, used, or where oxygen depletion could otherwise occur.

This document has 4 parts:

The main document is intended for line managers and supervisors and gives the background of the subject, the typical description of oxygen deficiency accidents and the recommended rescue preparations to be in place in case of accident.

Appendix A is a simplified summary of the main document, designed to be reproduced as a pamphlet for sharing with workers and end users.

Appendix B gives an introduction to rescue considerations from normally accessible rooms, confined spaces or pits and trenches.

Appendix C lists some actual accidents that have taken place in recent years, which can be used as examples to underline the potentially fatal hazards of inert gases.

Appendix D gives an example of a warning sign or poster to highlight the hazards of inert gases and asphyxiating atmospheres.

3 Definitions

Asphyxiation: the effect on the body of inadequate oxygen, usually resulting in loss of consciousness and/or death. This is also known as suffocation or **anoxia**.

Asphyxiant: any material which reduces the amount of available oxygen either by simple dilution or by reaction.

Inert gas: A gas that is not toxic, which does not support human breathing and which reacts little or not at all with other substances. The common inert gases are nitrogen and the rare gases like helium, argon, neon, xenon and krypton.

Flammable gas: a gas whose major hazard is flammability. Note that all flammable gases also act as asphyxiants.

User: for the purpose of this document this term covers any individuals, companies or other organisations that make use of the products sold by industrial gas companies. Users may be, but are not necessarily, customers.

4 General Information about Inert Gases and Oxygen Depletion

In spite of the wealth of information available, such as booklets, films and audio-visual aids, there are still serious accidents resulting in asphyxiation caused by the improper use of inert gases or by oxygen depletion. It is therefore absolutely essential to draw attention to the hazards of inert gases and oxygen depletion. Accidents due to oxygen depleted atmospheres are usually very serious and in many cases fatal.

Although carbon dioxide is not an inert gas, most of the information in this document is applicable as it too will cause oxygen depletion. However, the specific hazards and physiological effects of carbon dioxide are more complex than those of inert gases. This document does not cover these aspects. (See IGC Doc. 67 "CO2 cylinders at user's premises" for more details about the additional hazards of carbon dioxide).

4.1 Oxygen is essential for life

Oxygen is the only gas that supports life. The normal concentration of oxygen in the air we breathe is approximately 21 %. Concentration, thinking and decision-making are impaired when the oxygen concentration falls only slightly below this norm. These effects are not noticeable to the affected individual.

If the oxygen concentration in air decreases or, if the concentration of any other gases increase, a situation is rapidly reached where the risks of asphyxiation are significant. For this reason any depletion of oxygen below 21 % must be treated with concern:

Asphyxia – Effect of O_2 Concentration (from NLJ77 Campaign against Asphyxiation)

O_2 (Vol %)	Effects and Symptoms
18-21	**No discernible symptoms** can be detected by the individual. A risk assessment must be undertaken to understand the causes and determine whether it is safe to continue working.
11-18	Reduction of physical and intellectual performance **without the sufferer being aware**.
8-11	Possibility of fainting within a few minutes without prior warning. **Risk of death below 11%.**
6-8	Fainting occurs after a short time. **Resuscitation possible** if carried out immediately.
0-6	Fainting almost immediate. **Brain damage**, even if rescued.

***WARNING**: The situation is hazardous as soon as the oxygen concentration inhaled is less than 18 %.*
With no oxygen present, inhalation of only 1-2 breaths of nitrogen or other inert gas will cause sudden loss of consciousness and can cause death.

4.2 Inert gases give no warning

It is absolutely essential to understand that with inert gases such as nitrogen, argon, helium, etc., asphyxia is insidious - there are no warning signs!

- Inert gases are odourless, colourless and tasteless. They are undetectable and can therefore be a great deal more dangerous than toxic gases such as chlorine, ammonia, or hydrogen sulphide, which can be detected by their odour at very low concentrations.
- The asphyxiating effect of inert gases occurs without any preliminary physiological sign that could alert the victim. Lack of oxygen may cause vertigo, headache or speech difficulties, but the victim is not capable of recognising these symptoms as asphyxiation. Asphyxiation leads rapidly to loss of consciousness – for very low oxygen concentrations this can occur within seconds.

4.3 Inert gases act quickly

In any accident where the supply of oxygen to the brain is affected, prompt emergency treatment is critical. Proper medical treatment (resuscitation) if given quickly enough can prevent irreversible brain damage or even death in some instances.

Furthermore, and this is often poorly understood, the emergency rescue procedure to save the victim must be carefully thought out in advance to avoid a second accident, where members of the rescue

team can become victims. Unplanned interventions resulting in the fatalities of would-be rescuers are sadly not unusual.

4.4 The ambiguity of inert gases

Everyone, particularly customers, must be aware of the ambiguity of the expression "inert gas" (sometimes called "safety gas", when it is used to prevent fire or explosion), whereby an "inert gas" is often perceived, understood and wrongly taken to be a harmless gas!

4.5 Watchfulness with regard to inert gases and oxygen depletion

Considering the hazards mentioned above, it is essential to provide all those who handle or use inert gases (gas company personnel as well as customers) with all the information and training necessary regarding safety instructions. This includes the means of prevention and procedures to be respected to avoid accidents, as well as planned rescue procedures to be implemented in the event of an accident.

5 Some typical situations with inert gas and/or oxygen depletion hazards

5.1 Confined or potentially confined spaces and enclosures

Confined, restricted or enclosed spaces are particularly dangerous situations where an inert gas may be **normally present** (inside a process vessel), may have **accumulated** (from leaks or vents) and/or because the space has not been **adequately vented or purged**, and/or the renewal of air is poor or **ventilation is inadequate**.

Examples of such spaces include:

- Confined spaces: tanks, vessels, reservoirs, the inside of "cold boxes" of liquefaction equipment, cold storage rooms, warehouses with fire suppressant atmospheres, etc.
- Enclosures: analyzer or instrument cabinets, small storage sheds, temporary/tented enclosures, or spaces where welding protective gas is used, etc

The precautions required for safe access by personnel will be different in each of these cases as explained in Appendix B.

5.2 The use of inert cryogenic liquids

It is to be noted, that the use of inert cryogenic liquids such as nitrogen or helium is accompanied by two primary hazards:

- The fluids are very cold (-196°C for nitrogen and -269°C for helium) and can cause serious cold burns on contact with the skin.
- Once vaporised both products will generate a large volume of cold inert gas (e.g. 1 litre of liquid nitrogen will yield 680 litres gaseous product) that will displace ambient air, causing oxygen deficiency and may accumulate in low points.

In processes where cryogenic liquids are handled and vaporisation takes place, special care must be taken to avoid situations where personnel are exposed to oxygen deficiency. These may be in rooms which people regularly enter or work in.

Examples of such spaces include:

- The internal rooms of a building where cryogenic liquid cylinders/dewars are filled and/or stored,
- Laboratory rooms,
- Elevators (lifts) used for transport of dewars,
- Rooms where liquid nitrogen food freezers are operated. (Tunnel, cabinet)
- Rooms where Magnetic Resonance Imaging (MRI) scanner or other liquid helium cooled equipment is used
- Rooms in which cryogenic de-flashing equipment is operated.

Notes: Due to the extremely low temperature of liquid helium a secondary hazard may exist where the product is flowing through hoses or pipes. In this case it is possible for the components of air to liquefy on the outside of the hose/pipe, possibly leading to pooling of liquid containing levels of enriched oxygen. [See Ref. 7].

5.3 Areas near where inert gases are vented or may collect

The risk of asphyxiation can arise, even outdoors, in the vicinity of:
- Gas leaks
- Vent exhausts
- Outlet of safety valves and rupture disks
- Openings of machines in which liquid nitrogen is used for freezing
- Blind flanges
- Near manways/access to vessels or purged enclosures (e.g. ASU cold boxes, electrical enclosures)

Any cold gas or heavier-than-air gas will travel or "flow" – often unseen - and collect even outdoors, in low spaces such as:
- Culverts
- Trenches
- Machine pits
- Basements
- Elevator (lift) shafts

Similarly and just as dangerously lighter-than-air gases (e.g. helium) will rise and collect in unventilated high points such as:
- Behind false ceilings
- Under a roof

5.4 Use of inert gas instead of air

Planned Use
In many workplaces, there are often compressed inert gas distribution networks that are used for process applications, safety or instrumentation purposes, e.g. inerting/purging of reactors or using nitrogen as a pressure source to operate pneumatic equipment (such as jackhammers) or as instrument fluids.

Additionally, nitrogen is often used as either a backup to, or substitute for, an instrument air system. Where it is used as a backup supply in case of instrument air compressor failures it is quite common to find a nitrogen supply connected to an air supply by means of isolation valves, It must be appreciated that most pneumatically operated instruments vent continuously and that the vented nitrogen may accumulate in poorly ventilated control panels/cubicles or plant rooms. This can present a serious asphyxiation risk. Where nitrogen is used temporarily to substitute for compressed air in this way, it must be done under strictly controlled conditions such as a permit to work, and all relevant personnel shall be informed.

Improper Use
In situations where piped breathing systems exist there is always the potential for employees, who are insufficiently trained or not familiar with the systems, to connect the breathing apparatus to a nitrogen system with fatal results. Such systems must be clearly marked and ideally the breathing air system should have a dedicated connection type not used elsewhere in the premises.

5.5 Dangers of improper inhalation (abuse) of inert gases

There has been increased of reporting and presentations in TV-programmes on the careless approach and dangerous misuse of breathing in gases such as helium and other inert rare gases. The media reports in particular trivialise the effects of inhaling helium to achieve a very high-pitched voice. Inhalation of helium can lead to unconsciousness, cessation of breathing and sudden death.
[See Ref. 6 for more information]

6 Hazard mitigation and preventive measures

6.1 Information, training

All persons who handle or who use inert gases shall be informed of:
- Safety measures that should be adopted when using gases.
- The hazard represented by the release of inert gases in to the working space and the potential for oxygen depletion.
- Procedures to be observed should an accident occur.

This information and training should be systematically and periodically reviewed in order to ensure that it remains up to date and appropriate for the hazards identified.

6.2 Proper installation and operation

Equipment for the manufacture, distribution or use of inert gas must be installed, maintained and used in accordance with:
- All applicable regulations.
- The recommendations of the supplier
- Industrial gas industry standards and codes of practice

Newly assembled equipment for inert gas service must undergo a proof test and be leak-checked using suitable procedures.

Each inert gas pipeline entering a building should be provided with an easily accessible isolation valve outside the building. Ideally such valves should be remote activated by push buttons or other safety monitoring equipment.

Discontinued inert gas lines shall be physically disconnected from the supply system when not in use.

At the end of each work period, all valves that isolate the inert gas should be securely closed to avoid possible leakage between work periods.

6.3 Identification and safeguarding of potentially hazardous areas

Measures should be taken to identify potentially hazardous areas, or restrict access to them, e.g.
- Warning signs should be displayed to inform of an actual or potential asphyxiation hazard (An example is shown in Appendix D). The warning sign should be associated with measures to prevent unauthorised entry to the areas.
- Temporary or permanent barricades, for example physical lock on vessel manway or barricades around temporary excavations.
- Communication to site personnel to ensure awareness and understanding.

6.4 Ventilation and atmospheric monitoring for inert gases and oxygen deficiency

Typically there are three situations where the need for ventilation or atmospheric monitoring must be assessed in order to avoid asphyxiation accidents from inert gases and/or oxygen depletion:

6.4.1 Ventilation/ monitoring of rooms which people regularly enter or work in

Examples in this category would include:
- Rooms containing **inert gas pipelines** with possible leaks such as compressor houses, control rooms (with control/analyser panels).
- Rooms where **inert cryogenic liquid** is used or stored (see 5.2 above)

Building/room size, ventilation capacity, system pressures, etc. must be determined for each specific case. The following guidelines can be applied to ventilation system design:
- Ventilation must be continuous while the hazard exists. This can be achieved by interlocking the ventilation system with the process power supply.

- Ventilation system design should ensure adequate air flow around the normal operating areas.
- Good engineering practice indicates a minimum ventilation capacity of 6-10 air changes per hour.
- The use of devices to indicate correct system operation, such as:
  - Warning lights
  - "Streamers" in the fan outlet,
  - Flow switches in the suction channels (monitoring should not rely only upon secondary controls such as "power on" to the fan motor).
- Exhaust lines containing inert gases shall be clearly identified, and should be piped to a safe, well ventilated area outside the building, away from fresh air intakes.
- Consideration should be given to the use of workplace atmospheric monitoring, e.g. personal oxygen analyser or an analyser in the work area, location to be based on assessment of the areas described in 5.3.
- People working in or entering the area shall be aware of action required in event of alarms from atmospheric monitors or loss of ventilation.

6.4.2 Ventilation/ monitoring prior to entry into confined spaces or enclosures

As described in 5.1 above, these spaces would include enclosures or vessels which:
- Are not routinely entered and
- Are known to have contained inert gas or
- May contain inert gas or low concentration of oxygen
- Any vessel not known and verified to contain atmospheric air.

In these cases the following guidelines apply to prepare a safe atmosphere prior to entry:
- Sources of inert gas must be isolated from the space or enclosure by positive blinds or by disconnection of lines. Never rely only on a closed valve.
- The vessel or enclosure must be adequately purged with air (i.e. remove the inert gas and substitute with air).
  - It is necessary to have at least 3 complete air changes within the enclosure involved.
  - Purging shall continue until analysis confirms that the quality of the vessel atmosphere is safe for personnel entry. If there is any doubt that effective purging has taken place, the analysis should be made in the interior of the vessel by taking a sample at several locations by probe, or if this is not possible, by a competent person using a self contained breathing apparatus.
  - The purge system must ensure turbulence for adequate mixing of air and inert gas to take place (to avoid "pockets" of dense or light inert gases remaining or to avoid "channelling" of gases due to inadequate purging).
  - Removal of argon or cold nitrogen from large vessels and deep pits can be difficult due to the relatively high density of the gas compared with air. In that case the gas should be exhausted from the bottom of the space.
  - Ventilation should never be carried out with pure oxygen, but exclusively with air.
- Another method of removing inert gases is to fill the vessel with water and allow air to enter when the water is drained off.
- Oxygen content of the atmosphere in the enclosure/vessel shall be monitored continuously or repeated at regular intervals.
- Consideration should also be given to the use of personal oxygen monitors.

Where a safe atmosphere cannot be created and confirmed, then the task must only be performed by competent personnel provided with a positive breathing air supply.

6.4.3 Ventilation/monitoring for entry into other spaces where inert gases may be present

This type of confined space is one that has any of the following characteristics:
- Limited opening for entry and exit
- Unfavourable natural ventilation

Examples are listed in sections 5.1 and 5.3 and include;
- Underground works
- Trench/pit deeper than 1 metre
- Small rooms where gases are stored but not designed for continuous worker occupancy.

In the majority of these cases the presence of inert gases is not anticipated when entering such spaces. However, the one essential safeguard in all cases is to sample the atmosphere in the room, enclosure, trench, pit, etc. for oxygen prior to any entry. Where appropriate a continuous fixed point monitoring device should be used.

The fact that an oxygen deficient atmosphere is not normally expected is the greatest danger.

6.4.4 Notes on purging requirements

The guidance for air changes, mentioned in section 6.4.2, is valid where nitrogen is the inert gas involved because its density is very near to that of air and oxygen.

If the gas to be purged has a density very different from the density of air, such as helium, argon or carbon dioxide, etc. the ventilating air may not adequately mix and the purge may be inadequate.

For inert gases of this type the volume of gas to be displaced (air changes) must be at least 10 times that of the volume involved. The preferred method of removal of very dense gases (e.g. argon or cold nitrogen vapour) is to suck out the gas from the bottom of the space.

In the presence of toxic or flammable gases, it is mandatory to perform an additional analysis of the gases present in the confined space, before entry of personnel. For obvious reasons, the measurement of only the oxygen content is not sufficient in this case. All other dangerous toxic or flammable gases must also be analysed.

In the specific case of flammable gases, a nitrogen purge must be used first to prevent any explosion risk and then subsequently purge with ventilating air.

6.5 Testing of oxygen content

Historically, the need to check that an atmosphere is respirable has been considered to be of the greatest importance. In the past, simple means were employed, such as, for example, the lighted candle or the canary bird.

Currently, various types of oxygen analysers are available, which are often reliable and simple and to operate. The selection of the type of apparatus depends on the nature of the work in the place to be monitored (presence of dust, temperature and humidity, multiple detectors, portable equipment, etc.).

- Oxygen analysers are critical equipment and must be properly maintained and calibrated in order to sufficiently reliable. It is also important to ensure that fixed and portable detectors are properly positioned to measure a representative sample of the atmosphere.
- A simple way check to confirm that an oxygen analyser is operating properly before use is to measure the oxygen content of the open air (21 %). This check should be part of the work permit requirements.
- All oxygen analysers should be fitted with an alarm device to indicate possible defects (e.g. low battery).
- The minimum safe oxygen concentration for entry into a space that is being controlled or measured because of the risk is 19.5 % oxygen. There are applications with oxygen concentrations below 19.5 % where entry is permitted provided that further precautions are taken in accordance with proper risk assessment and national regulations (e.g. fire suppression). [See Ref 4]

6.6 Work permit

For certain types of work, safety instructions and a special work procedure must be set up in the form of a work permit, this particularly relates to any form of confined space entry. [See Ref 8]
This procedure is necessary during work carried out by subcontractors in air separation cold boxes, or where vessel entry is required.

It is important that a work permit procedure deals with the detailed information that must be given to involved personnel before the start of work. This information should include contractual conditions together with documented risk assessments, procedures and the training of site workers.

6.7 Lock-out Tag-out procedure

To ensure any sources of inert gas have been properly isolated, the implementation of a stringent, formal lock-out and tag-out procedure is necessary before safe entry into a confined space.

6.8 Protection of personnel

The type of work to be performed, the layout of the premises and the assessment of potential rescue scenarios will determine the provision of additional protective measures. This additional protection should include organisational measures and/or safety equipment such as:

- Fixed or personal oxygen monitoring equipment
- The wearing of a harness so that the worker can be easily and rapidly taken out of an enclosed space in the case of an emergency. Preferably, this harness is to be connected to a hoist to facilitate removing the victim. (In practice, it is extremely difficult for one person to lift up another person in the absence of a mechanical aid of some kind.)
- The provision of an alarm system in case of an emergency.
- The wearing of a self contained breathing apparatus (not cartridge masks, which are ineffective in a case of lack of oxygen).
- In the case of work inside a confined space, a standby person should be placed on watch outside the space/vessel.
- Having a self contained breathing apparatus on stand by.
- The wearing of other personal protective equipment such as safety boots, hard hat, goggles or gloves, depending on the hazards of the location and task.

7 Confined space entry

The employer has an overriding duty to ensure that tasks in confined spaces with potentially hazardous atmospheres are performed **without entry** whenever this is practical. Only if it there is no practical alternative shall people be required to enter confined spaces.

Any entry into a confined space or enclosure with a potentially hazardous atmosphere shall be carefully controlled and have:

- A written method statement for the work to be undertaken with the space.
- A documented risk assessment for performing this task in this particular vessel.
- Formal, stringent lock-out and tag-out procedures.
- An assessment of potential scenarios where rescue may be required.
- An emergency (rescue) plan to deal with any possible accident scenario related to entry in to the enclosure or vessel.
- Rescue personnel and equipment should be available as required by the rescue plan.
- Trained and competent personnel in roles of; entrant, stand-by watch, rescue team (where required) and supervisor/permit issuer.
- A safe work permit issued and signed before entry is allowed.

This document is not a detailed procedure for confined space entry, but focuses on the considerations which are important where there is an actual or potential hazard from inert gases or oxygen deficiency.

8 Rescue and first-aid

Awareness training in the hazards of inert gases and oxygen deficient atmosphere is of vital importance for everyone who might enter a space or who might discover and affected person in a space with potentially asphyxiant atmosphere, in order to prevent subsequent fatalities as result of "unplanned rescue" attempts.

Training in rescue work is fundamental since quickly improvised rescue without the formality of a procedure, often proves to be ineffective, if not catastrophic, i.e. the rescue worker lacking foresight becomes a second or even a third victim. This is one of the most common causes of multiple fatalities in cases involving asphyxiation.

8.1 Basic rules

If a person suddenly collapses and no longer gives any sign of life when working in a vessel, a partially enclosed space, a trench, a pit, a small sized room, etc., it MUST be assumed that the person may lack oxygen due to the presence of an inert gas (which is, as mentioned, odourless, colourless and tasteless):

WARNING: *the discoverer must assume that* ***his life is at risk*** *entering the same area!*

The risk is that the rescuer will become the second victim, which obviously must be avoided at all costs. Ideally he should raise an alarm and call for assistance so that a prepared rescue can be carried out.

Rescuers intent on saving a possible asphyxiation victim should only do so if they have the necessary equipment, have been suitably trained, have proper assistance and support.

8.2 Rescue plan elements

The method of rescue will be determined by the access to particular space. If practical a non-entry rescue is preferred. Appendix B lists the considerations which should be given to rescue plans from three different situations:

- Rescue from normally accessible rooms
- Rescue from Confined Spaces
- Rescue from pits, trenches or excavations

In each case the Rescue plan must have elements which address:

- How the alarm is raised
- Identification of possible rescue scenarios (not only for low oxygen effects)
- Any scenarios in the surrounding work place which may or may not require immediate exit from the space (e.g. site evacuation in event of fire elsewhere)
- Stand-by watch trained to keep visual and verbal contact with the entrant and to ensure the entrant exits the space if symptoms of oxygen deficiency are suspected or observed
- Any assistance which may be needed/given from outside the space to help entrant escape from the space, without further entry.
- Re-checking/confirmation of atmosphere prior to rescue
- Manpower and equipment required to move unconscious person from that space
- Provision of first aid/medical treatment (e.g. resuscitation and/or oxygen treatment) inside the space if necessary
- Safe access by rescue and/or medical personnel if necessary
- How to make the space safe/prevent further injury after the rescue.

8.3 Equipment

A successful rescue action may need some of the following equipment. The actual needs must be assessed as part of the rescue plan and made available and accessible during the confined space work:

- A portable audible alarm devices, e.g.; personal horn, whistle, klaxon etc. to alert nearby people that assistance is required.
- Telephone or radio at the work site so that an alarm can be raised in event of problems
- A safety belt or harness connected to a line
- Mechanical aid such as pulley, hoist, to extract the victim.
- Possibly a source of air or oxygen to ventilate the confined space, such as:
  - A compressed air hose connected to the plant compressed air network,
  - A ventilation device.

- Additional oxygen monitors for rescue team for re-checking conditions inside the space
- Positive pressure breathing air supply. This may be an externally fed breathing air system or self-contained breathing apparatus (SCBA).
  ***WARNING**: Cartridge masks for toxic gases are not suitable as they do not replenish missing oxygen.*
- A resuscitation kit supplied with oxygen for the victim. In general, such a kit includes a small oxygen cylinder, a pressure regulator, an inflatable bag, and a mask to cover both the nose and mouth of the victim.
- Stretcher to carry injured person out of the space, away from work place and/or to ambulance.

It should be noted that any equipment identified as necessary to carry out an emergency rescue from a confined space should be defined on the basis of a full risk assessment and the emergency plan developed from it. Where this equipment is not available, a rescue should not be undertaken.

8.4 Rescue training

Where an emergency plan considers that a rescue is to be performed, it is recommended that there is an annual programme of training including **practical rescue drills**. It is also a good practice to consider a rescue exercise before start of confined space work.

8.5 First Aid

Where there is a potential hazard from inert gases/oxygen deficiency it is advisable to have personnel available who are formally qualified to give first aid and/or perform **resuscitation** in the event of an accident. The simplest first aid treatment for someone suffering from effects of oxygen deficiency is to bring the affected person **into fresh air** – as long as it safe to do so!

In most countries additional training is required so that first aiders are qualified to **provide Oxygen** as medical treatment for anoxia and other conditions.

9 Conclusions

There are two essential points to remember related to oxygen deficiency accidents involving inert gases:

- Accidents resulting from oxygen deficiency due to inert gases happen unexpectedly and the reactions of personnel may be incorrect. To avoid this, all personnel who may work with, or may be exposed to, inert gases must have routine awareness training in respect of the hazards of these gases.
- Accidents involving asphyxiant atmospheres are always serious, if not fatal. It is absolutely necessary to carry out both regular and periodic awareness training sessions for all personnel, as well as rescue drills.

10 References

[1] CGA document SB-2 2007 Oxygen-Deficient Atmospheres

[2] EIGA Asphyxiation campaign documents 2003 – including Dangers of Asphyxiation leaflet; Oxygen Deficiency training presentation and Newsletter 77/xx

[3] Oxygen deficiency hazards. Video tape EIGA, 1997

[4] EIGA Position Paper PP-14: Definitions of Oxygen Enrichment/Deficiency Safety Criteria – August 2006.

[5] US Chemical Safety and Hazard Investigation Board website Video Room www.csb.gov

[6] EIGA position Paper PP-24: Abuse of Gases

[7] IGC Doc 004 Fire Hazards of Oxygen and Oxygen Enriched Atmospheres

[8] IGC Doc 040 Work Permit Systems

Appendix A: Summary for operators

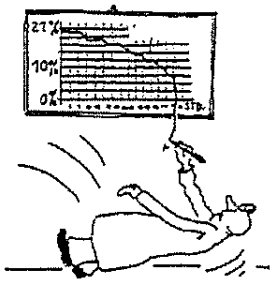
1 Why do we need oxygen?

OXYGEN IS ESSENTIAL FOR LIFE

WITHOUT ENOUGH OXYGEN WE CANNOT LIVE

When the natural composition of air is changed, the human organism can be affected or even severely impaired.

If gases other than oxygen are added or mixed with breathing air, the oxygen concentration is reduced (diluted) and oxygen deficiency occurs.



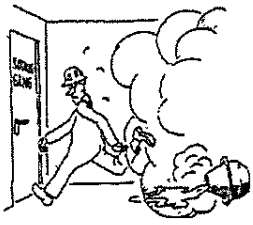
If oxygen deficiency occurs due to the presence of inert gases (e.g. nitrogen, helium, argon, etc.) a drop in physical/mental efficiency occurs without the person's knowledge; at about 11 % oxygen concentration in air (instead of the normal 21 % concentration) fainting occurs without any prior warning.

Below this 11 % concentration there is a very high risk that death due to asphyxiation will occur within a few minutes, unless resuscitation is carried out immediately!

See also EIGA Safety Newsletter **NL/77 Campaign against Asphyxiation**

2 Causes of oxygen deficiency

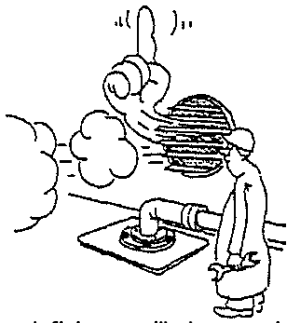
a) When liquefied gases (such as liquid nitrogen, liquid argon, or liquid helium) evaporate, one litre of liquid produces approximately 600 to 850 litres of gas. This enormous gas volume can very quickly lead to oxygen deficiency unless there is adequate ventilation.



b) In the event of gases other than oxygen leaking out of pipe work, cylinders, vessels, etc., oxygen deficiency must always be expected. Checks should be made periodically for possible leaks.

Spaces with limited or inadequate ventilation (e.g. vessels) must not be entered unless air analysis has been made, safe conditions are confirmed and a work permit has been issued.

c) If work has to be carried out in the vicinity of ventilation openings, vent pipes or vessel man ways for example, personnel must be prepared to encounter gases with low oxygen concentration or without oxygen at all, being discharged from these openings.



d) Oxygen deficiency will always arise when plant and vessels are purged with nitrogen or any other inert gases.

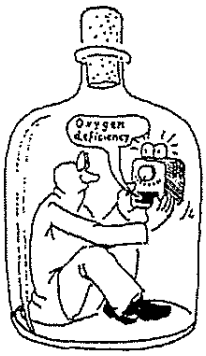
3 Detection of oxygen deficiency

HUMAN SENSES CANNOT DETECT OXYGEN DEFICIENCY

Measuring instruments give an audible or visual alarm of oxygen concentration and can indicate the oxygen content.

These instruments should always be tested in the open air before use.

If the presence of toxic or flammable gases is possible, specific instruments should be used.



4 Breathing equipment

Breathing equipment must be used in situations where oxygen deficiency has to be expected and which cannot be remedied by adequate ventilation.

Cartridge gas masks necessary for use in the presence of toxic gases (such as ammonia, chlorine, etc.) are useless for this purpose.

Recommended types of breathing equipment are:
- Self contained breathing apparatus using compressed air cylinders;
- Full-face masks with respirator connected through a hose to a fresh air supply.

NOTE:

- It should be born in mind that when wearing these apparatus, particularly with air filled cylinders, it might sometimes be difficult to enter manholes.
- Periodic inspection of the correct functioning of the equipment shall be carried out in accordance with local regulations.
- Users shall be trained and shall practice handling of the equipment regularly.

5 Confined spaces, vessels, etc.

Any vessel or confined space where oxygen deficiency is expected and which is connected to a gas source shall be disconnected from such a source:

By the removal of a section of pipe; or
by inserting a blanking plate before and during the entry period.

Reliance on the closure of valves alone might be fatal.

A space or vessel should be thoroughly ventilated, and the oxygen content shall be measured periodically before and during entry period.

If the atmosphere in such a vessel or space is not breathable, a qualified person shall use breathing equipment.

Permission to enter such a space shall be given **only after** the issue of an **entry permit** signed by a **responsible** person.

As long as a person is in a vessel or confined space, a watcher shall be present and stationed immediately outside of the confined entrance.

He shall have a self-contained breathing apparatus readily available.

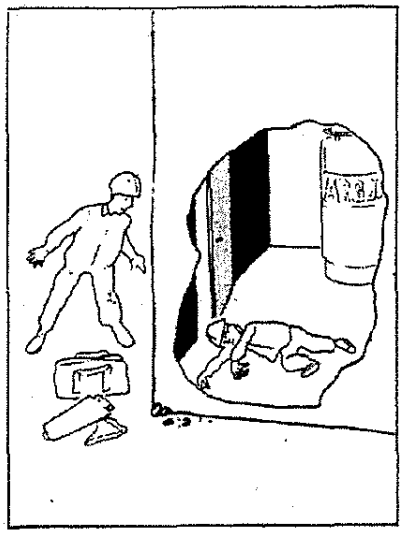
The person inside the confined space to facilitate rescue shall wear a harness and rope. The duty of the watcher should be clearly defined. A hoist may be necessary to lift an incapacitated person.

6 Emergency Measures

In the event of a person having fainted due to oxygen deficiency, he can only be rescued if the rescue personnel are equipped with breathing apparatus enabling them to enter the oxygen deficient space without risk.

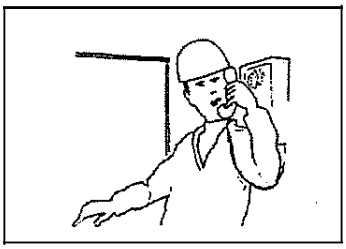
Remove the patient to the open air and administer oxygen without delay from an automatic resuscitator if available or supply artificial respiration. Guidelines and instructions for resuscitation can be obtained from the European Resuscitation Council (Internet Homepage: www.erc.edu).
Continue until patient revives or advised to stop by qualified medical personnel.

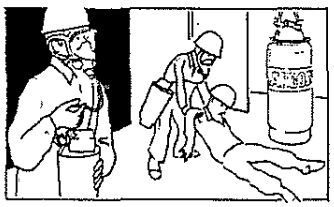
Appendix B1: Rescue considerations from normally accessible rooms

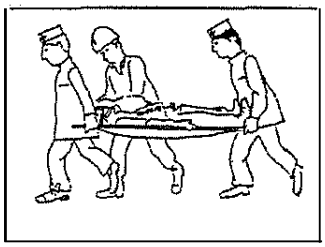


Planned Rescue Scenario:
If work is undertaken **on inert gas or cryogenic liquid systems within an enclosed room** it is suggested that:

- The entrant carries a personal oxygen monitor in addition to any fixed systems as the oxygen concentration may vary within the room if ventilation is absent or inadequate for the leak rate.
- The atmosphere within the space is checked before entry
- A stand-by watch is posted outside the space, to keep visual and verbal contact with the entrant and to ensure the entrant leaves the room unaided in case of early symptoms of oxygen deficiency
- The stand-by watch can raise an alarm by telephone or radio on event of problems
- The stand-by watch has Self Contained Breathing Apparatus (SCBA) ready so that he can safely enter the enclosed room to go to the assistance of, or to extract the victim if necessary.
- Unless a plan is in place so that the entrant can be safely removed by the standby-watch alone, then the rescue team should have been warned of the confined space entry work in progress, and be ready with Self Contained Breathing Apparatus (SCBA) and other equipment so that they can safely enter the Confined space to go to the assistance of, or to extract the victim if necessary.
- Plans have been made to obtain treatment/assessment from qualified medical personnel for the victim as soon as possible after he is retrieved from the room.





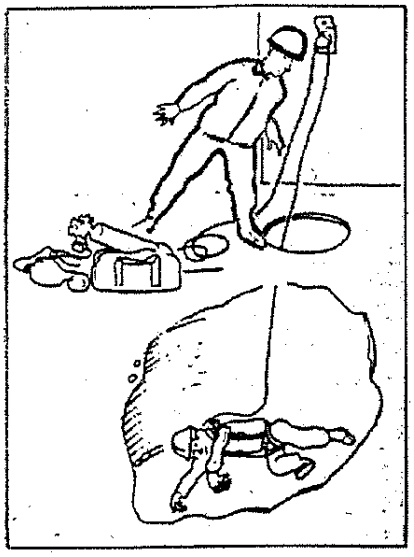


Unplanned Rescue Scenario:
If a person is found collapsed in a room where there is a potential inert gas leak / oxygen deficient atmosphere, then the discoverer must assume that **his life is at risk** entering the same area.
He should raise an alarm and call for assistance so that a prepared rescue can be carried out.

ONLY if the collapsed person can be reached, from outside the room should any consideration be given to extracting the victim from the space and bringing him out to fresh air and medical attention.

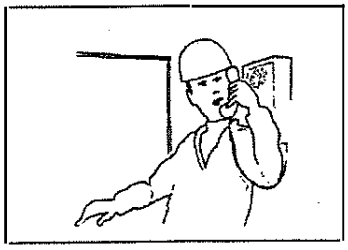
IF the victim has collapsed as a result of an oxygen deficient atmosphere and been there for any length of time it is very likely that he is dead and the discoverer's life is risked in vain.

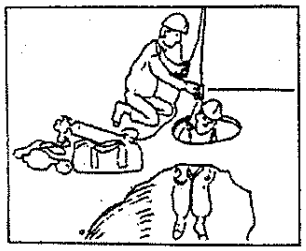
Appendix B2: Rescue considerations from Confined Spaces

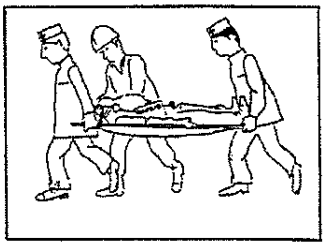


Planned Rescue Scenario:
If work is undertaken within a **Confined Space** such as a vessel or a difficult access space, with potential inert gas/ oxygen deficient atmosphere, it is essential that:

- The atmosphere within the space is made safe, ventilated and checked before entry
- The entrant carries a personal oxygen monitor.
- If practical the entrant wears a body harness with life line, so that he can be removed from the space by persons outside. A hoist or other mechanical aid may be needed
- A stand-by watch is posted outside the space, to keep visual and verbal contact with the entrant and to ensure the entrant exits the Confined Space if symptoms of oxygen deficiency are suspected or observed
- The stand-by watch can raise an alarm to call a trained rescue team by telephone or radio on event of problems
- The rescue team should have been warned of the confined space entry work in progress, and be ready with Self Contained Breathing Apparatus (SCBA) and other equipment so that they can safely enter the Confined space to go to the assistance of, or to extract the victim if necessary.
- The stand-by watch should never enter the Confined Space.
- Plans have been made to obtain treatment/assessment from qualified medical personnel for the victim as soon as possible after he is retrieved from the room.





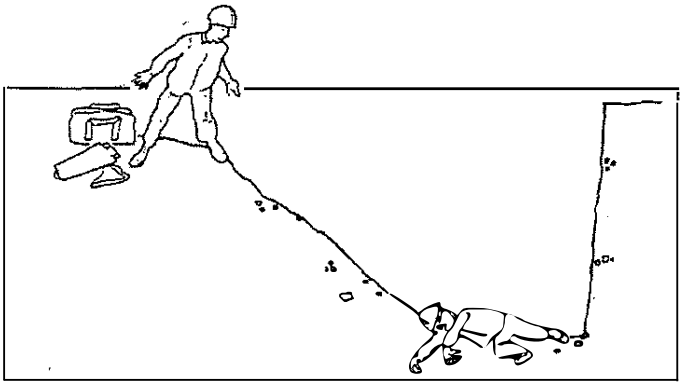


Unplanned Rescue Scenario:
All Confined Spaces shall be closed or barricaded to prevent unauthorised access. There should be no possibility for uncontrolled entry into the Confined Space, so the "unplanned rescue" situation should not occur!

If however a person is found collapsed in a Confined Space where there is a potential inert gas / oxygen deficient atmosphere, then the discoverer must assume that **his life is at risk** entering the same area. He must raise an alarm and call for assistance so that a prepared rescue can be carried out.

IF the victim has collapsed as a result of an oxygen deficient atmosphere and been there for any length of time it is very likely that he is dead and the discoverer's life is risked in vain.

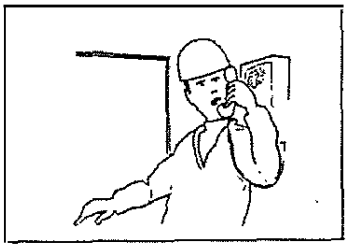
Appendix B3: Rescue considerations from pits, trenches

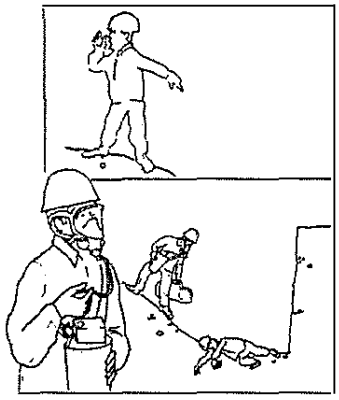


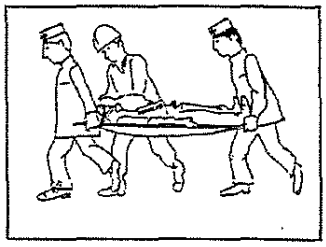
Planned Rescue Scenario:

If work is undertaken in an **excavation, trench, pit**, or other open spaces with potential inert gas / oxygen deficient atmosphere, it is strongly recommended that:

- The atmosphere within the space is checked before entry
- The entrant carries a personal oxygen monitor, as the oxygen concentration may vary within the space if there is limited fresh air circulation.
- A stand-by watch is posted outside the space, to keep visual and verbal contact with the entrant and to ensure the entrant exits the area unaided if symptoms of oxygen deficiency are suspected or observed.
- The stand-by watch can raise an alarm to call a trained rescue team by telephone or radio on event of problems.
- The stand-by watch has Self Contained Breathing Apparatus (SCBA) ready IF it is practical for him enter the enclosed room to go to the assistance of, or to extract the victim alone. OR
- The rescue team should have been warned of the confined space entry work in progress, and be ready with Self Contained Breathing Apparatus (SCBA) and other equipment so that they can safely enter the space to extract the victim if necessary
- Plans have been made to obtain treatment/assessment from qualified medical personnel for the victim as soon as possible after he is retrieved from the room.







Unplanned Rescue Scenario:
If a person is found collapsed in a trench, pit or other space where there is a potential inert gas leak / oxygen deficient atmosphere, then the discoverer must assume that **his life is at risk** entering the same area. He should raise an alarm and call for assistance so that a prepared rescue can be carried out.

IF the victim has collapsed as a result of an oxygen deficient atmosphere and been there for any length of time it is very likely that he is dead and the discoverer's life is risked in vain.
In addition it will often require several people to remove a victim from these kinds of spaces.

Appendix C: Accidents involving oxygen deficiency

The following list highlights real accidents recorded by EIGA, some of them very recent. The list illustrates how essential it is to regularly draw the attention of our personnel, as well as that of our customers, to the hazards of inert gases and oxygen deficiency.

1. A new pipeline in a trench was being proof tested with nitrogen. A charge hand entered the trench to investigate the cause of an audible leak. He was overcome by nitrogen and died.

2. A workman was overcome by lack of oxygen after entering a large storage tank, which had been inerted with nitrogen. Two of his workmates, who went to his aid, without wearing breathing equipment, were also overcome and all three died.

3. A man was overcome on entering a steel tank which had been shut up for several years. The atmosphere inside the tank was no longer capable of supporting life due to removal of oxygen from the air by the rusting of steel.

4. A worker from a contractor company had to carry out welds inside a vessel. The vessel had been under a nitrogen blanket, but was ventilated with air before work started. In order to be on the safe side, the welder was asked to wear a fresh air breathing mask. Unfortunately a fellow worker connected the hose to a nitrogen line and the welder died from asphyxiation.

   This accident happened because the nitrogen outlet point was not labelled and had a normal air hose connection.

5. Welding work with an argon mixture was performed inside a road tanker. During lunchtime the welding torch was left inside the tank, and as the valve was not properly closed, argon escaped. When the welder re-entered the tank, he lost consciousness, but was rescued in time.

   Equipment that is connected to a gas source, except air, must never be left inside confined spaces during lunch breaks, etc. Merely closing the valves is not a guarantee against an escape of gas. If any work with inert gas is carried out in vessels, etc. take care with adequate ventilation or the use of proper breathing equipment.

6. A driver of a small-scale liquid nitrogen delivery service vehicle was making a delivery. He connected his transfer hose to the customer-installed tank, which was situated in a semi-basement. After he had started to fill, one of the customer's employees told him that a cloud of vapour was forming around the tank. The driver stopped the filling operation and returned to the area of the tank to investigate. On reaching the bottom of the stairs, he collapsed, but fortunately he was seen by one of the customer's staff that managed to put on breathing apparatus, go in and drag the man to safety. The driver fully recovered.

   Unknown to the driver, the bursting disc of the storage tank had failed prior to the start of his fill and as soon as he started filling, nitrogen escaped in the vicinity of the storage tank. The oxygen deficient atmosphere overcame him when he went down to investigate without wearing his portable oxygen monitor, which would have warned him of the oxygen deficiency. The installation had been condemned and was no longer being used. Not only was the tank situated in a semi-basement, but the relief device was also not piped to a safe area.

7. During a routine overhaul of an air separation plant, a maintenance technician had the task of changing the filter element on a liquid oxygen filter. The plant was shut down and a work permit was issued each day for each element of work. In spite of these precautions, the technician collapsed when he inadvertently worked on the filter after it had been purged with nitrogen. The fitter collapsed apparently asphyxiated by nitrogen. All efforts to revive him failed.

8. At a cryogenic application, the equipment pressure relief valve located on the equipment **inside** the building opened because the pressure in the storage tank **outside** increased above the setting of the equipment pressure relief valve. Personnel about to enter the room the next morning were warned by the frosted appearance and did not enter.

9. A customer was supplied with 2 low temperature-grinding machines, which were located in the same area in the factory. The customer installed a joint nitrogen extraction system between the two machines. One machine was switched off for cleaning while the other machine was left running. One of the operators who had entered the unit for cleaning fell unconscious and was asphyxiated before help arrived. The linked extraction system had allowed exhausted nitrogen from the operating machine to flow into the unit to be cleaned.

10. A driver was fatally asphyxiated during commissioning of a nitrogen customer station. The customer station tank was located in a pit that was not recognized as a confined space by the design team, distribution operation team or the driver. The driver was sent to do the commissioning by himself.
    During the commissioning the driver made a mistake in opening the liquid supply line valve, instead of the gas vent valve, for purging and cool down of the tank. It is believed he did not immediately notice the valving error partially due to a modified manifold that allowed gas to vent from an uncapped drain in the liquid supply line. When the driver opened the valve gas started venting as would normally occur except from the wrong location. Once he noticed that liquid rather than gas venting, he went into the pit to correct the valving error. At this point he walked into a nitrogen rich/oxygen deficient atmosphere.

11. A group of workers were routinely working at the in-feed end of a tunnel freezer. As the temperature of the tunnel was approaching the desired set point, a new operator noticed that there was a cloud of N_2 gas coming out at exit end of the freezer. He suddenly increased the speed of the scroll fan in order to remove the gas from exit to product entrance. The exhaust and scroll fans were running on manual mode. As a result, the N_2 cloud moved to product entrance and five workers who were working around the loading table passed out. Fortunately, there were no serious injuries and all of them returned to work after taking a rest.

12. On an ASU still in commissioning phase three painters from a sub-subcontractor were working on a ladder to complete external painting works on nitrogen/water tower. To complete the painting of top tower section a wooden plank was put across the exhaust section to atmosphere. One painter climbed on the plank, surrounded by the nitrogen stream, and fell off inside the tower. The two other painters rushed from the ladder to the plank to rescue their team mate. Both collapsed into the tower as well. The three painters died before they could be rescued.

13. An experienced contractor was used to purge a natural gas pipeline, 0.5m diameter 10 km long, with nitrogen before start-up. When one contractor employee and two customer employees entered the remotely located chamber, they were asphyxiated and later found dead in the chamber. Two blind flanges were leaking and the oxygen monitor was not used.

14. A customer nitrogen tank, volume 10 m^3, on a PSA plant was to be inspected by the competent body. The inspector entered the tank and lost consciousness immediately. Two persons from the gas company participating in the inspection managed to bring the inspector out without entering the tank. The inspector recovered.

15. A liquid CO_2 tank was installed. The tank should be purged with air but mistakenly the hose was connected to nitrogen. The tank manhole was situated 4 m above ground. For reasons unknown, a contract employee brought a ladder, entered the tank and was asphyxiated. Previously that morning employees had been told not to enter the tank before the atmosphere was officially checked.

16. Employee stepped into a control cubicle where the instrument air was temporarily replaced with N2 during shutdown. The green light outside the door was on indicating safe atmosphere. As soon as he stepped into the cubicle his personal O_2 monitor alarmed indicating 18% O_2 or less. After exiting safely he opened the door and when O_2 level was OK, checked the fan. The ventilation fan was not running. The light was wrongly wired.

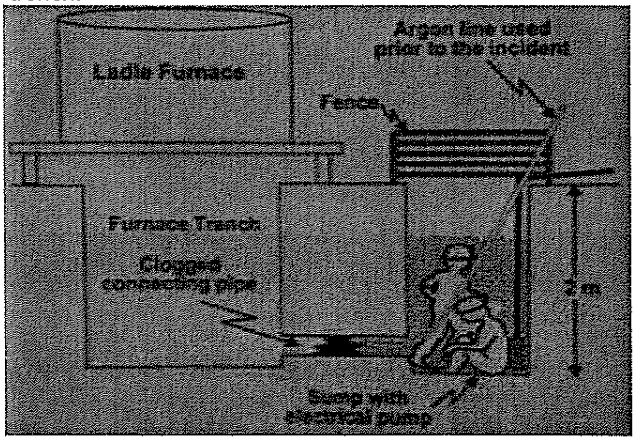
17. The perlite in a storage tank under erection had to be emptied by a contractor company, familiar with this job. During this work one of the workers fell down in the perlite, depth approximately 3m, and was asphyxiated.

18. During the cleaning and painting maintenance of the internal and external surfaces of a water tank, one operator suffered anoxia due to nitrogen being used to purge the vessel instead of air. Two employees tried to rescue the victim and fainted. These two operators were rescued and transported to hospital for intensive care however the original operator died.

19. During the installation of a new LIN phase separator on LIN pipe work at a customer site, a technician went into the roof space. His personal oxygen-monitoring device began to alarm immediately, indicating low oxygen levels. The technician left the roof space immediately and informed the customer. Later in the same week, the customer owned food-freezing machinery was operating, and a project engineer measured concentrations far below 19% in the production room. He left the room, asked all subcontractors to stop work and leave the room, and informed the customer. Investigation showed that the customer had not connected the exhaust ducting to the food-freezing machine that they owned and installed. The exhaust pipes ended in the attic space, not being extended to the atmosphere. Customer had "bridged" the alarm/trip output so LIN supply would not be shut off by low O_2 concentrations.

20. An experienced site employee wanted to take some photographs to add to a report concerning production problems relating to problems with leaks in the argon condenser. In the control room he asked a Contractor to accompany him to take photographs of equipment in the cold box. One hour later the two men were found unconscious in a manhole access to the cold box. Emergency authorities were called and declared the two men dead.

21. Two people on a customer's site were asphyxiated and died whilst attempting to unblock a pipe, using Argon gas in a confined space. The use of Argon gas in this application is not authorised. The incident took place in a sump 2 metres below ground level, which is used to drain water from a nearby trench.



22. An air compressor that provided instrument air to an acetylene plant and for breathing air failed. A back-up nitrogen supply from a liquid cylinder was connected to the piping system to replace the function of the air compressor. An operator put on a full respiratory face mask to load Calcium Carbide into the hopper and inhaled nitrogen. He died.

Appendix D: Hazard of inert gases sign

DANGER OF DEATH

Potential Asphyxiating Atmosphere

Safety Bulletin
U.S. Chemical Safety and Hazard Investigation Board

HAZARDS OF NITROGEN ASPHYXIATION

No. 2003-10-B | June 2003

Introduction

Every year people are killed by breathing "air" that contains too little oxygen. Because 78 percent of the air we breathe is nitrogen gas, many people assume that nitrogen is not harmful. However, *nitrogen is safe to breathe only when mixed with the appropriate amount of oxygen.*

These two gases cannot be detected by the sense of smell. A nitrogen-enriched environment, which depletes oxygen, can be detected only with special instruments. If the concentration of nitrogen is too high (and oxygen too low), the body becomes oxygen deprived and asphyxiation occurs.

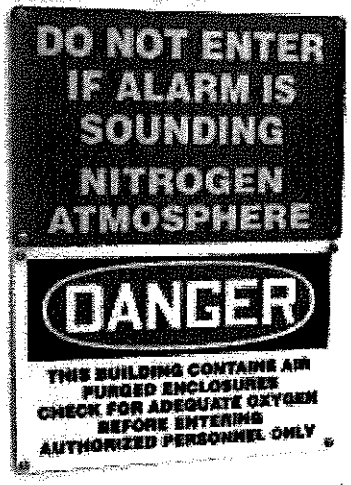
This Safety Bulletin is published to bring additional attention to the continuing hazards of nitrogen asphyxiation.[1]

- Nitrogen is widely used commercially. It is often used to keep material free of contaminants (such as oxygen) that may corrode equipment, present a fire hazard, or be toxic.
- Nitrogen asphyxiation hazards in industry resulted in 80 deaths from 1992 to 2002. These incidents occurred in a variety of facilities, including industrial plants, laboratories, and medical facilities; almost half involved contractors.
- Good practices and awareness of hazards minimize the risk of nitrogen asphyxiation (Figure 1).

Many incidents reviewed by CSB were caused by inadequate knowledge of the hazard or inadvertent use of nitrogen rather than breathing-air delivery systems.

This bulletin focuses only on the hazard of asphyxiation, though nitrogen also presents cryogenic and high-pressure hazards.

* Figure 1. Sign warning of nitrogen hazard.



Commercial Uses of Nitrogen

One of the most important commercial uses of nitrogen is as an inerting agent to improve safety. Nitrogen is inert under most conditions (i.e., it does not react with or affect other material).

It is often used to keep material free of contaminants, including oxygen— which can corrode equipment or present a fire and explosion hazard when in contact with flammable liquids or combustible solids. In such cases, a flow of nitrogen is maintained in a vessel to keep oxygen out. Nitrogen is also used to purge air from equipment prior to introducing material, or to purge flammable or toxic material prior to opening equipment for maintenance.

In industrial and commercial settings where a nitrogen-enriched environment may present a hazard, such as when using supplied air or working in or around spaces that are confined,

[1] In 1998, the U.S. Chemical Safety Board (CSB) investigated a nitrogen asphyxiation incident that occurred in Hahnville, Louisiana. As part of that investigation, CSB reviewed the prevalence of asphyxiation incidents.

precautions must be taken to ensure that sufficient oxygen is provided to personnel.

* Nitrogen is safe to breathe only when mixed with the appropriate amount of oxygen.

Effects of Oxygen-Deficient Atmosphere

Nitrogen is not a "poison" in the traditional sense. It presents a hazard when it displaces oxygen, making the atmosphere hazardous to humans. Breathing an oxygen-deficient atmosphere can have serious and immediate effects, including unconsciousness after only one or two breaths. The exposed person has no warning and cannot sense that the oxygen level is too low.

The Occupational Safety and Health Administration (OSHA) requires employers to maintain workplace oxygen at levels between 19.5 and 23.5 percent. As shown in the table on page 3, the human body is adversely affected by lower concentrations.

As the oxygen concentration falls below 16 percent, the brain sends commands to the breathing control center, causing the victim to breathe faster and deeper. As the oxygen level continues to decrease, full recovery is less certain. An atmosphere of only 4 to 6 percent oxygen causes the victim to fall into a coma in less than 40 seconds. Oxygen must be administered within minutes to offer a chance of survival. Even when a victim is rescued and resuscitated, he or she risks cardiac arrest.

* In industrial and commercial settings where a nitrogen-enriched environment may present a hazard, . . . precautions must be taken to ensure that there is sufficient oxygen in the atmosphere.

* Nitrogen . . . presents a hazard when it displaces oxygen.

Statistics on Nitrogen Asphyxiation

From reported data for the United States, CSB identified 85 nitrogen asphyxiation incidents that occurred in the workplace between 1992 and 2002. In these incidents, 80 people were killed and 50 were injured.[2]

Profile of Affected Industries and Activities

Of the 85 incidents reported, 62 percent occurred in chemical plants and refineries, food processing and storage facilities, metal and manufacturing operations, and other industrial, maritime, and manufacturing sites, including nuclear plants.

Approximately 13 percent of the incidents involved maintenance

CSB Safety Bulletins offer advisory information on good practices for managing chemical process hazards. Case studies provide supporting information. Safety Bulletins differ from CSB Investigation Reports in that they do not comprehensively review all the causes of an incident.

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[2] Data sources for the CSB review include regulatory agencies, media reports, technical publications, and contacts with safety personnel; however, only those incidents that were reported and accessible are represented. Although the summary data reported above are not all-inclusive, the numbers clearly indicate that nitrogen asphyxiation presents a serious hazard in the workplace. Statistical analysis is based on available, limited information.

Effects of Oxygen Deficiency on the Human Body

Atmospheric Oxygen Concentration (%)	Possible Results
20.9	Normal
19.0	Some unnoticeable adverse physiological effects
16.0	Increased pulse and breathing rate, impaired thinking and attention, reduced coordination
14.0	Abnormal fatigue upon exertion, emotional upset, faulty coordination, poor judgment
12.5	Very poor judgment and coordination, impaired respiration that may cause permanent heart damage, nausea, and vomiting
<10	Inability to move, loss of consciousness, convulsions, death

SOURCE: Compressed Gas Association, 2001.

* CSB identified 85 nitrogen asphyxiation incidents that occurred in the workplace between 1992 and 2002 . . . 80 people were killed and 50 were injured.

activities, such as railcar and tank truck cleaning, painting, maintenance, and repair. These incidents are categorized as "maintenance" because incident reports do not include enough information on the type of industrial setting; they could have occurred at manufacturing sites, which would increase the 62 percent estimate above.

Likewise, trenches and manholes—not specifically identified as being in manufacturing facilities—account for about 14 percent of the incidents. The remainder of the incidents occurred in laboratories and miscellaneous industries, such as medical and transportation.

The data show that employees and contractors alike are victims of asphyxiation. Of the 85 incidents reviewed, 42 involved contractors, including construction workers;

* Of the 85 incidents reviewed, 42 involved contractors, including construction workers; these 42 incidents account for over 60 percent of the fatalities.

* . . . 130 workplace fatalities and injuries occurred from breathing nitrogen-enriched air. Over 60 percent of these victims were working in or next to a confined space.

these 42 incidents account for over 60 percent of the fatalities.

Causal Information

From the CSB data, a combined total of 130 workplace fatalities and injuries occurred from breathing nitrogen-enriched air. Over 60 percent of these victims were working in or next to a confined space.[3,4]

One characteristic of a confined space is its capability to contain an atmosphere that may be totally different from outside air. Confined spaces in manufacturing sites typically include equipment such as reactors, vessels, tanks, and boilers. Other such spaces are railcars, trenches, and areas accessible by manholes.

[3] "Next to a confined space" means that a person's breathing zone is affected by the atmosphere emanating from the space. The person may be standing in the immediate area but not actually in the space.

[4] According to OSHA, a confined space can be entered to perform work, has limited means of egress, and is not designed for continuous employee occupancy. A "permit-required confined space" includes a space that contains or has the potential to contain a serious safety or health hazard, such as a hazardous atmosphere.

Failure to Detect Oxygen-Deficient Atmosphere

Failure to detect an oxygen-deficient (nitrogen-enriched) atmosphere was a significant factor in several incidents.

In the data evaluated for this study, 67 of the 85 incidents involved circumstances where personnel were in or around a confined area—such as a railcar, room, process vessel, or tank (Figure 2)—and nitrogen was initially present in high levels or later collected in the area. These incidents accounted for 62 fatalities and 33 injuries. In each of the 67 incidents, personnel failed to detect elevated levels of nitrogen and take appropriate precautions.

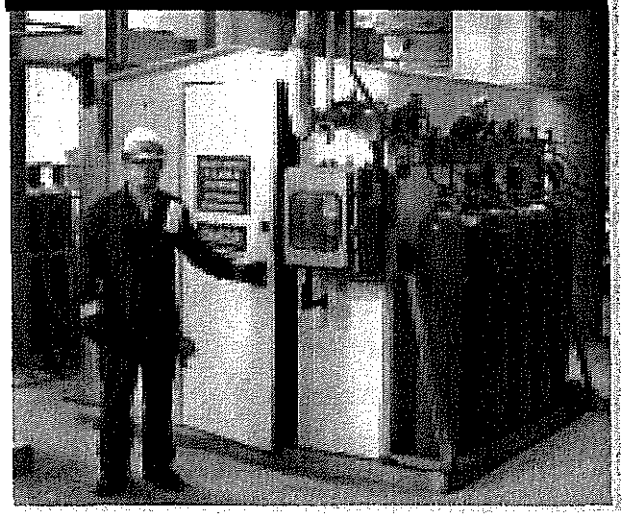
When fatalities and injuries occurred in "open areas" (including areas with ventilation, laboratories, buildings, and outside in the vicinity of equipment), the hazard of asphyxiation was not expected and personnel were typically caught off guard. In some cases, personnel unknowingly created a nitrogen-enriched atmosphere by mistakenly using nitrogen instead of air to flush equipment prior to entry. In either situation, inadequate knowledge of the hazard and failure to detect additional nitrogen resulted in a fatal concentration of gas.

* When fatalities and injuries occurred in "open areas" . . . the hazard of asphyxiation was not expected and personnel were typically caught off guard.

Mix-Up of Nitrogen and Breathing Air

Confusing nitrogen gas with air and problems with breathing-air delivery systems accounted for 12 of the 85 incidents, and approximately 20 percent of fatalities.

* Figure 2. Confined area.



The data provide examples of workers inadvertently using nitrogen instead of air because of interchangeable couplings on lines and poor or nonexistent labeling.

In one incident, a worker mistakenly used nitrogen instead of air to purge a confined space. An inert atmosphere was unexpected and undetected. One worker was killed, and a colleague also died while attempting rescue. In another case, workers inadvertently connected the hose for their breathing-air respirator to a pure nitrogen line.

* In one incident, a worker mistakenly used nitrogen instead of air to purge a confined space . . . In another case, workers inadvertently connected the hose for their breathing-air respirator to a pure nitrogen line.

Fatalities and Injuries During Attempted Rescue

One of the most difficult issues concerning hazardous atmosphere emergencies is the human instinct to aid someone in distress. Approximately 10 percent of fatalities from the CSB data were due to attempts to rescue injured persons in confined spaces.

* Approximately 10 percent of fatalities from the CSB data were due to attempts to rescue injured persons in confined spaces.

Asphyxiation Hazards Outside Industry and Effect on General Public

Asphyxiation hazards may also be present outside industry, especially among people who use breathing air, such as firefighters, divers, and medical patients. Statistics on these types of incidents are difficult to collect and are not included in this bulletin, though one such case is summarized below.

Selected Case Studies

Failure to Recognize Asphyxiation Hazards Near Confined Spaces

Employee Dies After Partially Entering a Nitrogen-Purged Tank

Two coworkers and the victim were cleaning filters in a hydrogen purifying tank. The tank was partly purged with nitrogen to remove internal dust particles. The victim used a lift to access the *external* area of the upper tank, which was fitted with a manway. As he leaned into the tank opening, his coworkers noticed that he was not responding to their communication. They found the victim unconscious, and he later died as a result of oxygen deficiency.

Employee Overcome While Testing Atmosphere

An operator was conducting a flammable gas test on a tower feedline that discharged into a low-pressure flare gas header. The test was required for a hot work permit to take flash photos.

The chief operator issued a work permit that required a supplied-air respirator. Two contractor pipefitters wore respirators and removed the safety valve. The operator, however, wore no respiratory protection. After climbing the scaffold, he was overcome by nitrogen gas from the open flare line before he could complete atmospheric sampling.

The operator backed away, turned, and slumped to his knees. He was disoriented and briefly lost consciousness. An investigation concluded that the incident was due to elevated levels of nitrogen gas that had inadvertently entered the flare system.

Inadequate Monitoring of Atmosphere

Contractor Asphyxiated Inside Tank Car

White mineral oil in a tank car at an oil refinery was offloaded by injecting nitrogen gas into the car. An employee of a railcar cleaning company was asphyxiated while cleaning the nitrogen-filled tank car.

Corrupt Breathing Air Supply

Two Laborers/Painting Contractors Asphyxiated

Two painting contractors were abrasive-blasting tubes inside a boiler at a chemical plant. They each wore supplied-air respirators connected to a 12-pack cluster of compressed air cylinders. Another subcontractor monitored the work outside the confined space.

Work proceeded normally throughout the night shift; however, at 3:00 am, the attendant got no response after repeatedly sounding the air horn. When another contractor employee was sent into the boiler to assess the situation, he found the two men lying on opposite ends of the scaffolding.

When the plant health, safety, and environmental department tested the compressed air 12-pack, they found that it contained less than 5 percent oxygen. The "air" had been manufactured with too low a

concentration of oxygen. (Note: This fatal incident prompted OSHA to issue a safety alert on the batch of breathing air.)

Mix-Ups Between Nitrogen and Air

Three Employees Asphyxiated in Coating Tank

The atmosphere inside a coating tank was tested and ventilated the day before work was to be performed. On the following day, a contractor entered the tank to clean it and collapsed. Two plant employees entered to attempt rescue, but they were also overcome.

The tank had been ventilated with what was thought to be compressed air but was actually nitrogen. The atmosphere was not tested prior to beginning work. All three men were asphyxiated.

Employee Killed by Overexposure to Pure Nitrogen

A contractor planned to use an air-powered hammer to chip residue from a furnace in an aluminum foundry. He wore an airline respirator. Of two compressed gas lines with fittings, one was labeled "natural gas" and the other had an old paper tag attached with "air" handwritten on it. However, this line actually contained pure nitrogen.

A splitter diverted one part of the gas stream to the air hammer and the other part to the airline respirator. Once the respirator was in place, the worker breathed pure nitrogen and was asphyxiated.

Four Killed and Six Injured in Nursing Home

A nursing home routinely ordered large pure oxygen compressed gas cylinders for residents with respiratory system diseases. The supplier mistakenly delivered one cylinder of pure nitrogen with three cylinders of oxygen; a nursing home maintenance employee mistakenly accepted the nitrogen tank.

Another maintenance employee took this cylinder, which had a nitrogen label partially covering an oxygen label, to connect it to the oxygen supply system. The tank was fitted with nitrogen-compatible couplings. The employee removed a fitting from an empty oxygen cylinder and used it as an adapter to connect the nitrogen tank to the oxygen system. Four deaths and six injuries occurred as a result of pure nitrogen being delivered to the patients.

Good Practices for Safe Handling of Nitrogen

Implement Warning Systems and Continuous Atmospheric Monitoring of Enclosures

The atmosphere in a confined space or small enclosed area may be unfit for breathing prior to entry, or it may change over time, depending on the type of equipment or work being performed. Recognizing this hazard, good practice calls for continuous monitoring of a confined space to detect oxygen-deficient, toxic, or explosive atmospheres. The entire confined space should be monitored—not just the entry portal.

* The atmosphere in a confined space or small enclosed area may be unfit for breathing prior to entry, or it may change over time . . .

Warning and protection systems include flashing lights, audible alarms, and auto-locking entryways to prevent access. Such devices, if properly installed and

maintained, warn workers of hazardous atmospheres. Personal monitors can measure oxygen concentration and give an audible or vibration alarm for low oxygen concentrations.

* Good practice calls for continuous monitoring of a confined space to detect oxygen-deficient, toxic, or explosive atmospheres.

Ensure Ventilation With Fresh Air

Because the atmosphere of a confined space or small/enclosed area often changes during the course of work, it is essential to maintain continuous forced draft fresh-air ventilation before the job begins through to completion. Areas with the potential to contain elevated levels of nitrogen gas should be continuously ventilated prior to and during the course of the job.

Ventilation is also required in rooms and chambers into which nitrogen may leak or vent. In a few of the study cases, people who were simply working close to the nitrogen-containing confined space, room, or enclosure were asphyxiated.

Systems must be in place to properly design, evaluate, and maintain ventilation systems. A warning system will alert workers of a dangerous atmosphere. Personnel should be trained on how to properly respond and evacuate in the event of failure of the system.

Implement System for Safe Rescue of Workers

Rescue may be necessary in the event of continuous monitoring, ventilation failure, or another emergency condition. The ability to immediately retrieve immobilized workers is a critical component of confined space entry preplanning.

* It is essential to maintain continuous forced draft fresh-air ventilation before the job begins through to completion.

One method is to attach a body harness and lifeline to personnel entering confined areas. This procedure also benefits potential rescuers because they do not have to enter the confined area to retrieve the victim. However, when a worker enters a pipeline, some furnaces, ducts, or other narrow-diameter confined spaces, pulling on a line attached to a body harness may cause the person to bunch up and become stuck inside.

Depending on the situation, wristlets or anklets attached to a lifeline and a retrieval mechanism allow the confined space attendant to pull the person out by the arms or legs. The attendant and rescue personnel should be available at all times. Rescuers must have an effective system to communicate with personnel inside enclosures. No one should enter a dangerous atmosphere without proper personal protective equipment.

The last measure of defense requires personnel to actually enter the confined area to retrieve the victim. This approach should be used only when personnel are appropriately trained, have donned rescue equipment, and have dependable breathing air.

Approximately 10 percent of fatalities from the survey data occurred to personnel attempting rescue. These deaths could have been prevented if a reliable retrieval system was in place. Such a system would also prevent many entry worker fatalities because it provides for quickly removing the worker from a dangerous atmosphere to a safe one.

Ensure Uninterrupted Flow and Integrity of Breathing Air

Breathing air must be supplied when workers enter environments where oxygen is or may become deficient. Workers may use either a self-contained breathing apparatus (SCBA) or an airline respirator, which consists of a long hose connecting a breathing air supply to the respirator or hood.

Because a worker using an airline respirator does not control the

* Breathing air must be supplied when workers enter environments where oxygen is or may become deficient.

source of supply, air may suddenly or inadvertently be interrupted. For example, a power failure may stop an air compressor, the air supply may simply run out, or the supply hose may become twisted or obstructed (e.g., by a vehicle). When supplied air is used, facility management systems must protect against interruption of airflow and provide alternate sources of power for the compressors.

A comprehensive management system includes the following:

- Continuous monitoring of air supply.
- Routine inspection and replacement of supplied-air hoses.
- Restriction of vehicular traffic in the area of supply hoses.

When using supplied air, a worker should carry a small backup cylinder (escape pack)—attached to a different supplied-air system—with enough breathing air to last 5 to 10 minutes.

Breathing air is manufactured either by purifying and compressing air or by mixing nitrogen and oxygen to the appropriate ratio. A breathing-air compressor and its hoses should be specifically manufactured for and dedicated to breathing-air systems. The compressor should have a moisture trap, an oil trap, and a carbon monoxide sensor and alarm. When breathing air is manufactured by mixing nitrogen and oxygen, the pressure of the cylinders during filling must be known to ensure that the correct amounts are mixed. The final product must be tested to ensure its integrity.

Prevent Inadvertent Mix-Up of Nitrogen and Breathing Air

To prevent interchanging compressed nitrogen with compressed industrial grade air or compressed breathing-quality air, specific fittings should be used for each cylinder. Cylinders for nitrogen, industrial grade air, and breathing-quality air have distinct, incompatible fittings that cannot be cross-connected.

* Personnel should understand that the fittings are *intended* to be incompatible to ensure safety.

Personnel should understand that the fittings are *intended* to be incompatible to ensure safety. Cylinders should be clearly labeled; typical cylinders are shown in Figure 3. Labels on piping systems, compressors, and

* Figure 3. Compressed gas cylinders.

fittings are additional reminders of which gas is contained inside. Color coding also helps to identify systems.

Develop and Implement Comprehensive Training Programs

The good practices for safe handling of nitrogen, described above, are effective only if personnel are trained on the importance of the following:

- Use of ventilation systems, retrieval systems, and atmospheric monitoring equipment—both how to use them and how to determine when they are not working properly.
- Dangers of nitrogen-enriched atmospheres and the systems to

prevent interchanging breathing air and nitrogen.

- Implementing good hazard communication, which includes safe handling of air and nitrogen delivery systems.
- Mandatory safety practices and procedures for entry into confined spaces, such as permits, providing an attendant, monitoring, ventilating, rescue, and contractor oversight.
- Precautions when working around equipment that may contain elevated levels of nitrogen.
- The reason for special fittings on compressed gas cylinders.
- Proper use of air supply equipment.

Training should cover new and revised procedures for confined space entry, and establish measurements for employee proficiency. Contractors as well as employees should be trained.

* Contractors as well as employees should be trained.

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J. clin. Path., **30**, Suppl. (Roy. Coll. Path.), **11**, 181-187

Experimental hypoxic brain damage

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The majority of hypoxic episodes that result in histologically proven damage in the human brain cannot be adequately defined in physiological terms. They are usually accidents so that basic information such as the precise duration of a cardiac arrest or the blood pressure and heart rate during a period of severe hypotension is very rarely available. In such cases, neuropathological descriptions, however exhaustive, may well explain the final neuropsychiatric status of the patient but can at best indicate only tentatively the nature of the episode itself.

The experimental approach is justified if it can indicate whether damage of a particular type in neurones and in white matter is or is not a direct consequence of a particular hypoxic stress adequately delineated in physiological terms.

At the outset it must be recalled that the energy for the normal functioning of the central nervous system is derived from the oxidative metabolism of glucose. A deficiency of oxygen or glucose will impair function and if severe and protracted enough will lead to irreversible brain damage. Interruption of the oxygen supply produces the most rapid impairment of brain function. Thus consciousness is lost about 10 sec after circulatory arrest. Abrupt anoxia exemplified by inhalation of an inert gas or sudden decompression to an altitude above 50 000 ft leads to loss of consciousness after a slightly longer interval (17-20 sec). This rapid loss of consciousness in instances of profound hypoxia may well be responsible for the widely held view that enduring brain damage may begin soon after consciousness is lost.

Types of hypoxia

Before considering the relationships between the known neuropathological patterns in the human brain that are ascribed to hypoxia and their apparent counterparts in the brains of experimental animals, it will be useful to classify the several types of hypoxia. However, it will be shown that there is no justification for the assumption that each type of hypoxia can, *per se*, give rise to brain damage. The original classification of Barcroft (1925) must be modified in the light of subsequent information from human and experimental animals sources as follows:

1 ISCHAEMIC
Blood flow is arrested in the brain as a whole or in the territory of a single artery.

2 OLIGAEMIC
A reduction in blood flow in the brain as a whole or within the territory of a single artery may occur as a result of a greatly reduced cardiac output or major systemic hypotension from any cause.

3 ANOXIC
The arterial oxygen tension is 0 mm Hg. It occurs if inert gases are inhaled, if there is total obstruction of the upper respiratory tract or in the event of sudden exposure to an altitude greater than 50 000 ft (the combined tensions of water vapour and carbon dioxide within the pulmonary alveoli then exceed the ambient pressure and no oxygen can enter the lungs).

4 HYPOXIC
There is some reduction in a pO_2 short of anoxaemia. This occurs in chronic pulmonary disease and in congestive heart disease; when the inspired oxygen is diluted by an inert gas (as in some anaesthetic accidents) and also in exposures to altitudes less than 50 000 ft.

5 ANAEMIC
There is some reduction in the amount of circulating haemoglobin available for combination with oxygen. It can occur after severe haemorrhage, in severe hypochromic anaemia but the commonest apparent cause of anaemic brain damage is carbon monoxide intoxication.

6 HISTOTOXIC
This implies the poisoning of oxidative enzymes within neuronal mitochondria. Cyanide and azide are examples.

7 HYPOGLYCAEMIA
A deficiency of the principal substrate, glucose, *per*

se can also give rise to ischaemic cell change even if the level of arterial oxygenation is normal.

The previous contributors to this section of the Symposium have defined the nature and time course of ischaemic cell change and have pointed out that it is the principal neuronal response to all types of hypoxia in the brains of rodents as well as in those of primates including man. In this survey of the brain damage attributable to hypoxia in all its forms, only the patterns of distribution of ischaemic cell change will be considered with emphasis on the contributions from experimental studies.

1 Ischaemic

Arrest of circulation within a single brain artery results in an infarct which can range in size from the 'total territory' in an anatomical sense to a small volume of tissue close to the point of arterial occlusion. Where the cortex of cerebrum or cerebellum is concerned the extent of infarction is determined by the level of systemic blood pressure at and after the instant of occlusion and, in particular, by the functional efficiency of the leptomeningeal vessels that anastomose with the cortical branches of neighbouring arteries. If these anastomotic systems and the major arteries in the neck and the circle of Willis are normal, the cortical infarct will be small. If one or both are the site of occlusive vascular disease, the infarct will be larger.

It must be borne in mind that the basal ganglia and the internal capsule, in particular, are supplied by end-arteries (penetrating or ganglionic branches of the major cerebral arteries). Occlusion of an arterial trunk proximal to the ganglionic branches produces an infarct in these deeply placed regions of grey and white matter even in the healthy experimental primate. Evidently the retrograde flow of blood from leptomeningeal anastomoses into the arterial stem may never enter all its ganglionic branches or, if it does so, it may be too little and too late to avert irreversible tissue damage. Thus, for example, division of the middle cerebral artery close to its origin from the internal carotid artery in the baboon leaves the sensory and motor cortex intact and cortical infarction is confined to some portion of the insula. A variable hemiparesis involves only the contralateral face and upper limb and its neuropathological basis has been shown to lie entirely within white matter, ie, in the genu and supralentiform portions of the internal capsule, where after a survival of three years there is a sharply circumscribed cystic infarct (Symon and Brierley, 1976). The limited neurological deficit and the small, deeply placed infarct that follow division of the middle cerebral artery in a healthy experimental primate are sharp reminders that such 'models' cannot provide two of the most important factors in the aetiology of 'stroke' in man. These are some impairment in cardiac function (leading to some reduction in cerebral blood flow) and some degree of occlusive vascular disease. These factors, singly or together, account for the extension of the infarct into the centrum semi-ovale and even into the whole of the anatomical cortical territory. It follows, that in the human brain, ischaemic necrosis in some portion of an arterial territory can seldom be explained satisfactorily without careful examination of the myocardium, the coronary arteries and the major arteries of the neck and brain.

Overall or global arrest of the brain circulation leads to a loss of consciousness in eight to 10 sec and the EEG is isoelectric a few seconds later. Respiration fails at about the same time while the heart may continue to beat for a matter of minutes. Neuropathological descriptions of the consequences of circulatory arrest (including 35 personal cases) provide the best examples of the involvement of the 'selectively vulnerable' regions of the brain in hypoxia. Frequently, little of the cerebral cortex is normal but damage is usually greater in the posterior half of each cerebral hemisphere, in the floors of sulci rather than over the crests of gyri and in the third, fifth and sixth layers rather than in the second and fourth. Certain portions of the hippocampus (zones h.1—Sommer sector—and h.3-5,—endfolium) are vulnerable as are the Purkinje cells of the cerebellum. Many sensory nuclei in the brain stem are vulnerable in the infant and young child (Ranck and Windle, 1959; Brierley, 1965, 1976).

Where circulatory arrest has been studied in the experimental animal, it is important to recognize that earlier studies were concerned to define the maximum period of arrest of the cerebral circulation beyond which some degree of irreversible brain damage would occur. Attempts to define such a 'threshold' have been reviewed by Hoff *et al* (1945), Meyer (1963) and Brierley (1976). The general conclusion from these studies has been stated by Schneider (1963) as follows: 'A complete revival without neurological or histological damage cannot be brought about after a complete stop of brain circulation of more than four to five min duration'.

In contrast to the experiments summarized above, certain recent studies have attempted to define a much greater period of circulatory arrest after which there can be some evidence of recovery in at least a neurophysiological sense and histological examination can show that some parts of the brain are normal. Thus Hossmann and Sato (1970) claimed that '... unequivocal signs of neuronal recovery can be detected after complete ischaemia of more than one

hour's duration'. Hirsch *et al* (1975) failed to confirm these results and attributed 'recovery' after such protracted ischaemia in the experiments of Hossmann and Sato (1970 and subsequent studies) to the protective effects of anaesthesia and the progressive fall in temperature that must occur in the isolated head during such periods of time.

It must be emphasized that experimental studies of the effects of circulatory arrest (or any other form of hypoxia) on the brain, whether directed towards the definition of a 'threshold' for a particular hypoxic stress or to the capacity for recovery after an extended period of the same stress, have clinical relevance only if spontaneous respiration has been resumed in the unmedicated animal, and detailed neurological assessments, together with serial recordings of the EEG, have been made during an adequate period of survival. All these are essential for a meaningful appraisal of 'recovery'. Finally, after *in-vivo* perfusion-fixation of the brain, neuropathological examination of the brain must be comprehensive. Unfortunately clinico-pathological studies according to such standards have not yet been reported in support of the claim that 'recovery' of the central nervous system can occur after periods of circulatory arrest far in excess of those hitherto accepted as 'critical' where the inception of minimal brain damage is concerned.

2 Oligaemic hypoxia

A reduction of blood flow in a single artery of the human brain is usually due to a combination of systemic hypotension and occlusive disease in the vessel itself. If flow is sufficiently impaired the outcome will be an infarct involving grey and white matter. Such a local reduction in flow can only be inferred if thrombosis and embolism can be excluded. There are, as yet, no experimental models of this particular situation.

Global oligaemia implies some reduction in the overall flow of blood through the brain. Experimental studies in the Rhesus monkey have shown that, if arterial oxygenation remains normal, cerebral perfusion pressure (mean arterial blood pressure – venous sinus pressure) must be reduced to 25 mm Hg for at least 15 min before brain damage is produced (Brierley *et al*, 1969; Meldrum and Brierley, 1969). However, it was only possible to damage the brain if the profound hypotension was continued beyond the point of apnoea when mechanical ventilation was required in order to maintain a normal arterial oxygen tension. These experiments clearly demonstrated that in the healthy spontaneously breathing primate, global oligaemia *per se* is unlikely to lead to brain damage if respiration does not fail. In these monkeys, typical ischaemic neuronal alterations were not evenly distributed in the cerebral cortex but were restricted to the arterial boundary zones of the cortex of the cerebrum and also of the cerebellum. They were variable in the basal ganglia. The pysiological basis of lesions along arterial boundary zones has been discussed by Zülch and Behrend (1961) and by Meldrum and Brierley (1971). When perfusion pressure falls below 45-50 mm Hg the capacity of the vascular bed to maintain a constant cerebral blood flow (autoregulation) is lost (there is then maximum vasodilatation) and flow becomes directly dependent upon perfusion pressure. The reduction in flow is greatest in the vessels most remote from the arterial stem, ie, at the boundary of each arterial territory.

In the clinical situation, a reduction in brain perfusion pressure while arterial oxygenation remains normal is virtually confined to the technique of hypotensive anaesthesia with controlled ventilation and then only when perfusion pressure through the brain is lowered by excessive head-up tilt (Brierley and Cooper, 1962). The two additional factors that may result in brain damage after a period of relatively moderate hypotension are some degree of hypoxaemia and some element of occlusive disease in the extra- and/or intracranial arteries. The frequency of these two factors in addition to the reduction in brain blood flow due to the initial systemic hypotension is largely responsible for the fact that ischaemic damage along arterial boundary zones of the cortex of cerebrum and cerebellum is the commonest neuropathological outcome of hypoxia in all its forms. It is important to appreciate that no experimental model permitting the introduction and control of oligaemia, hypoxaemia and partial vascular occlusion is yet available.

Previous contributors to this section of the Symposium have emphasized that this 'boundary zone' pattern of brain damage can only be identified if blocks for histological examination are selected with an awareness of the anatomical distribution of the cortical arteries of cerebrum and cerebellum.

3 Anoxic

Anoxia, induced by breathing pure nitrogen, has been studied in human volunteers by Gastaut *et al* (1961) and Ernsting (1963). After a few seconds the EEG shows low voltage activity at 11 to 13 c/s and consciousness is lost at 17 to 20 sec. In experimental animals, longer periods of nitrogen breathing lead, after an initial hyperventilation, to slowing of respiration, bradycardia and a falling blood pressure. Apnoea occurs at about the third minute while blood pressure is still appreciable (5-20 mm Hg) at

the fifth minute (Swann and Brucer, 1949). In the Rhesus monkey, the responses to nitrogen breathing are similar and if mechanical ventilation is begun soon after the 'last breath', the blood pressure rises, spontaneous respiration is resumed and the EEG, previously isoelectric, returns to normal. Subsequent neuropathological examination reveals no brain damage (Brierley and Meldrum, unpublished observations). Evidently the period of anoxaemia and of secondary circulatory impairment is too brief to lead to ischaemic neuronal alterations so that it must be concluded that pure anoxic anoxia cannot produce brain damage.

4 Hypoxic

In spontaneously breathing experimental animals, including primates, the minimal level of arterial oxygen tension that does not lead to early apnoea and cardiac failure is about 20 mm Hg. At this level the cerebral vascular bed is fully dilated, the cerebral A-V oxygen difference is reduced (due to reduced oxygen consumption and increased blood flow) but the EEG is normal. This precarious state can be disturbed by a slight fall in perfusion pressure and the immediate decline in the EEG is evidence of some reduction in cerebral blood flow. This may occur as a consequence of a period of cardiac arrhythmia. A progressive fall in heart rate and blood pressure together with slowing of respiration herald the cardio-respiratory crisis that sets the limit to the period during which the organism can tolerate this level of hypoxia. Where the circulatory failure is concerned the final bradycardia and falling blood pressure may not be a direct effect of hypoxia on the myocardium but a consequence of the stimulation of chemoreceptors in the carotid bodies or brain stem (Cross *et al*, 1963). As blood pressure continues to fall respiration ceases and the EEG becomes isoelectric at about the same time. Adequate resuscitation commenced soon after the 'last breath' can, as after anoxic anoxia, allow the heart to recover, spontaneous respiration to be resumed and the EEG to return to normal. Brain damage is rarely seen and only when there has been a prolonged period of cardiac impairment and an even longer period of isoelectric EEG (Brierley, Prior, Calverley, and Brown—unpublished results). Brain damage in such animals consists of ischaemic neuronal alterations along the arterial boundary zones of the cerebrum and cerebellum and sometimes in the basal ganglia. This pattern of damage, indistinguishable from that seen after oligaemic hypoxia, underlines the fact that systemic hypoxaemia can only bring about brain damage through the medium of a secondary reduction in perfusion pressure.

In the human subject exposed to hypoxia not severe enough to bring about failure of respiration and the heart, the initial increase in cerebral blood flow may be so restricted by occlusive vascular disease in the arteries of the brain and/or neck that ischaemic brain damage may ensue.

5 Anaemic

There is no convincing evidence that a simple reduction in circulating haemoglobin due to severe hypochromic anaemia (iron-deficient or haemolytic) or to haemorrhage can result in brain damage. Carbon monoxide intoxication remains the sole example of anaemic hypoxia (due to the formation of stable carboxyhaemoglobin) that can be associated with ischaemic cell change and also with damage in white matter. The pathology in the human brain has been reviewed by Meyer (1963), Lapresle and Fardeau (1966) and Brierley (1976). Ischaemic alterations may be seen in the vulnerable regions of the cortex of cerebrum and cerebellum and of the hippocampus. Necrosis in the globus pallidus is not invariable (Meyer, 1928; Lapresle and Fardeau, 1967) and damage in white matter varies considerably.

The presence of some element of perfusion failure in the genesis of, at least, the cortical damage was suggested by the report of Poursines *et al* (1956). A woman, aged 33 years, lived 26 days after attempted suicide with illuminating gas. In her brain, laminar necrosis was distributed along arterial boundary zones but information concerning respiratory and cardiac functions early in the survival period was lacking. The case of Neubuerger and Clarke (1945), dying 13 days after carbon monoxide poisoning, exhibited patchy myocardial infarction suggesting a direct effect of carbon monoxide on the myocardium.

Among experimental studies, that of Lewey and Drabkin (1944) in the dog was important because, after intermittent exposures to carbon monoxide for up to 11 weeks the electrocardiograms were abnormal and the brain damage was considered to be similar to that seen in man but was not described in detail. Further details of electrocardiographic abnormalities were presented by Ehrich *et al* (1944). Recently Ginsberg *et al* (1974) exposed 19 Rhesus monkeys to 0·2 or 0·3 per cent carbon monoxide for 60 to 325 min with a carboxyhaemoglobin level of 72 to 77 per cent throughout. Cardiac arrhythmias and some degree of hypotension were common but the EEG was only intermittently isoelectric. Grey matter damage (globus pallidus and hippocampus) was seen in less than a fifth of the brains while white matter was abnormal in the majority. Apparently the degree of intoxication was not sufficient to produce the

more extensive grey matter damage so often seen in the human brain.

Further confirmation of a direct effect of carbon monoxide on the heart was provided by Hodjati *et al* (1976) who irrigated the cerebral circulation of one dog from one carotid artery of a donor animal. A mean carboxyhaemoglobin level of 52 per cent in the donor animal led to bradycardia, hypotension and its death in 10 to 15 min. All the recipients survived.

6 Histotoxic

Cyanide, the best known cause of histotoxic hypoxia, acts by inhibiting cytochrome oxidase in mitochondria while the oxygen tension and content of arterial blood remain normal. The few human cases with delayed death and evidence of brain damage have been reviewed by Brierley (1976). There was loss of neurones in cerebral cortex and cerebellum and a single case showed haemorrhagic necrosis in each globus pallidus. Hyperaemia and haemorrhages occurred in white matter.

Numerous experimental studies have suggested that cyanide, in any form and administered by any route, can damage neurones and myelin sheaths. In the first experimental study (Meyer, 1933) subcutaneous injections of potassium cyanide in dogs and rabbits produced typical ischaemic alterations in cerebral cortex, globus pallidus, hippocampus and cerebellum. White matter damage was most marked in the corpus callosum. Subsequent studies were more concerned with white matter damage because of its apparent similarity to the plaques of multiple sclerosis. However, the report of Levine and Stypulkowski (1959) was noteworthy because it suggested that grey matter damage in the rat brain after the administration of cyanide was largely due to concomitant ischaemia and hypoxic hypoxia. Brierley *et al* (1976) gave sodium cyanide to rats by intravenous infusion. There was full physiological monitoring in an anaesthetized group and restricted monitoring in the unanaesthetized remainder. White matter, particularly the corpus callosum, was damaged in six of 19 animals and grey matter additionally in only one. In the latter animal bradycardia, epileptic seizures and hypotension were particularly marked and it was concluded that the neuronal damage was brought about through the medium of the secondary effects of cyanide on the circulation. In a recent study in *M mulatta* (Brierley *et al*, 1977) sodium cyanide was given by intravenous infusion. The effects of the infusion on respiration, heart rate, blood pressure, blood gases and the EEG were monitored in the lightly anaesthetized animals. Brain damage was seen in four of 11 animals. It involved white matter in all four but ischaemic cell change was restricted to the striatum of a single animal. In the latter there had been a period of bradycardia, hypotension and raised central venous pressure. It was concluded that in the lightly anaesthetized and spontaneously breathing Rhesus monkey, as in the rat, there is no evidence for the entity of hypoxic neuronal damage of purely histotoxic type.

7 Hypoglycaemia

Hypoglycaemic damage in the human brain is usually associated with irreversible coma and Meyer (1963) stated that the neuropathological findings '. . . closely resemble those which occur in other types of anoxia'. Most of the selectively vulnerable regions may be involved but with a tendency to spare the globus pallidus and cerebellum. Although hypoglycaemic coma may be associated with cardiovascular disturbances and epileptic seizures the ability of hypoglycaemia *per se* to produce ischaemic damage in physiologically monitored experimental primates has been demonstrated only recently.

Kahn and Myers (1971) and Myers and Kahn (1971) studied the long-term effects of insulin-induced hypoglycaemia in Rhesus monkeys. Blood glucose fell to 20 mg/100 ml after one and a half to three h and was maintained at this level for four to 10 h with normal blood oxygenation. In seven of 11 animals there was neuronal loss with a gliomesodermal reaction in striatum, cerebral cortex and hippocampus.

In order to define the earliest neuronal alterations due to insulin-induced hypoglycaemia, lightly anaesthetized Rhesus monkeys received insulin intravenously while EEG, EKG, heart and respiratory rates were recorded and blood gas tensions, pH and glucose content were measured at intervals (Meldrum *et al*, 1971). When blood glucose was below 20 mg/100 ml for more than two h and the brains were fixed by perfusion, typical ischaemic cell change (from the stage of microvacuolation) was seen in the cortex and occasionally in striatum, hippocampus and cerebellum. Thus a major deficiency in substrate alone can produce the same type of neuronal damage as a deficiency of oxygen.

Conclusion

It will be evident from this brief review that ischaemic cell change is the cytopathological common denominator in all types of hypoxia. Nevertheless there is no pattern of its distribution specific for each category with the exception of circulatory arrest (global ischaemia) and pure hypoglycaemia after both of which ischaemic neuronal alterations may occur

uniformly within the 'selectively vulnerable' regions of the brain. In the remaining categories of hypoxia, ie, oligaemic, anoxic, hypoxic, histotoxic and probably anaemic (carbon monoxide), an initially pure hypoxic stress in the intact and spontaneously breathing animal gives rise, sooner or later, to terminal secondary impairments of respiration and particularly of circulation. In the healthy experimental animal, however, it is only rarely that the associated period of reduced cerebral blood flow is long enough to cause brain damage but not too long to preclude recovery. In such instances, brain damage consists of a concentration of ischaemic cell change along the arterial boundary zones.

Experimental studies have shown that the terminal hypoxic cardio-respiratory deterioration or crisis consists of a slowing of respiration to the point of apnoea with a fall in blood pressure and in heart rate (but the heart may continue to beat long after the 'last breath'). There is a more or less parallel decline in EEG background activity and an isoelectric state is reached at about the time of the 'last breath'. There is no evidence to suggest that systemic hypoxia of any type can lead to brain damage unless the EEG has been isoelectric for an appreciable period. In the paralyzed and mechanically ventilated animal exposed to systemic hypoxia, initial hyperventilation as well as the 'last breath' cannot occur and the duration of hypoxia may be considerably prolonged. For this reason 'thresholds' for brain damage defined in such preparations must be applied with considerable caution to the spontaneously breathing experimental animal and to man.

There is now ample evidence to show that in the intact healthy, and spontaneously breathing animal tolerance to hypoxia is limited by the respiratory and circulatory systems and not by the intrinsic energy reserves of the brain itself. If effective resuscitation is begun soon after the 'last breath' the EEG will return and the brain will be undamaged. Thus a depression of central nervous system function up to and some time after the 'last breath' and the appearance of transiently isoelectric EEG need have no structural consequences.

The relative frequency of all degrees of ischaemic damage in the human brain after hypoxic episodes does not, however, necessarily imply a greater susceptibility of the brain itself. The existence of a single type of hypoxia in human patients is rare. It should be stressed that several types of hypoxia, each constituting a relatively mild stress can, in combination, produce brain damage. The additional factors most probably responsible for the increased extent and frequency of brain damage in man are twofold. Preexisting cardiac disease will impair the capacity to maintain a high level of blood flow through a cerebral vascular bed initially fully dilated by hypoxia. It will also impair the rapid restoration of normal cerebral blood flow after any terminal cardio-respiratory crisis. Secondly, preexisting occlusive disease in the arteries of brain and neck and any impairment of the normal reactivity of the smaller cerebral vessels will further reduce cerebral blood flow during and after hypoxia.

In conclusion, experiments in physiologically monitored, spontaneously breathing animals can show that hypoxia gives rise to an integrated series of responses in the respiratory and circulatory systems and in the nervous system itself. Initially these serve to maintain brain function and respiration in particular. Ultimately these compensatory cardio-respiratory responses may fail. Experiments have also shown that where the human brain is concerned the commonest cause of damage must be sought in some failure of brain perfusion.

The author is greatly indebted to Dr Pamela F. Prior (The EEG Department, the London Hospital) for many helpful suggestions and comments in the preparation of the manuscript.

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J. Physiol. (1963), **169**, *pp.* 292–311
With 9 text-figures
Printed in Great Britain

THE EFFECT OF BRIEF PROFOUND HYPOXIA UPON THE ARTERIAL AND VENOUS OXYGEN TENSIONS IN MAN

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(*Received* 23 *January* 1963)

The partial pressure of oxygen in the alveolar gas may be reduced either by decreasing the total pressure of the environment or by replacing the oxygen normally present in the inspired air by an inert gas. The severe anoxia induced by rapid decompression from 565 to 155 mm Hg absolute, whilst breathing air, may be terminated by the delivery of 100% oxygen to the respiratory tract. The effects of such brief profound anoxia upon the alveolar and arterial gas tensions and upon the central nervous system have been studied extensively (Ernsting & McHardy, 1963; Ernsting, Gedye & McHardy, 1960; Ernsting, 1962). The effect of the resultant severe but short-lived arterial hypoxaemia upon the supply of oxygen to various organs of the body is of considerable interest. The oxygen content of the venous blood flowing from a region reflects the balance between the supply of oxygen to it and its metabolic oxygen consumption. Continuous measurements of the oxygen content of the venous blood flowing from several regions have been made in subjects exposed to brief but profound hypoxia. In the experiments described in this paper a short period of overventilation, nitrogen being used as the inspired gas, was employed in place of rapid decompression to induce hypoxia. This method allowed more extensive observations to be made than were considered practical in a decompression chamber.

METHODS

Induction of hypoxia. Three healthy men, aged from 33 to 38 years, were used. The subject lay on a couch and breathed through a valve box, to the inlet of which two taps were connected in series. The side arm of the tap next to the box was open to the atmosphere. One arm of the second tap was connected to a demand valve which was supplied with nitrogen, whilst the other arm was connected to a second demand valve supplied with oxygen. Before the experiment was started the hoses between the two demand regulators and the second tap were purged with the gas delivered by the corresponding regulator. The dead space between the two taps was purged with nitrogen to ensure that 100% nitrogen was delivered directly the first tap was operated. During each rest period the first tap was positioned so that the subject breathed air. Nitrogen was administered by instructing the subject to expire maximally at the end of a normal expiration, and at this instant the first tap was turned so that the subject breathed from the demand valve which supplied nitrogen.

During the period of breathing nitrogen the subject was instructed to breathe as deeply as possible at a rate of about 20 breaths per minute. After 7–20 sec over-ventilation with nitrogen the first tap was returned to its original position so that air was breathed again. At the same time the subject was told to cease over-breathing.

Respired gas tensions. The partial pressures of oxygen and carbon dioxide in the gas passing the subject's lips were recorded continuously in all the experiments by means of a respiratory mass spectrometer (Fowler & Hugh-Jones, 1957). Preliminary studies showed that the output of the instrument was linearly related to the partial pressure of each of these gases. The delay between a sudden change of partial pressure of either at the sampling tip and the beginning of the response of the recording pen motor was 0·2 sec and 90% of the total response occurred in a further 0·1 sec. Calibrations employing gas mixtures of known composition were performed at intervals throughout each experiment. Over a 30 min period no significant change occurred in the sensitivity of the instrument. The pulmonary ventilation was recorded in some of the experiments by collecting the expired gas in a recording Tissot spirometer.

Blood sampling. In separate experiments blood was sampled continuously from various sites in the cardiovascular system. Blood was obtained from the brachial artery and the femoral vein through a Cournand needle introduced into the vessel after local analgesia had been produced with 2% lignocaine. A catheter was introduced into the right side of the heart through a large-bore needle which had been inserted into a vein in the antecubital fossa. The position of the catheter was determined during its introduction by recording the pressure at the tip by means of a strain-gauge pressure transducer. The catheter was advanced until its tip lay in the pulmonary artery. Blood flowing through the internal jugular vein was sampled by means of a radio-opaque catheter which was introduced into a vein which had been exposed through an incision in the right antecubital fossa. This catheter was advanced under direct fluoroscopic control with the subject's head held against his left shoulder. The catheter entered the right internal jugular vein and was placed so that its end lay above the level of the tip of the right mastoid process. When in place, the patency of the Cournand needle or the intravascular catheter was maintained when sampling was not in progress by a flow of sterile physiological saline (NaCl 0·9 g/100 ml.), approximately 2 ml./min containing heparin (200 i.u./100 ml.).

Recording of blood oxygen saturation and pH. The blood from the intravascular needle or catheter flowed through a tubular cuvette oximeter (Fig. 1) and was then diluted 1:10 with neutral physiological saline to which heparin had been added (Sherwood-Jones, Robinson & Cooke, 1960). The diluted suspension of blood was then passed through a microflow-glass-electrode–calomel-reference-electrode system. The saline reservoir and microflow-electrode system were immersed in a water-bath which was maintained at 38° C. The flow of blood and the desired dilution of the blood with saline were produced by means of a two-cylinder pump with a single piston, the velocity of which could be varied. The pump was constructed so that the cross-sectional area of one cylinder, which was charged with saline, was 10/11 of that of the other cylinder into which the mixture of saline and blood was drawn after it had passed through the glass-electrode system. In all the experiments a blood sampling rate of 20 ml./min was used.

The outputs of the oximeter amplifier and of the pH meter were fed on to two of the pen motors of a recorder. Preliminary experiments showed that the output of the oximeter amplifier was linearly related to the oxygen saturation of the blood flowing through the cuvette. At the beginning and end of each period of recording the output of the oximeter was calibrated by drawing a fully saturated sample of blood and a second sample of a known degree of unsaturation through the cuvette. A linear relation was also found between the pH of the blood and the output of the pH meter. The output of the latter was calibrated at intervals by using two phosphate buffers (pH 6·84 and 7·60). The time course of the response of the entire measuring system to a sudden change in the oxygen saturation and pH of the blood entering the sampling system was determined at the end of each experiment.

When sampling was required the drip of heparinized saline was turned off and the speed of the sampling pump was increased until blood was withdrawn at 20 ml./min. Sampling was continued for 1 min before the subject breathed nitrogen and was maintained until all the disturbances produced by the procedure had subsided.

Electroencephalogram (e.e.g.) and electrocardiogram (e.c.g.) recording. In many of the experiments the e.e.g. was recorded. Two pairs of saline pad electrodes were placed on the scalp over the frontal and occipital regions of the left side of the head. The potential changes from each pair of electrodes were amplified and recorded at a high paper speed. In addition, lead II of the e.c.g. was recorded.

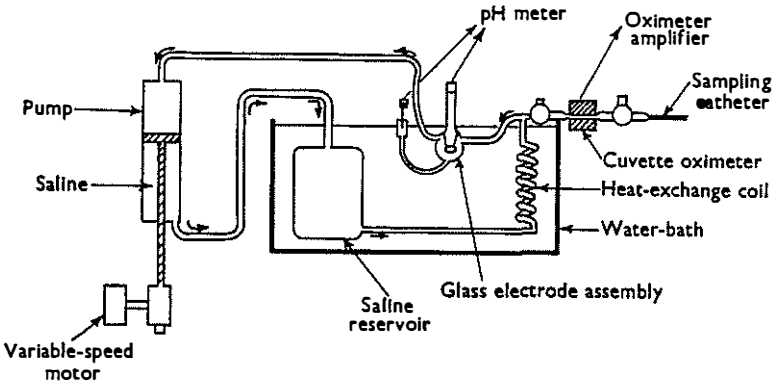

Fig. 1. Apparatus for the continuous measurement of the oxygen saturation and pH of blood. Blood is drawn into the apparatus through a catheter and then it passes through the cuvette oximeter. Saline at 38° C driven by the pump in the direction indicated by the arrows mixes with the blood and the diluted blood flows through the pH electrode assembly back to the pump.

Arterial pressure and calf blood flow. The arterial blood pressure was recorded through a Riley needle by means of an unbonded strain-gauge pressure transducer which was filled with physiological saline containing heparin. The needle was connected to the transducer by means of a 3 cm length of polyethylene tubing with an internal diameter of 1 mm. Preliminary measurements demonstrated that the complete recording system faithfully reproduced the magnitude and phase of sinusoidal pressure fluctuations at frequencies of up to 20 c/s. The Riley needle was inserted into the brachial artery and the transducer was placed on the same horizontal plane as the tip of the needle. The output of the amplifier connected to the transducer, which was fed to one channel of the recorder, was calibrated by means of a mercury manometer before and after each series of measurements. Blood flow through the calf was measured by means of venous occlusion plethysmography, with a mercury-in-rubber strain gauge (Whitney, 1953) to measure changes in the circumference of the calf. The lower limb was supported so that the lower border of the calf was just above the horizontal level of the sternal angle. The circulation to the foot was occluded by means of a cuff placed around the ankle, which was inflated to 250 mm Hg 1 min before the calf blood-flow measurements were started. The venous outflow from the calf was obstructed for 5 sec of every 10 sec period by inflating the cuff placed around the lower part of the thigh to between 30 and 40 mm Hg. The exact pressure used in the venous cuff was adjusted at the beginning of each experiment so that the circumference of the calf increased at a constant rate during each collection period. The output of the gauge was calibrated while it was in position by producing a known reduction of its length. The circumference of the calf at the level at which the gauge was fixed was measured at the end of each experiment.

In all the experiments the subject was carefully observed during and following the period of over-ventilation with nitrogen. If any severe disturbance of consciousness or respiration occurred, oxygen was administered.

RESULTS

Effect upon consciousness. The increase of pulmonary ventilation achieved by each subject during nitrogen breathing was measured from the spirometer records. The mean pulmonary ventilation of the three subjects was increased to 80 l./min at b.t.p.s. during the period of over-ventilation. When the duration of over-ventilation with nitrogen was greater than 8–10 sec the subject reported a transient dimming of vision. In the experiments in which nitrogen breathing was carried out for 15–16 sec the subject experienced some general clouding of consciousness and impairment of vision. Vision was frequently lost in these experiments for a short period. In the few experiments in which nitrogen was breathed for 17–20 sec unconsciousness supervened and was accompanied on most occasions by a generalized convulsion. The duration of the interval between the start of over-ventilation with nitrogen and the onset of symptoms was 12–14 sec.

End-tidal gas tensions. A typical record of the partial pressures of oxygen and carbon dioxide in the gases flowing through the mouth-piece is presented in Fig. 2. The end-tidal oxygen tension fell very rapidly when the subject commenced over-ventilation with nitrogen. It reached a value of less than 10 mm Hg at the end of the third expiration and remained below this level until air was inspired after 16 sec of nitrogen breathing. During the over-ventilation period the end-tidal carbon dioxide tension also fell rapidly. With the restoration of air breathing and the cessation of over-breathing the end-tidal oxygen and carbon dioxide tensions rose gradually to regain their control values. Each of the three subjects over-ventilated, whilst breathing nitrogen for a period of 15–16 sec on six separate occasions. The time course of the changes of the end-tidal tensions of oxygen and carbon dioxide has been measured for each of these 18 experiments and mean curves for each of these variables are presented in Fig. 3.

Arterial blood oxygen saturation and pH. Blood was sampled from the brachial artery of each subject on three separate occasions during which the subject over-ventilated with nitrogen for 16 sec. The records of the response of the entire system to a sudden change in the composition of blood at the tip of the Cournand needle showed a mean delay of 0·7 sec to the beginning of the response of the pen motor recording oxygen saturation and a further 0·9 sec elapsed before 90 % of the total response had occurred. The corresponding times for the response of the pH recording system were 1·4 sec and 2·0 sec respectively. Corrections for these delays in response were applied to the recorded values of oxygen saturation and pH. A

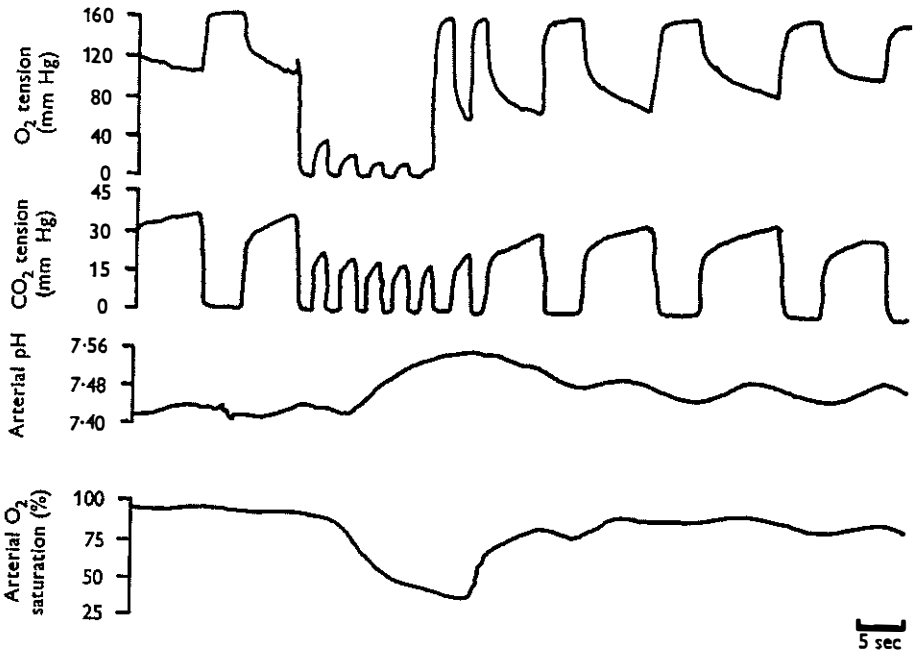

Fig. 2. Respiratory gas tensions and systemic arterial oxygen saturation and pH before, during and after 16 sec over-ventilation with nitrogen. The tensions of oxygen and carbon dioxide were recorded at the lips, whilst the blood was sampled continuously from the brachial artery. Delay time of oxygen saturation record, 0·7 sec of pH record, 1·5 sec.

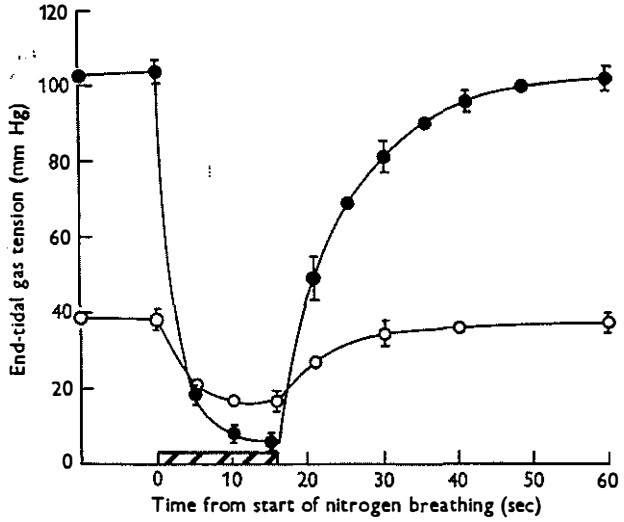

Fig. 3. Effect of over-ventilation with nitrogen upon end-tidal tensions of oxygen (●) and carbon dioxide (○). Each point represents the mean of eighteen values from three subjects; each bar represents ± 1 S.E. of the mean. The period of over-ventilation with nitrogen is indicated by the hatched bar.

typical experimental record of the arterial oxygen saturation and pH is presented in Fig. 2. The arterial oxygen saturation and hydrogen-ion concentration began to fall 4–5 sec after the commencement of nitrogen breathing and both fell very rapidly at first and then more slowly until air breathing was started again at 16 sec. The oxygen saturation then increased rapidly whilst the pH gradually returned to its control value. The mean time courses of the changes of arterial oxygen saturation and pH have been calculated for the nine experiments and these values together with their standard errors are shown in Fig. 4.

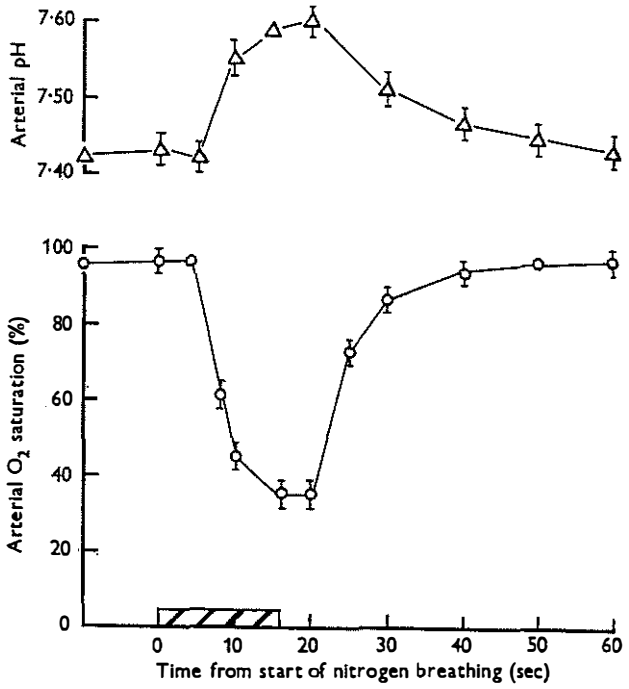

Fig. 4. Effect of over-ventilation with nitrogen upon arterial oxygen saturation (○) and arterial pH (△). Each point represents the mean of nine values from three subjects; each bar represents ±1 S.E. of the mean.

Venous blood oxygen saturation and pH. Blood was sampled from the femoral vein, the pulmonary artery and the right jugular bulb on separate occasions in each of the subjects. The delay in the response of the recording systems was lengthened considerably when intravascular catheters were employed. On none of these occasions did any significant change of pH occur during the period of nitrogen breathing. The mean time courses of the oxygen saturation of the venous blood drawn from these three sites are presented in Fig. 5.

Electroencephalogram changes. The resting e.e.g. shows no specific electrical activity and no change occurred in any experiment until 15–18 sec after the beginning of the period of over-ventilation with nitrogen. When nitrogen over-breathing was carried out for 8–12 sec low voltage

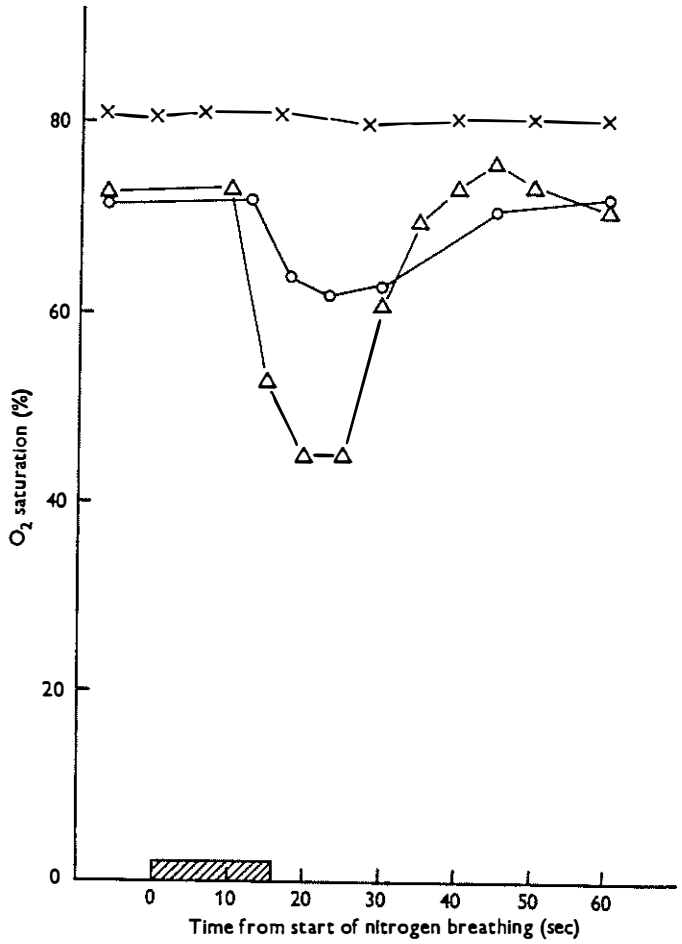

Fig. 5. Effect of over-ventilation with nitrogen upon the oxygen saturation of blood flowing through the femoral (×) and internal jugular (△) veins and the pulmonary artery (○). Each point represents the mean of three values obtained from three subjects.

activity at 11–13 c/s appeared in both channels of the e.e.g. 15 sec after the beginning of the procedure and persisted for 7–9 sec. When the duration of nitrogen over-ventilation was extended to 15–16 sec, similar changes arose in the e.e.g. but they persisted for slightly longer. Occasionally the

11–13 c/s activity was replaced by high-voltage 2–4 c/s activity, which appeared 4–6 sec after the beginning of the change of the e.e.g. This slow activity generally persisted for 4–6 sec. When nitrogen breathing was extended to 18–20 sec the initial fast, low-voltage activity was always replaced by high-voltage 2–4 c/s activity after 5 sec, which lasted for about 10 sec. Control experiments in which a subject over-ventilated for a similar period whilst breathing air produced no change of e.e.g. activity.

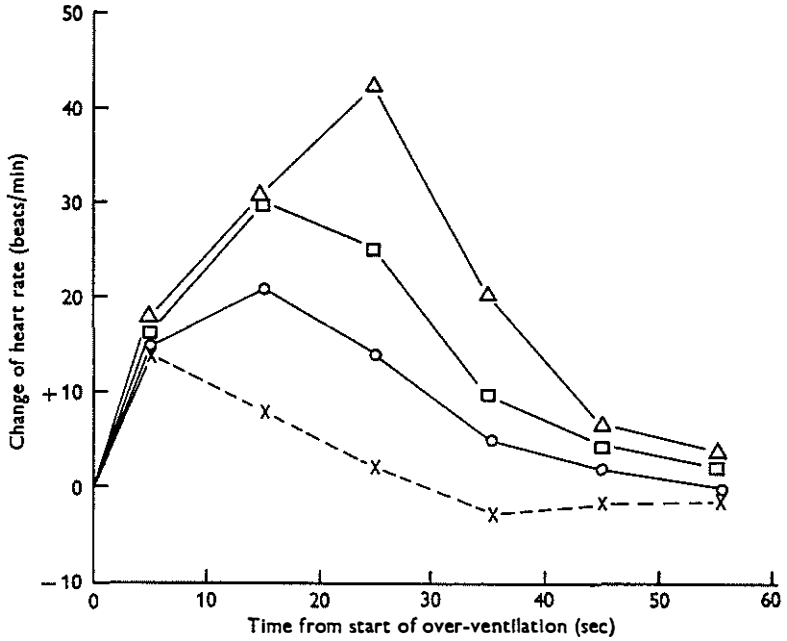

Fig. 6. Effect of over-ventilation with nitrogen for various periods upon the heart rate. △, nitrogen for 17 sec; □, nitrogen for 11 sec; ○, nitrogen for 8 sec; ×, air for 15 sec. Each point represents the mean of three values obtained from three subjects.

Cardiovascular changes. The period of over-ventilation with nitrogen produced a transient acceleration of the heart rate. This commenced at the beginning of the period of over-ventilation and reached a maximum about 30 sec later. The magnitude of the increase varied directly with the duration of the nitrogen over-ventilation. The mean changes of the heart rate for the three subjects when they over-ventilated with nitrogen for various periods are presented in Fig. 6. There were no consistent changes in the shape of the e.c.g. in these experiments. In one subject, however, there was a transient flattening of the 'T' wave, which started 5 sec after the beginning of the nitrogen over-ventilation and persisted for 10 sec. In

several experiments the subjects over-ventilated whilst breathing air. This caused a relatively small and transient increase of heart rate which had subsided 10 sec after the end of the over-ventilation period (Fig. 6).

The period of over-ventilation produced marked respiratory variations of the arterial blood pressure. The mean and pulse pressure were both increased during the deep expiratory efforts and decreased during each inspiration. The mean blood pressure was increased by about 20 mm Hg during the period of over-breathing. Directly the subject ceased over-ventilation the arterial pressure fell and reached a minimum after some 15 sec from the beginning of nitrogen breathing. The minimal value was less than the mean blood pressure before the over-ventilation period. The fall of mean pressure was accompanied by a reduction of the pulse pressure. It was followed by a secondary rise of pressure and an increase of pulse pressure, both of which reached a maximum at about 30 sec after the beginning of the period of over-ventilation with nitrogen. In all, two separate periods of over-ventilation with nitrogen were studied for each of the three subjects and the mean values of arterial pressure before, during and after the period of over-ventilation with nitrogen are presented in Fig. 7. The blood flow through the calf was calculated from the rate at which the circumference of the part increased during each venous-congestion period (Whitney, 1953). The mean value for the calf blood flow obtained in twelve separate periods of over-ventilation with nitrogen in the three subjects are shown in Fig. 7. The flow of blood into the calf was increased during the period of over-ventilation, following which it returned to the resting level, to increase again between 20 and 40 sec after the beginning of over-ventilation.

DISCUSSION

Preliminary experiments in which the subjects over-ventilated with nitrogen for various periods showed that unconsciousness supervened if the duration of this procedure exceeded 16–17 sec. In the majority of these experiments, therefore, the period of over-ventilation with nitrogen was limited to 16 sec. This period of nitrogen over-breathing produced only a transient disturbance of the e.e.g. The low-voltage 8–13 c/s activity was generally associated with a transient dimming of vision and could not be distinguished from that produced by closure of the eyelids. Further, apart from a transient flattening of the 'T' wave on one occasion, no significant change was seen in the e.c.g., although only a standard limb lead (II) was recorded. In view of these findings it was considered that the degree of hypoxia induced by over-ventilation with nitrogen for 15–16 sec was within acceptable limits for resting subjects.

The concentration of oxygen in the gas contained within the respiratory tract at the beginning of the nitrogen breathing period was reduced very rapidly by the very large voluntary increase of pulmonary ventilation. The reduction of the lung volume to a minimum before the first breath of nitrogen was taken decreased the quantity of oxygen to be washed out. The combination of these two manoeuvres resulted in a very rapid fall of end-tidal oxygen tension to 10 mm Hg after 8 sec of over-ventilation. The rate of rise of the end-tidal oxygen tension following the cessation of nitrogen over-ventilation and the return to breathing air was considerably less than the rate at which it had fallen. This difference reflects the reduction of alveolar ventilation associated with the resumption of a more normal breathing pattern.

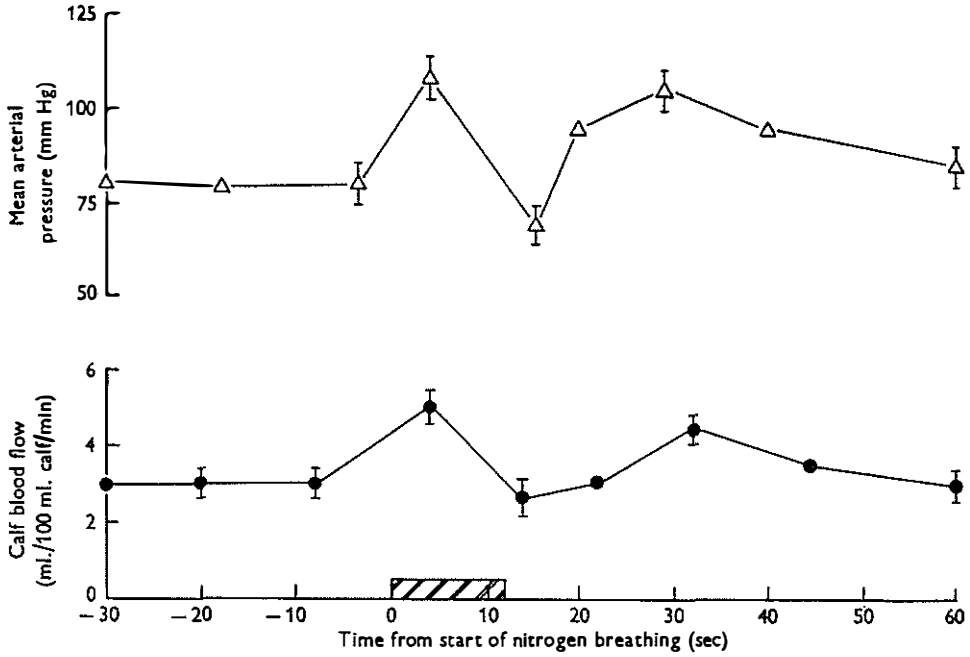

Fig. 7. Effect of over-ventilation with nitrogen upon the mean systemic arterial pressure (△) and the blood flow through the calf (●). The results are from three subjects, each pressure point representing the mean of six values whilst each blood flow point is the mean of twelve values; each bar depicts ±1 S.E. of the mean value.

Arterial oxygen saturation and pH

The delay of 4–5 sec between the beginning of nitrogen breathing and the reduction of the oxygen saturation of the brachial artery blood was a reflexion of the circulation time from the pulmonary capillaries to the sampling point in the systemic arterial tree. A similar delay occurred

between the restitution of air breathing and the subsequent increase of the arterial oxygen saturation. The reduction of the end-tidal oxygen tension to below 10 mm Hg was associated with an arterial oxygen saturation of less than 40 %. The increase of the pH of the arterial blood was related to the fall of the alveolar carbon-dioxide tension and the reduction of the blood oxygen saturation (Christiansen, Douglas & Haldane, 1914). The mean increase of the arterial pH produced by the over-ventilation amounted to 0·18 unit. This gave a calculated value for the minimal arterial carbon-dioxide tension of 22·5 mm Hg as compared with the observed end-tidal value of 17 mm Hg. The changes of arterial oxygen tension produced by over-breathing with nitrogen have been calculated from the simultaneous measurements of the oxygen saturation and pH of the arterial blood by means of standard oxygen dissociation curves (Dill, 1944). The mean time course of the oxygen tension for all the experiments is presented in Fig. 8. together with the curve for the end-tidal oxygen tension. During over-ventilation the end-tidal oxygen tension may be taken as representative of the mean alveolar tension of this gas. When allowance is made for the 4 sec delay between the change of alveolar gas composition and the resultant change of the oxygen tension of the arterial blood at the sampling point, it is apparent that the arterial oxygen tension fell in the same manner as the alveolar oxygen tension until this was less than 16 mm Hg. Beyond this point the systemic arterial oxygen tension was consistently greater than that of the alveolar gas until air breathing was restored. There was a statistically significant difference ($P < 0{\cdot}01$; $n = 9$) between the oxygen tensions of the arterial blood and of the alveolar gas for the last 7 sec of the period of nitrogen breathing. The oxygen tension of the mixed venous blood during nitrogen breathing was between 35 and 40 mm Hg (Fig. 9), and hence the oxygen tension of the alveolar gas was less than that of the blood entering the pulmonary capillaries for nearly the whole period of nitrogen over-ventilation. During this procedure, therefore, there was a reversal of the normal oxygen-tension gradient between the alveolar gas and the mixed venous blood. Since the oxygen saturation of the systemic arterial blood was considerably less than that of the mixed venous blood, oxygen must have passed from the blood flowing through the pulmonary capillaries into the alveolar gas during the latter part of the nitrogen-breathing period. Such a reversal of the normal direction of passage of oxygen across the alveolar capillary membrane has been demonstrated following rapid decompression to high altitude (Luft, Clamann & Adler, 1949; Ernsting & McHardy, 1960) and during rapid ascent following a breath-holding dive to a water depth of 60–100 ft. (18–30 m; Rahn, 1963). In both these situations the oxygen tension of the alveolar gas is reduced rapidly below that of the mixed venous blood.

Venous pH and oxygen saturation

The absence of any detectable change of the pH of the blood sampled from the three venous sites following the period of over-ventilation with nitrogen demonstrated the marked carbon dioxide buffering power of the peripheral tissues and the rapid diffusibility of this gas. The constancy of the venous pH was unexpected, since the reduction of the oxygen saturation of the venous blood would of itself have produced an increase of pH (Christiansen *et al.* 1914). At a constant carbon-dioxide tension the greatest increase of pH due to this mechanism, associated with the decrease of

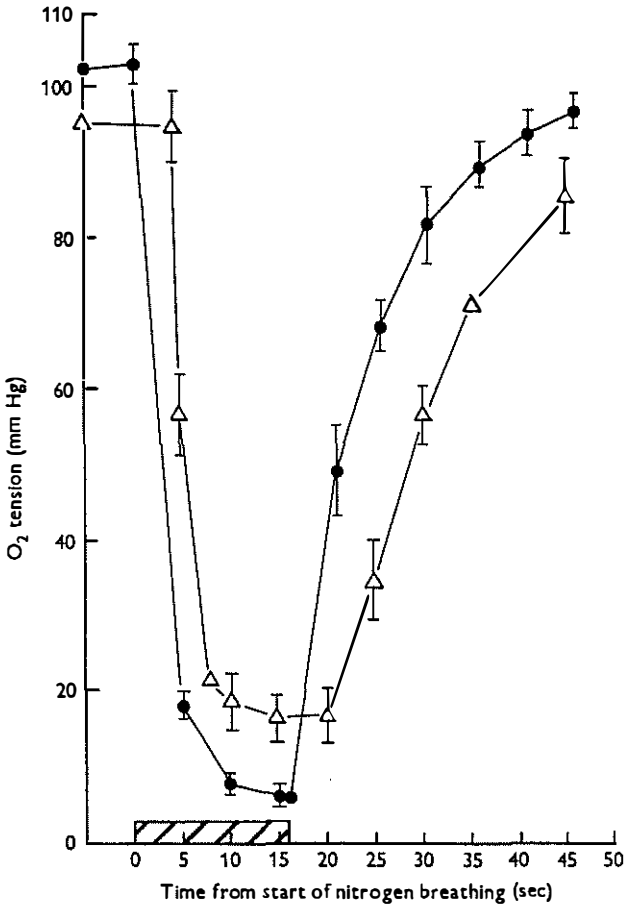

Fig. 8. Effect of over-ventilation with nitrogen upon end-tidal oxygen tension (●) and systemic arterial oxygen tension (△). Each point represents the mean of eighteen end-tidal values and nine arterial values. Each bar denotes ± 1 S.E. of the mean value.

oxygen saturation of the cerebral venous blood by 27 %, was calculated to be of the order of 0·012 unit. The over-all sensitivity of the system used for the measurement of the pH of the venous blood was such, however, that a change of this magnitude might not have been detected.

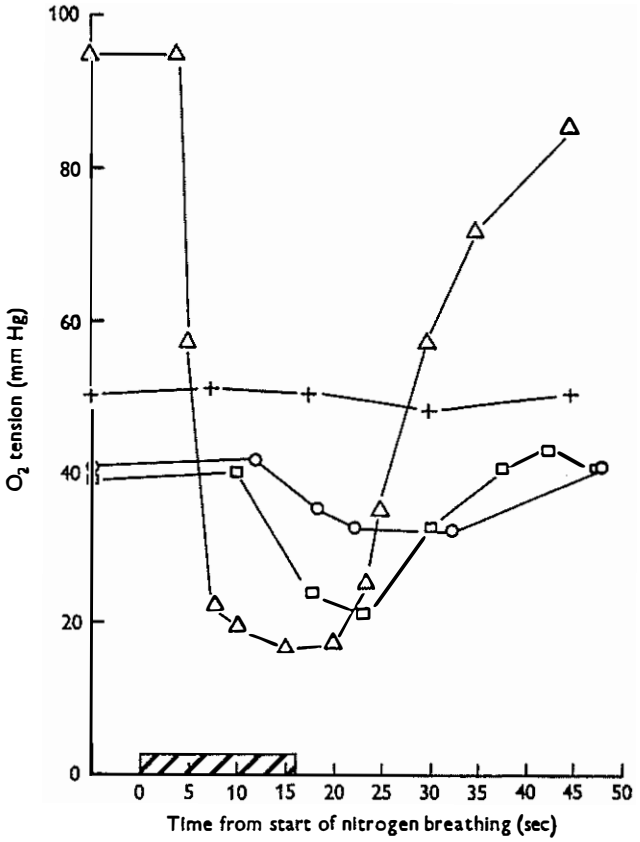

Fig. 9. Effect of over-ventilation with nitrogen upon the oxygen tension of the systemic arterial (△), femoral venous (+), internal jugular (□) and pulmonary arterial (○) blood. Each point represents the mean of the values obtained from three subjects.

The pattern of the reduction of the oxygen saturation of the venous blood produced by the period of nitrogen breathing varies markedly with the site of sampling (Fig. 5). The oxygen content of the jugular venous blood was the first to change and it exhibited the greatest reduction and the most rapid recovery. In contrast the oxygen saturation of the femoral venous blood started to fall last, was reduced by the smallest amount and recovered the most slowly. Mixed venous blood showed changes which

were intermediate between those of the jugular and femoral venous bloods. The maximal fall of the oxygen saturation of the femoral venous blood was half that which occurred in the blood sampled from the pulmonary artery, whilst the maximal reduction of the oxygen content of the jugular blood was more than twice the latter. The changes of the oxygen tension of the blood sampled from these venous sites have been calculated from the measured values of oxygen saturation and pH and the mean curves are presented in Fig. 9, together with the mean curve for the arterial oxygen tension. It is apparent that during the period of severe hypoxia the oxygen tension of the blood flowing from the lower limbs, the brain and the whole body was greater than that of the arterial blood flowing into these regions.

Cardiovascular effects of profound hypoxia

The limited measurements made in this study demonstrate that the period of over-ventilation with nitrogen produced significant changes in the cardiovascular system. The control experiments in which the subject over-breathed with air make it possible to distinguish two phases in the cardiovascular response. First, during the period in which the pulmonary ventilation was increased there was a moderate rise of heart rate and the arterial pressure and calf blood flow were raised (Fig. 7). Immediately the over-ventilation ceased the arterial pressure and calf blood flow returned to their resting values. These changes occurred when either air or nitrogen was breathed. When the over-breathing was performed with nitrogen the rise of heart rate persisted for considerably longer and there was a secondary increase of arterial pressure and calf blood flow. These secondary changes were absent when air was substituted for nitrogen and were due, therefore, to the severe hypoxia induced by the nitrogen. Throughout each experiment the calf blood flow was directly proportional to the mean systemic arterial pressure. Thus the observed changes of calf blood flow were a result of the concomitant changes of arterial pressure. The secondary changes which occurred after over-ventilation with nitrogen were probably the result of an increase of cardiac output and of systemic arteriolar constriction which were produced reflexly by chemoreceptor stimulation. It is apparent that the arterioles of the calf did not contribute to this vasoconstriction, and the most probable sites for the increase of peripheral resistance were the splanchnic and cutaneous circulations. The rise of the oxygen saturation of the jugular venous blood above the control value when air breathing was restored (Fig. 5) suggests that there was an increase of the over-all cerebral blood flow at this time. In the steady state moderate arterial hypoxaemia, even when accompanied by hypocapnia, is known to produce a dilatation of the cerebral vessels (Kety &

Schmidt, 1948). The rate at which the cerebral vasodilatation develops when arterial hypoxaemia is induced suddenly is not known, but the present experiments suggest that the cerebral vessels respond to a fall of arterial oxygen tension within 20 sec.

Pulmonary gas exchange in profound hypoxia

The arterial oxygen-tension values derived in this study demonstrated that during over-ventilation with nitrogen the oxygen tension of the arterial blood was significantly greater than that of the alveolar gas. The time for which this state existed was only 7–8 sec, although during this period the rates of change of alveolar and arterial oxygen tensions were relatively slow. Furthermore, this length of time is large relative to the average transit time of 0·73 sec (Roughton, 1945; Roughton & Forster, 1957) for a red cell through the pulmonary capillaries lining ventilated alveoli. It would appear, therefore, that the observed difference between systemic arterial and alveolar oxygen tensions cannot be accounted for on the basis of the short period for which the condition existed. Such a difference could be produced by the presence of either a shunt of venous blood into the systemic arterial tree or a higher tension of oxygen in the blood leaving the pulmonary capillaries than in the alveolar gas. Mixed venous blood flowing into the systemic arterial tree without having transversed the capillaries of ventilated alveoli would raise the oxygen tension of the systemic arterial blood above that of the alveolar gas. The effect of the normal quantity of venous admixture upon the arterial oxygen tension would be insignificant, because of the relative steepness of the blood-oxygen dissociation curve over the range concerned here. If, however, the proportion of the cardiac output perfusing ventilated alveoli was reduced during nitrogen breathing, this effect could become significant. In order for this mechanism to account for the total observed oxygen-tension gradient the venous-arterial shunt would have to amount to at least half of the total cardiac output. There is at present no evidence in favour of such a degree of shunting during severe hypoxia. It would appear probable, therefore, that the tension of oxygen in the blood leaving the pulmonary capillaries is considerably greater than that in the alveolar gas during over-ventilation with nitrogen.

Since no measurements were made of the rate of gaseous exchange during the period of over-ventilation with nitrogen it is impossible to examine quantitatively the factors affecting the exchange of oxygen between the pulmonary capillary blood and the alveolar gas. It is of value, however, to compare the effects of over-ventilation with nitrogen with those produced by moderate hypoxia in the steady state. Thus, Lilienthal, Riley, Proemmel & Franke (1946) found that at an alveolar

oxygen tension of 46 mm Hg at rest the difference between the tensions of oxygen in the alveolar gas and the systemic arterial blood amounted to 9·1 mm Hg. They calculated that under these circumstances the oxygen tension of the mixed venous blood was 19 mm Hg less than that of the alveolar gas and that the oxygen tension of the blood leaving the pulmonary capillaries was about 8 mm Hg less than that of the alveolar gas. Although in the nitrogen over-ventilation experiments the oxygen tension gradient between the alveolar gas and the mixed venous blood was reversed, it was of the same order as that which existed in the experiments performed by Lilienthal *et al.* (1946). Furthermore, the mean difference between the oxygen tensions of the arterial blood and the alveolar gas obtained in the present study, which amounted to 11 mm Hg, was only slightly greater than that found in moderate hypoxia by Lilienthal *et al.* (1946). The arterial–alveolar oxygen-tension difference observed in nitrogen over-ventilation experiments was probably due, therefore, to a mechanism analogous to that which was deduced by Lilienthal *et al.* (1946) to be responsible for the existence of an alveolar to end-pulmonary capillary blood-oxygen tension difference in moderate hypoxia. The limited rate at which oxygen was transferred from chemical combination in the pulmonary blood into the alveolar gas under the circumstances which existed in the nitrogen-breathing experiments gave rise to a large oxygen-tension difference between the blood leaving the pulmonary capillaries and the alveolar gas.

Exchange of oxygen between blood and peripheral tissues in profound hypoxia

The reduction in the rate at which oxygen is carried to a part caused by a short period of arterial hypoxaemia depends upon the degree and duration of the desaturation of the arterial blood and the arterial flow to the part. In the resting state the total blood flow to the brain is over twice that to the lower limbs. Thus in the present experiments the deficit of the oxygen supply to the brain was twice that to the lower limbs. The effect of such a deficit in the oxygen supply to a region upon the oxygen content of the blood flowing from it will be determined in part by the relation between the magnitude and nature of its oxygen store and its metabolic oxygen consumption. Where the available oxygen store is small in relation to the oxygen uptake, the venous oxygen saturation will be reduced to a greater extent than when the store is large in relation to the oxygen consumption. Quantitatively the most important oxygen store is that contained by the blood, and the greater proportion of this resides in the small and large veins. Muscle possesses in addition a specific oxygen storage mechanism in the form of oxymyoglobin. The amount of oxygen stored in this manner in man is, however, relatively small (Drabkin, 1950)

and the oxygen tension in muscle must be reduced below 10 mm Hg before a significant proportion of the oxygen held in this form is liberated (Hill, 1936). Finally, all tissues contain oxygen in simple physical solution, although quantitatively this store is relatively small. The brain, in contrast to the lower limbs and the body as a whole, has a high arterial inflow, a high oxygen consumption and a small oxygen store. For a specified transient arterial hypoxaemia all these factors tend to produce a greater fall of the oxygen saturation in the jugular blood than in the blood flowing from the lower limbs.

The pattern of the fall of the saturation of venous blood caused by a transient arterial hypoxaemia will be modified by changes of blood flow into the region and of the capacity of its vascular bed. In the present experiments there were transient changes of calf blood flow during and after the period of hypoxaemia. There was also evidence which suggested that the cerebral blood flow changed, although no direct measurements of this quantity were made. If an increase of blood flow occurred during the period of hypoxaemia, the deficit of the oxygen supply would have been increased. If, however, the increase of blood flow did not occur until the arterial oxygen saturation was rising, it would have produced a more rapid recovery of the venous oxygen saturation, or even a rise to above the control value. Although no direct measurements of the capacity of the vessels of the calf were made, it was noted that the volume of this region was decreased by the period of over-ventilation with nitrogen. Eckstein, Hamilton & McCammond (1958) have shown that the reflex reduction of the distensibility of the capacity vessels produced by over-ventilation is in part due to the hypocapnia and in part a result of the intrathoracic pressure changes associated with the over-ventilation. Such a reduction of the blood content of the calf would have tended to increase the venous desaturation produced by the arterial hypoxaemia.

During the period of over-ventilation with nitrogen, the oxygen tension of the arterial blood was reduced to 20–30 mm Hg below that of the venous blood normally flowing from the regions studied. Thus the oxygen tension of the arterial blood during this period was lower than the mean capillary oxygen tension (Barcroft, 1938) which existed before nitrogen breathing was commenced. Furthermore, during the period of profound hypoxaemia the oxygen tension of the blood flowing from the regions under investigation was greater than that of the arterial blood perfusing them. Although the oxygen content of the blood leaving the tissue capillaries was probably raised by admixture with the blood already present in the venules and veins of the part, it is apparent that during the period of severe hypoxaemia the oxygen tension of the capillary blood was markedly reduced. Thus the diffusion of oxygen into the various tissues from the blood flowing through

them was severely reduced by the period of hypoxia. Indeed, in some areas, especially those with a relatively high capillary blood flow, the capillary oxygen tension may have been reduced below that of the surrounding tissues, so that oxygen actually diffused into the blood as it flowed through them. Thus direct measurements of the oxygen tension of the grey matter of the cerebral cortex in animals breathing air have given values of the order of 18--25 mm Hg (Cater, Garattini, Marina & Silver, 1962), whilst in the present experiments the arterial oxygen tension was reduced to about 17 mm Hg. The effect of a given reduction of the rate at which oxygen diffuses into a tissue upon the cellular oxygen tension will depend upon the relation between the cellular oxygen consumption and the extravascular oxygen store. There is considerable evidence that the cellular oxidative enzyme systems will continue to function normally until the local oxygen tension is reduced to below 5 mm Hg (Keilin, 1930). Thus the cellular metabolic oxygen uptake will probablyremain unchanged until severe hypoxia is induced. In the brain, where the only extravascular oxygen store is oxygen dissolved in tissue fluid, and the metabolic oxygen uptake is high, sudden arterial hypoxaemia will produce a very rapid fall of the cellular oxygen tension.

In the present series of experiments it was found that unconsciousness ensued if over-ventilation with nitrogen was continued for longer than 17 sec. A more rapid fall of arterial oxygen tension can be produced by sudden reduction of the environmental pressure to below 140 mm Hg whilst air is breathed. Thus in one series of experiments in which the arterial oxygen tension was reduced to below 20 mm Hg in about 1 sec, unconsciousness ensued 8 sec after the induction of arterial hypoxaemia (Ernsting *et al.* 1960). The delay between a sudden occlusion of the cerebral circulation and loss of consciousness in man also amounts to between 7 and 8 sec (Rossen, Kabat & Anderson, 1943). Thus the time which elapses between a sudden reduction of the arterial oxygen tension to below 20 mm Hg and the onset of unconsciousness is very similar to the interval which occurs between sudden occlusion of the cerebral circulation and loss of consciousness. Kety (1950) has calculated that at any one moment the total oxygen content of the brain and of the cerebral capillary blood is about 7 ml. Thus at the normal level of cerebral oxygen consumption the oxygen tension of the brain following cessation of the supply of this substance would be reduced to zero in about 8 sec. These results suggest that when unconsciousness supervenes following the sudden induction of severe cerebral hypoxia the cellular oxygen tension in many regions of the brain will be virtually zero. This conclusion is in close agreement with the results of calculations made by Thews (1962) with respect to hypoxia of slow onset. His calculations suggest that when the arterial oxygen tension is

reduced to the level which produces unconsciousness, the oxygen tension of the neurones which are furthest from their vascular supply will be of the order of 2–4 mm Hg.

SUMMARY

1. Brief profound hypoxia was induced by voluntary over-ventilation whilst breathing nitrogen. Unconsciousness ensued when this procedure was performed for longer than 16 sec. Voluntary over-ventilation with nitrogen for 16 sec reduced the end-tidal oxygen tension to below 10 mm Hg for 8 sec.

2. Continuous recordings were made of the systemic arterial oxygen saturation and pH during 16 sec of nitrogen over-ventilation. The calculated minimal arterial oxygen tension was 16 mm Hg. There was therefore a reversal of the normal alveolar-arterial oxygen tension difference.

3. The oxygen saturation and pH of venous blood flowing through the jugular bulb, the femoral vein and the pulmonary artery were recorded continuously. The oxygen tension of the jugular blood exhibited the most rapid and most profound reduction when nitrogen was breathed. The femoral-vein oxygen tension exhibited only a very transient and slight fall, whilst the oxygen tension of the blood flowing through the pulmonary artery exhibited a moderate fall.

The author wishes to thank the Director General Medical Services, Royal Air Force, for permission to submit this paper for publication.

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Pathology of hypoxic brain damage in man

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The energy requirements of the brain demand amongst other things adequate supplies of oxygen and glucose. These are provided by the functions of respiration and circulation. Neurons are particularly susceptible to hypoxia since they have an obligative, aerobic, glycolytic metabolism. The adult brain receives about 15 per cent of the cardiac output, or as expressed in terms of blood flow, about 45 ml/100 g/minute in the adult and about twice as much in children (McIlwain, 1966). The respiratory quotient of the brain is almost unity and glucose is the principal source of energy by oxygenation. If the supply of oxygen or glucose is reduced below a critical level consciousness is lost after a few seconds and irreversible brain damage may occur if the 'hypoxia' is more prolonged.

Physiology

The supply of oxygen to the brain depends on the cerebral blood flow (CBF) and the oxygen content of the blood. Cerebral blood flow in turn depends on the cerebral perfusion pressure (CPP) which is defined as the difference between the mean systemic arterial pressure (SAP) and the cerebral venous blood pressure. Blood flow to the brain shows a remarkable capacity for remaining constant, only hypercapnia, hypoxia and extreme hypotension affecting it to any marked extent. The preservation of CBF in response to changes in arterial blood pressure is brought about by autoregulation which can be defined as the 'maintenance of a relatively constant blood flow in the face of changes in perfusion pressure' (Harper, 1972). The mechanism of this autoregulation is still uncertain but it appears to be lost or at least severely impaired in a wide range of acute conditions producing brain damage (Bruce *et al*, 1973; Harper *et al*, 1975). Thus there are many situations in which cerebral autoregulation may be impaired before an episode of hypoxia. The level of CPP at which brain damage is produced is not known in man but in the presence of normal autoregulation the critical level of SAP is about 50 mm Hg (Harper, 1972). In primates with a normal PaO_2, it would appear that brain damage does not occur until the CPP falls to less than 25 mm Hg (Brierley *et al*, 1969).

The energy state of the brain may also be severely reduced in the presence of normal supplies of oxygen and glucose by substances which poison the oxidative enzymes of nerve cells. These considerations form the basis of the various categories of brain hypoxia (Brierley, 1976; Adams, 1976).

Categories of brain hypoxia

1 STAGNANT
(a) Ischaemic is due to local or generalized arrest of blood supply; (b) oligaemic is due to local or generalized *reduction* in blood supply.

2 ANOXIC AND HYPOXIC
(a) Anoxic, an absence of oxygen in the lungs which leads to tissue anoxia; (b) hypoxic, a reduced oxygen tension in the lungs which leads to tissue hypoxia.

3 ANAEMIC
Anaemic is where there is insufficient haemoglobin in the blood to carry the oxygen in chemical combination.

4 HISTOTOXIC
Histotoxic is due to poisoning of neuronal respiratory enzymes.

5 HYPOGLYCAEMIC
Hypoglycaemic is due to a deficiency of the substrate glucose.

6 FEBRILE CONVULSIONS AND STATUS EPILEPTICUS

Hypoxic brain damage

Hypoxic brain damage may occur in any situation where there is an inadequate supply of oxygen or glucose to nerve cells. It is therefore a potential hazard to any patient subjected to general anaesthesia, a severe episode of hypotension, cardiac arrest, status epilepticus, carbon monoxide or

barbiturate intoxication and hypoglycaemic coma. The eventual degree of clinical recovery will be determined by whether or not satisfactory resuscitation can be achieved before permanent brain damage ensues. Crises of this kind are not uncommon in clinical practice but the central question as to 'what duration of anoxia or ischaemia defines the watershed between recovery of the tissue and extensive permanent injury?' has not been critically defined in man (Plum, 1973). Reasons for this include the lack of precise physiological data about a patient's cardiovascular and respiratory status at the time of a crisis since the immediate priority is resuscitation, and the inadequate neuropathological examination of the brains from fatal cases.

Postmortem examination of patients with severe hypoxic brain damage is usually carried out under warrant by the forensic pathologist who often feels obliged to slice the unfixed brain in the mortuary. Under these conditions it is impossible to recognize recent hypoxic brain damage up to and including frank cerebral infarction even when subsequent histological examination shows severe and extensive neuronal necrosis. When the brain has been properly dissected after adequate fixation (up to three weeks' immersion in buffered 10 per cent formol saline) an infarct of about 18 to 24 hours' duration may just be recognizable but even an experienced neuropathologist may fail to identify extensive diffuse hypoxic brain damage if it is less than some three to four days' duration (figs 1 and 2). The extent and severity of hypoxic brain damage can be identified and its distribution analysed only by the microscopical examination of many large, bilateral and representative sections of the brain.[1] It is, however, often possible to establish that a patient has suffered hypoxic brain damage on the basis of a more restricted histological examination provided that the pathologist knows that certain parts of the brain are selectively vulnerable and is familiar with the cytological and histological appearances of ischaemic nerve cell change.

The identification of ischaemic cell change is made difficult in the human brain because of the frequent occurrence of histological artefact. The commonest artefacts are 'dark cells', 'hydropic cells' and 'perineuronal and perivascular spaces' (Cammermeyer, 1961). They are due partly to postmortem handling and to the slow penetration of fixative. Studies in experimental primates and in selected human material have shown that there is an identifiable process, namely ischaemic cell change, which is the neuropathological common denominator in all types of hypoxia.

The earliest histological stage of recent hypoxic neuronal damage in experimental animals in perfusion-fixed material is microvacuolation (Brown and Brierley, 1966; Brierley *et al*, 1971a and b; Meldrum and Brierley, 1973). This rather subtle histological change is difficult to identify in human material so that perhaps the earliest incontrovertible evidence in man of hypoxic brain damage is the second stage, ie, ischaemic cell change. The cell body and nucleus are shrunken and become triangular in shape. The cytoplasm, which usually still contains microvacuoles, stains intensely with eosin and from bright blue to dark mauve with the very useful Luxol fast blue/cresyl violet technique (Adams and Miller, 1970); the nucleus stains intensely with basic aniline dyes. The succeeding stage of ischaemic cell change with incrustations is characterized by

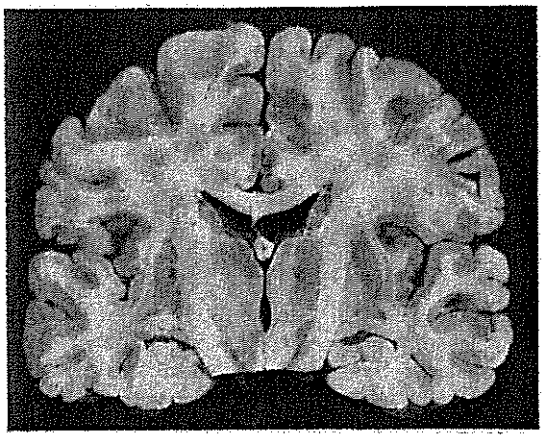

Fig 1 *Coronal section of brain from patient who survived 48 hours after cardiac arrest. There are no macroscopic abnormalities.*

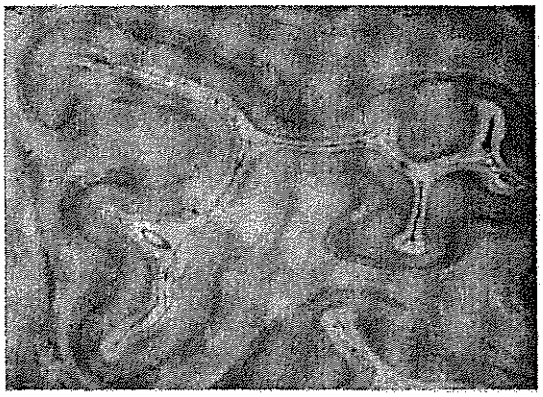

Fig 2 *Same patient as in figure 1. Note subtotal ('laminar') necrosis of the third, fifth and sixth cortical layers with relative sparing of the second and fourth layers (darker staining). Cresyl violet.* × *4.*

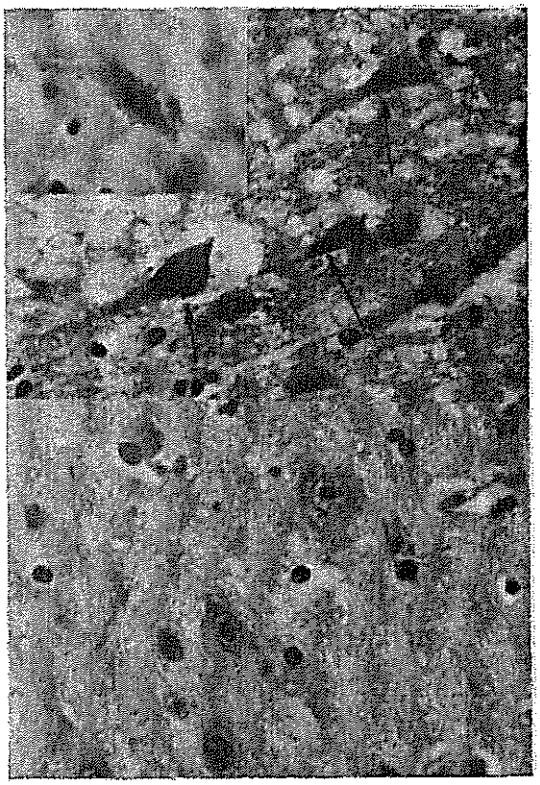

Fig 3

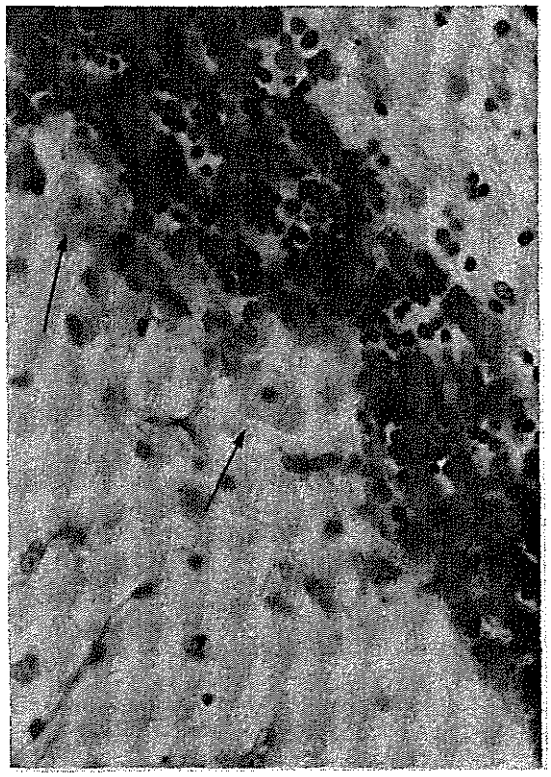

Fig 4

Fig 3 *Bottom: normal cortex. H and E × 500. Top: Ischaemic cell change. The nerve cells are small and triangular and contain hyperchromatic nuclei (arrows). The cytoplasm is intensely eosinophilic. There is also some disintegration of the neuropil. H and E × 500. Top inset: Ischaemic cell change with incrustations. Note the granules on the surface of the cell. H and E × 500.*

Fig 4 *Homogenizing cell change. Note the Purkinje cells with swollen homogeneous cytoplasm and hyperchromatic nuclei (arrows). Cresyl violet. × 500.*

further shrinkage of the nerve cell cytoplasm and the development of small, relatively dense granules lying on or close to the surface of the nerve cell (fig 3). Finally the neuron undergoes homogenizing cell change when the cytoplasm becomes progressively paler and homogeneous and the nucleus smaller. This type of change is most commonly seen in the Purkinje cells (fig 4) of the cerebellum. The time course of ischaemic cell change is relatively constant for neurons according to their size and site so that the interval between a hypoxic episode and death if between two and 18 to 24 hours can be assessed with reasonable accuracy. If the patient survives for more than 24 to 36 hours more advanced changes occur in neurons, and early reactive changes appear in astrocytes, microglia and endothelial cells. After a few days the dead nerve cells disappear and reactive changes become more intense, including the formation of lipid phagocytes, even though the latter may not appear if damage is restricted to neuronal necrosis. When survival is for more than a week or so the damaged tissue becomes rarefied due to loss of myelin and there is a reactive gliosis. Collagen and reticulin fibres are also laid own, the whole appearing as a glio-mesodermal reaction.

The differing susceptibility of nerve cells to hypoxia has been known for many years. According to Jacob (1963), 'in general the nerve cells are the most sensitive followed by oligodendroglia and astrocytes while the microglia and the cellular elements of the vessels are the least vulnerable'. Recent work suggests that local metabolic rather than vascular factors largely determine the pattern of selective vulnerability (Brierley, 1976).

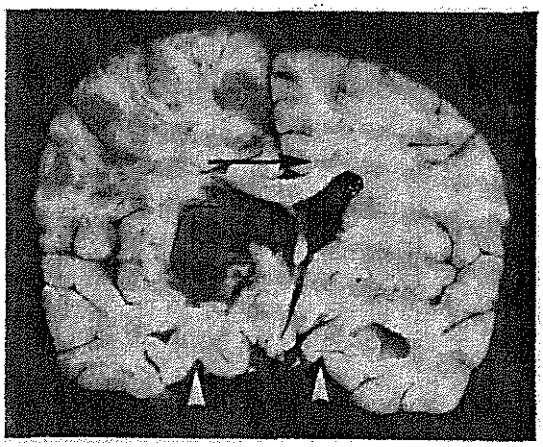

Fig 5 *Coronal section of brain from patient who survived three days after sudden stroke. There is a large recent swollen infarct in territories of left middle and anterior cerebral arteries. Part of the infarct is 'anaemic' and part is 'haemorrhagic'. Note the asymmetry of the lateral ventricles, the displacement of the midline structures to the right, the supracallosal hernia to the right (black arrow) and deep grooving (white arrows) along the line of bilateral tentorial herniae.*

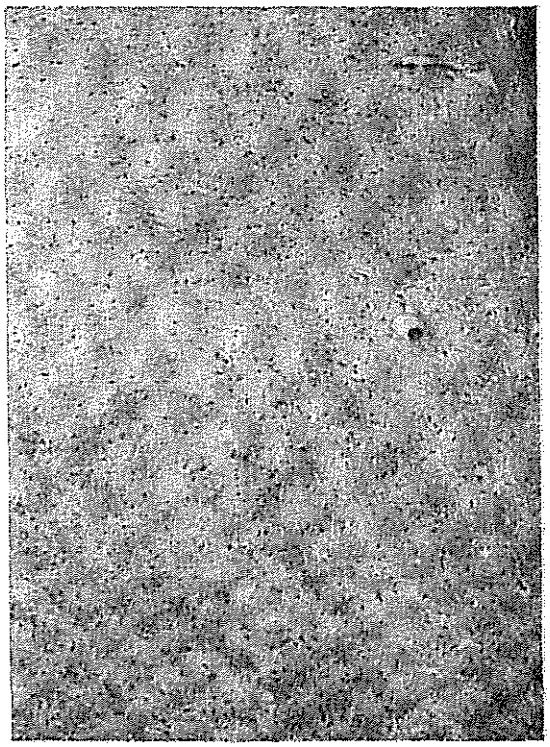

Fig 6 *Recent infarction in cerebral cortex. There is irregular pallor (infarction) of staining of the affected areas. H and E × 15·6.*

1 STAGNANT HYPOXIC BRAIN DAMAGE

This is divided into two main types, viz, ischaemic and oligaemic.

Ischaemic

If the blood flow through an artery is arrested, eg by thrombus or an embolus, an infarct will develop within part or the whole of the distribution of the occluded vessel. The earliest macroscopic change is swelling of the infarct and its edges may be just discernible in the fixed brain within 12 to 18 hours. The lesion may be 'haemorrhagic' or 'anaemic' (fig 5) and at an early stage there is irregular, blotchy pallor of the affected cortex (fig 6). A sharp

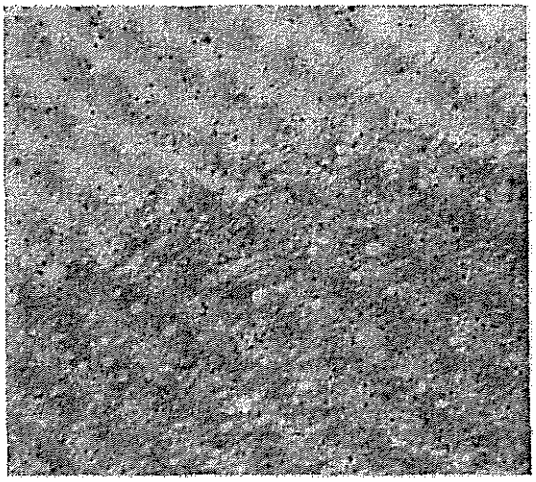

Fig 7 *Recent infarction in white matter. There is a sharply defined border between the abnormal (pale) and normal white matter. H and E × 40.*

and often very irregular line of demarcation between normal and abnormal myelin also appears early, the abnormal myelin staining palely (fig 7). A large infarct may swell sufficiently to constitute a space-occupying mass within 24 to 48 hours (Adams, 1966) resulting in tentorial herniation with secondary distortion of the mid-brain and infarction in the medial occipital (calcarine) cortex. The necrotic tissue is ultimately removed and replaced by a rather shrunken and cystic gliomesodermal scar.

A generalized arrest of blood flow to the brain is most commonly the result of cardiac arrest. This is usually a complication of some surgical procedure under general anaesthesia. Milstein (1956) estimated that about 300 deaths in the United Kingdom were caused by cardiac arrest related to surgery but by 1970 the number of such deaths had dropped to 100

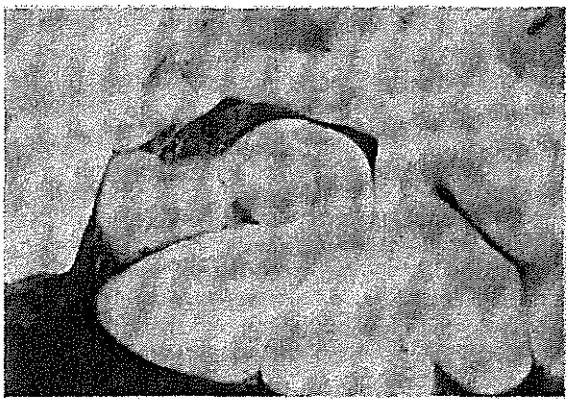

Fig 8a *Normal right Ammon's horn to compare with figure 8b.*

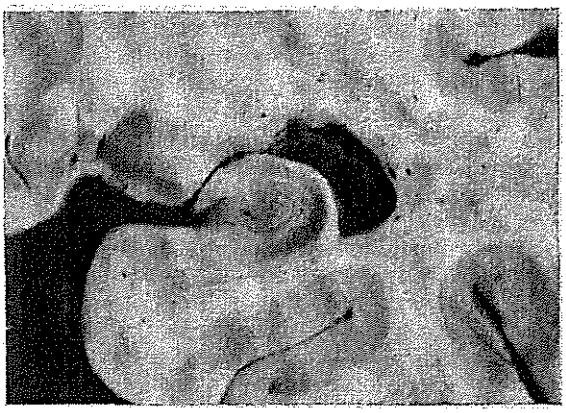

Fig 8b *Right Ammon's horn. Necrosis in the Sommer sector is seen macroscopically.*

Fig 9a *Normal right Ammon's horn. To compare with figure 9b. The arrows delineate the Sommer sector. Cresyl violet.* × 9.

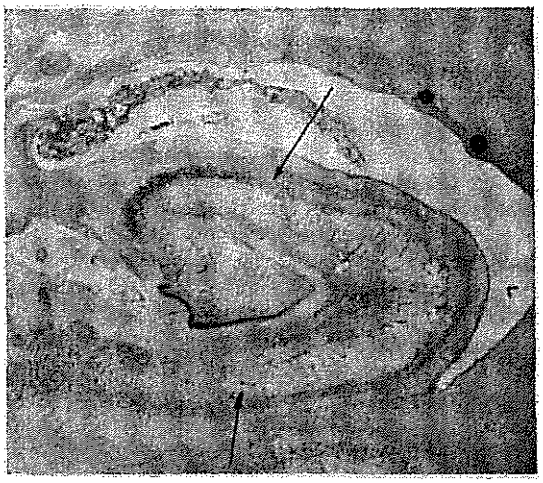

Fig 9b *Right Ammon's horn showing recent selective neuronal necrosis of Sommer sector (between arrows) and in endfolium. Cresyl violet.* × 9.

per annum in England and Wales (Wylie, 1975), the difference in mortality being attributed to better methods of resuscitation.

If cardiac arrest is of abrupt onset and occurs in a patient at normal body temperature, complete clinical recovery is unlikely if the period of arrest is more than five to seven minutes (Brierley, 1972). A short period of cardiac arrest combined with periods of reduced cerebral perfusion pressure before or after the arrest may be as important as the duration of complete arrest (Miller and Myers, 1972) and may lead to accentuation of the ischaemic damage in the arterial boundary zones (Brierley, 1976).

If death occurs within 24 to 36 hours of the arrest, the brain, apart from a variable degree of swelling, may appear normal externally and on section even after adequate fixation. Within 36 to 48 hours it is sometimes possible to identify laminar or patchy discolouration in the depths of sulci, particularly in the posterior halves of the brain and selective necrosis in the Sommer sector of the Ammon's horn (fig 8a and b). Microscopy reveals diffuse neuronal necrosis with a characteristic pattern of selective vulnerability. Ischaemic damage is commonly greater within sulci than at the crests of gyri and is maximal in the third, fifth and sixth layers of the parietal and occipital lobes (fig 2). In the Ammon's horn the Sommer sector and endfolium are the most vulnerable (fig 9a

and b). These changes are sometimes associated with necrosis of the baso-lateral portion of the amygdaloid nucleus. The pattern of damage in the basal ganglia is less constant and tends to be most frequent in the outer halves of the head and body of the caudate nucleus, and in the outer half of the putamen. Damage in the globus pallidus may occur in all types of hypoxia but is especially common in carbon monoxide intoxication. Primary hypoxic damage in the thalamus is most common in the anterior, dorsomedial and ventro-lateral nuclei. In the cerebellum there is characteristically diffuse necrosis of Purkinje cells. Damage to the brain stem nuclei tends to be more severe in infants and young children than in adults.

Patients with severe diffuse brain damage due to cardiac arrest rarely survive for more than a few days (Bell and Hodgson, 1974) but occasionally they may remain alive in a persistent vegetative state for up to six months or longer (Brierley *et al*, 1971; Jennett and Plum, 1972). With increasing survival, the necrotic tissue is replaced by a gliomesodermal scar. When this occurs there may be an appreciable reduction in the weight of the brain and evidence of atrophy of both the cortical gyri and cerebellar folia. In coronal slices ventricular enlargement may be considerable. Whereas the cortex of the parietal and occipital lobes will be reduced to a thin band of discoloured tissue, often with a line of cleavage between it and the underlying white matter, that of the frontal and temporal lobes may appear essentially normal. While the parahippocampal gyri are usually normal, the hippocampi may show the features of Ammon's horn sclerosis. Even when cortical necrosis is severe and survival is for only a few weeks the thalami may appear grossly normal. Eventually evidence of retrograde degeneration will be seen in the corresponding thalamic association nuclei (fig 10).

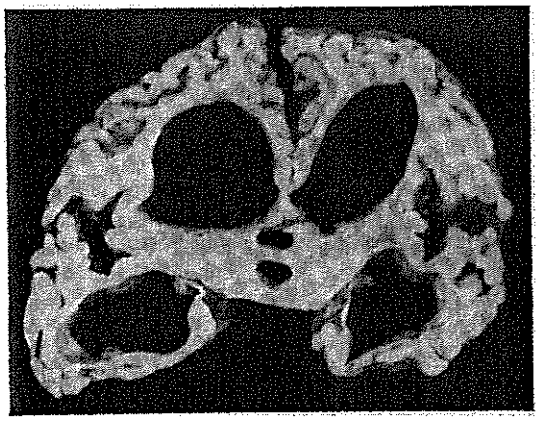

Fig 10 *Coronal section of brain from patient who survived for four years in a persistent vegetative state after cardiac arrest. The cortex is greatly narrowed and there is gross essentially symmetrical enlargement of the ventricles. The Ammon's horns and the thalami are also small.*

Oligaemic

Because of autoregulation a moderate fall in cerebral perfusion pressure does not lead to a reduction in cerebral blood flow. However, when vasodilatation is maximal, autoregulation ceases and the cerebral blood flow will fall parallel to the perfusion pressure. Oligaemic brain damage due to systemic arterial hypotension conforms to one of three patterns (Adams *et al*, 1966), of which the first two types are the most common.

1 Ischaemic damage is concentrated along the boundary zones between the arterial territories of the cerebral cortex and in the cerebellum (fig 11). If the lesions are large and of several days' duration they can be recognized macroscopically provided that the brain is cut in the coronal plane (fig 12a). They vary in size from foci of necrosis in the cortex to large, wedge-shaped lesions extending from the cortex almost to the angle of the lateral ventricle. In the cortex, damage is most frequent and most severe in

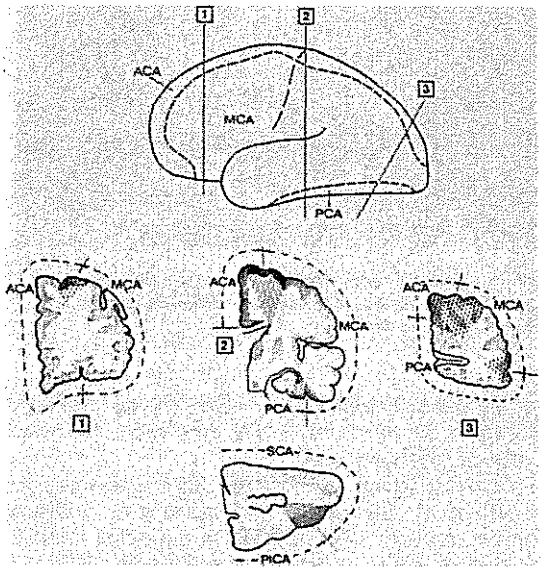

Fig 11 *Diagram to show arterial boundary zones in cerebral and cerebellar hemispheres. The right cerebral hemisphere is shown at three levels, viz, 1 = frontal, 2 = mid-temporal and 3 = occipital. Each boundary zone is stippled. ACA = anterior cerebral artery, MCA = middle cerebral artery, PCA = posterior cerebral artery, SCA = superior cerebellar artery and PICA = posterior inferior cerebellar artery.*

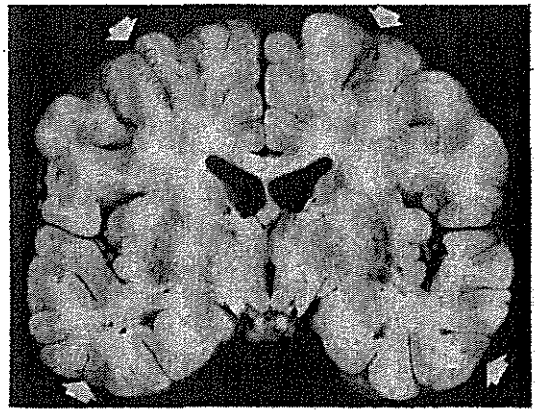

Fig 12a

Fig 12a *Coronal section of brain from patient who survived for 17 days after a myocardial infarct. Note focally haemorrhagic infarcts (arrows) in the boundary zones between the anterior and middle cerebral arterial territories, and between the middle and posterior cerebral arterial territories. Compare distribution of lesions with figure 11.*

Fig 12b *Same case as illustrated in figure 12a. Slices of cerebellar hemispheres to show duskily haemorrhagic infarcts at dorsal angle of each hemisphere, ie, in the boundary zones between the superior and posterior inferior cerebellar arterial territories. Compare with figure 11.*

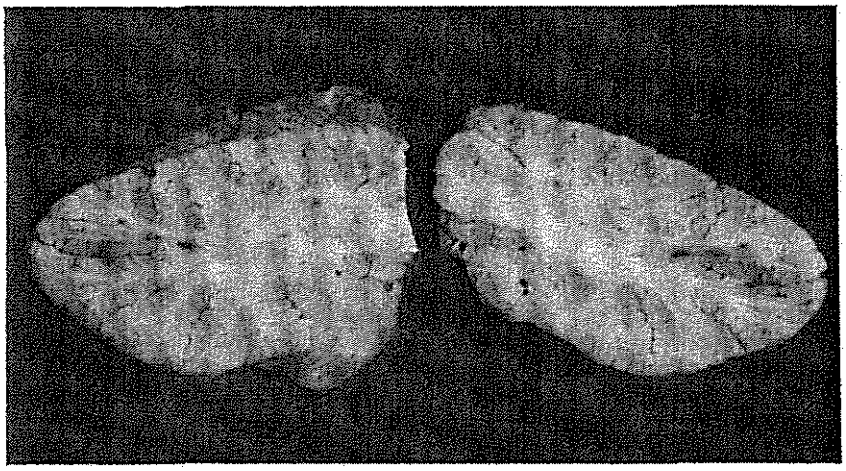

Fig 12b

the parieto-occipital regions, ie, in the common boundary zone between the territories of the anterior, middle and posterior cerebral arteries: it decreases towards the frontal pole along the intraparietal and the superior frontal sulci, ie, between the anterior and middle cerebral arterial territories, and towards the temporal pole along the inferior temporal gyrus, ie, between the middle and posterior cerebral arterial territories. The lesions are usually asymmetrical and may be unilateral, the pattern of ischaemic damage often being determined by atheroma and variations in the calibre of the vessels forming the circle of Willis. In the cerebellum the boundary zone between the territories of the superior and posterior inferior cerebellar arteries lies just beneath the dorsal angle of each hemisphere (fig 12b). There is variable involvement of the basal ganglia particularly in the head of the caudate nucleus and the upper part of the putamen. The Ammon's horn and brain stem are usually not involved. While infarction in the cortical boundary zones may occur in the absence of ischaemic lesions in the basal ganglia and cerebellum the converse is not common.

On the basis of clinical evidence (Adams *et al*, 1966; Adams, 1974) and experimental studies on primates (Brierley *et al*, 1969) this type of brain damage appears to be caused by a major and abrupt episode of hypotension followed by a rapid return to a normal blood pressure. It is often seen after a conscious patient has collapsed as a result of a sudden reduction in cardiac output, viz, due to ischaemic heart disease, and it may occur in the anaesthetized subject during dental or neurosurgical procedures, particularly in the sitting position (Brierley, 1970). More recently it has been described following the use of methylmethacrylic bone cement (Adams *et al*,

1972), in patients undergoing emergency treatment with antihypertensive agents (Graham, 1975) and in patients dying from blunt head injury (Graham *et al*, 1975). Because of the precipitate decrease in arterial pressure there is a transient failure of autoregulation and a severe reduction in CBF in the regions most removed from the parent arterial stems, ie, the boundary zones.

2 Ischaemic damage is generalized in the cortex of the cerebrum and cerebellum, is minor or absent in the hippocampi and is often severe in the thalami. The number of reported cases is small (Brierley and Cooper, 1962; Adams *et al*, 1966) but it would seem that this type of damage appears to be associated with hypotension of a relatively slow onset but of long duration.

3 Ischaemic damage is generalized in the cortex of the cerebrum and cerebellum but with variable accentuation along the arterial boundary zones. The hippocampi are usually spared and there is patchy damage in the basal ganglia. This type of damage appears to be associated with the abrupt onset of hypotension which is responsible for the accentuation of damage within the boundary zones followed by a sustained period of less severe hypotension which causes the diffuse damage.

2 ANOXIC AND HYPOXIC BRAIN DAMAGE

These terms imply that the blood leaving the lungs is either devoid of or has a greatly reduced oxygen content. Hypoxaemia of this severity will occur if there is obstruction of the air passages, after the inhalation of inert gases and in aviation accidents producing decompression. Even though it is still widely believed that brain damage can result from a simple reduction in the oxygen content of arterial blood, there is a lack of critical physiological data about cases purporting to show a correlation between neurological dysfunction and brain damage ascribed to the hypoxaemia. Indeed there is good experimental evidence in Rhesus monkeys and in baboons (Brierley, 1972) that the severity of the hypoxia required to produce brain damage also produces myocardial depression and a reduction in cardiac output. Thus, Brierley concluded that hypoxic hypoxia can produce brain damage only through the medium of a secondary depression of the myocardium, the pattern of damage being similar to that of oligaemic hypoxic brain damage as described above.

3 ANAEMIC BRAIN DAMAGE

This occurs classically in carbon monoxide poisoning. The neurological complications of carbon monoxide poisoning are many (Garland and Pearce, 1967) but there is not a combination of neurological and psychiatric symptoms that can be regarded as the specific consequences of such poisoning since similar symptoms and signs may be encountered after cardiac arrest, hypoglycaemia, etc.

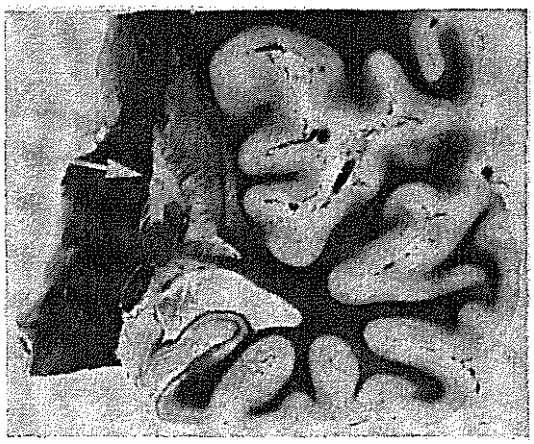

Fig 13 *Carbon monoxide poisoning. There is infarction of the superior pole of the globus pallidus (arrow). Celloidin section—myelin stain.* × *1·6.*

When death occurs within a few hours after poisoning, the organs display the pink/red colour characteristic of carboxyhaemoglobin. When survival is for 36 to 48 hours, the brain shows evidence of congestion, and petechiae are frequently seen in the white matter and the corpus callosum. Although there is a particular predilection for infarction of the globus pallidus in carbon monoxide poisoning (fig 13), there is also neuronal necrosis in other selectively vulnerable regions such as the Ammon's horn and the cerebral and cerebellar cortex.

Changes in the white matter are a common and often conspicuous neuropathological consequence of carbon monoxide poisoning. Damage to white matter tends to occur, particularly in patients who develop delayed signs of intoxication after a period of relative normality following acute poisoning.

Recent experimental work in the Rhesus monkey (Ginsberg *et al*, 1974) has underlined the importance of systemic circulatory factors in the production of brain damage, the concentration of damage in the white matter possibly being due to a combination of a toxic effect of carbon monoxide together with a moderate reduction in blood flow and perhaps an additional acidosis.

4 HISTOTOXIC BRAIN DAMAGE

The histotoxic effects of the cyanide ion and sodium azide are due to the inhibition of cytochrome oxidase. In acute intoxication death ensues rapidly from respiratory failure. In such cases the brain shows

hyperaemia and multiple petechial haemorrhages. In longer surviving cases necrosis has been identified in the lentiform nucleus and in the cortex of the cerebrum and cerebellum (Brierley, 1976). Experimental studies have now shown that brain damage produced by either cyanide (Brierley, 1975) or azide (Mettler and Sax, 1972) cannot be attributed to histotoxic hypoxia alone but results from their secondary effects on respiration and circulation.

5 HYPOGLYCAEMIC BRAIN DAMAGE

Hypoglycaemia in man may lead to permanent brain damage. It may be due to an excess of insulin given either for the treatment of diabetes mellitus or psychosis and in rare instances of islet cell tumour of the pancreas and in examples of idiopathic hypoglycaemia in infants (Brierley, 1976).

In cases of short survival the brain may appear normal. There may be atrophy of the cortex and hippocampi and enlargement of the ventricular system in cases surviving for a number of weeks. Microscopy shows that the brain damage is very similar in type and distribution to that seen in ischaemic hypoxic brain damage, ie, nerve cell loss and a glio-mesodermal reaction in the striatum, the cortex and the hippocampus, except that there is often relative sparing of the Purkinje cells in the cerebellum.

Studies of hypoglycaemia in experimental animals have shown that ischaemic cell change is the principal neuropathological consequence of uncomplicated hypoglycaemia (Meldrum *et al*, 1971; Brierley *et al*, 1971a and b) and in longer surviving animals there is nerve cell loss and a variable glio-mesodermal reaction in the striatum, the cerebral cortex and the hippocampus (Kahn and Myers, 1971). These experiments show that the blood glucose level must fall to about 1 mmol/l (20 mg/100 ml) if uncomplicated hypoglycaemia is to produce brain damage, though a higher level of blood sugar may produce similar damage if complicated by some hypotension, hypoxaemia or epileptic activity. It is therefore quite possible that if a patient has been in hypoglycaemic coma for some time, both oligaemic and hypoxic factors may have contributed to the brain damage.

A different type of neuropathological change has been described in the human infant as a consequence of hypoglycaemia (Anderson *et al*, 1967). Neuronal changes were generalized and included chromatolysis with cytoplasmic vacuolation in some and fragmentation of nuclear chromatin in others. It has, however, been suggested that these appearances could be attributed to autolysis (Brierley, 1976).

6 FEBRILE CONVULSIONS AND STATUS EPILEPTICUS

Status epilepticus may be defined broadly as a convulsive episode lasting over an hour without an intervening period of consciousness (Corsellis and Meldrum, 1976). It has long been recognized as a serious danger to life at any age but it offers a special threat in childhood. The basic neuropathology is that of severe and diffuse ischaemic damage of stagnant hypoxic type in which there is widespread necrosis of the cortex, Ammon's horn, basal ganglia, thalamus, cerebellum and parts of the brain stem (fig 14). Thus status epilepticus, particularly in children, constitutes a medical emergency. Fortunately many patients make an uneventful recovery but some have a permanent intellectual or neurological deficit caused by hypoxic brain damage.

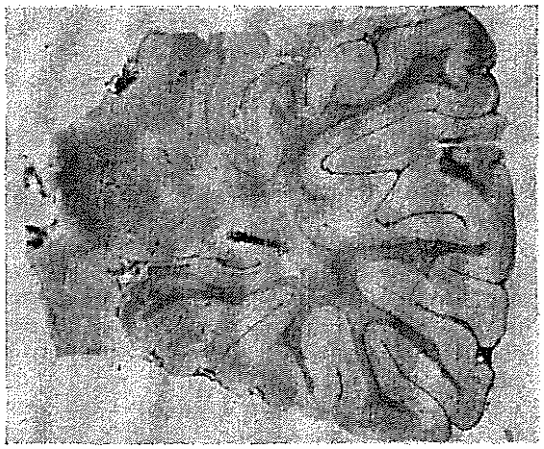

Fig 14 *Status epilepticus. Celloidin section of right temporal lobe from a child who died in coma five days after a series of convulsions. Note widespread neuronal necrosis in cortex and Ammon's horn. There is also some nerve cell loss in the thalamus. Cresyl violet.* × *1·8.*

Experimental studies in subhuman primate (Meldrum and Horton, 1973; Meldrum and Brierley, 1973; Meldrum *etal*, 1973) have emphasized that several factors may contribute to the brain damage, eg, arterial hypotension and hyperpyrexia. Evidence of an impaired neuronal energy metabolism was also found due to a combination of excessive neuronal activity and accumulative effects of secondary changes such as hypoxia, hypoglycaemia, hypotension, etc.

Conclusions

Hypoxic brain damage may occur in diverse clinical situations where there is an inadequate supply of oxygen or glucose to nerve cells. Many patients who experience an episode of severe hypoxia die within a few hours when the pathologist will not be able to

identify any macroscopic abnormalities in the brain. If the patient survives for more than a few hours, however, varying degrees of damage are easily identified, particularly if the brain has been properly dissected after adequate fixation.

The identification of early hypoxic brain damage is made difficult in the human brain because of histological artefact. The earliest clearly identifiable structural damage is selective neuronal necrosis as shown by ischaemic nerve cell change with incrustation formation. If the hypoxic insult is more severe then frank infarction may occur. In each instance the necrotic tissue is replaced by a glio-mesodermal reaction.

The distribution of hypoxic damage is most easily assessed in large representative sections of the brain. It is not usually feasible for the general pathologist to undertake a comprehensive neuropathological analysis in every case of suspected hypoxic brain damage. Fortunately, however, it is possible to establish that a patient has experienced an episode of hypoxia sufficiently severe to produce widespread hypoxic damage by the histological examination of bilateral small blocks from the 'selectively vulnerable areas', namely, the arterial boundary zones, the Ammon's horns, the thalamus and the cerebellum.

My thanks to Professor J. H. Adams for helpful criticism, to Mrs Ann Gentles for typing the manuscript and to Mrs Margaret Murray for photographic assistance.

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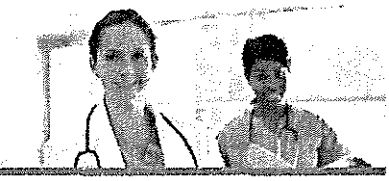
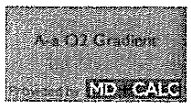


Respiratory Acidosis

Respiratory acidosis is primary increase in PCO_2 with or without compensatory increase in HCO_3^-; pH is usually low but may be near normal. Cause is a decrease in respiratory rate, volume (hypoventilation), or both due to CNS, pulmonary, or iatrogenic conditions. Respiratory acidosis can be acute or chronic; the chronic form is asymptomatic, but the acute, or worsening, form causes headache, confusion, and drowsiness. Signs include tremor, myoclonic



Treatment

- Adequate ventilation
- $NaHCO_3$ almost always contraindicated

Treatment is provision of adequate ventilation by either endotracheal intubation or noninvasive positive pressure ventilation (for specific indications and procedures, see Respiratory Failure and Mechanical Ventilation). Adequate ventilation is all that is needed to correct respiratory acidosis, although chronic hypercapnia generally must be corrected slowly (eg, over several hours or more), because too-rapid P_{CO_2} lowering can cause a posthypercapnic "overshoot" alkalosis when the underlying compensatory hyperbicarbonatemia becomes unmasked; the abrupt rise in CNS pH that results can lead to seizures and death. Any K^+ and Cl^- deficits are corrected.

$NaHCO_3$ is almost always contraindicated, because HCO_3^- can be converted to P_{CO_2} in serum but crosses the blood-brain barrier slowly, thus increasing serum pH without affecting CNS pH. One exception may be in cases of severe bronchospasm, in which HCO_3^- may improve responsiveness of bronchial smooth muscle to β-agonists.

Key Points

- Respiratory acidosis involves a decrease in respiratory rate and/or volume (hypoventilation).
- Common causes include impaired respiratory drive (eg, due to toxins, CNS disease), and airflow obstruction (eg, due to asthma, COPD, sleep apnea, airway edema).
- Recognize chronic hypoventilation by the presence of metabolic compensation (elevated HCO_3^-) and clinical signs of tolerance (less somnolence and confusion than expected for the degree of hypercarbia).
- Treat the cause and provide adequate ventilation, using tracheal intubation or noninvasive positive pressure ventilation as needed.

Last full review/revision February 2013 by James L. Lewis, III, MD
Content last modified October 2013

Suicide By Asphyxiation Due to Helium Inhalation

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Abstract: Suicide by asphyxiation using helium is the most widely promoted method of "self-deliverance" by right-to-die advocates. However, little is known about persons committing such suicides or the circumstances and manner in which they are completed. Prior reports of suicides by asphyxiation involving helium were reviewed and deaths determined by the North Carolina Office of the Chief Medical Examiner to be helium-associated asphyxial suicides occurring between January 1, 2000 and December 31, 2008 were included in a new case series examined in this article. The 10 asphyxial suicides involving helium identified in North Carolina tended to occur almost exclusively in non-Hispanic, white men who were relatively young (M age = 41.1 ± 11.6). In 6 of 10 cases, decedents suffered from significant psychiatric dysfunction; in 3 of these 6 cases, psychiatric disorders were present comorbidly with substance abuse. In none these cases were decedents suffering from terminal illness. Most persons committing suicide with helium were free of terminal illness but suffered from psychiatric and/or substance use disorders.

Key Words: asphyxia, helium, suicide, right-to-life

(*Am J Forensic Med Pathol* 2010;XX: 000–000)

Publication, in 1991, of the right-to-die manifesto and suicide "how-to" guide, Final Exit: The Practicalities of Self-Deliverance and Assisted Suicide for the Dying,[1] raised a maelstrom of controversy regarding the appropriateness of suicide as a response to terminal or "hopeless" physical illness and exposed divisions within the right-to-die movement itself. In the 1990s, many right-to-die advocates were engaged in public education as to the purported virtues of advanced directives, living wills, and legalized physician-assisted suicide.[2] At the same time, other elements of this movement, including the Self-Deliverance New Technology (NuTech) Group, were developing technologies to "empower people to die on their own terms by controlling the timing and manner of their own death."[2 (p. 8)] NuTech members, including Derek Humphry, author of Final Exit, sought to identify multiple suicide methods that were swift, painless, failure-proof, inexpensive, and nondisfiguring. The group also considered it vital that the method be simple, leave little or no indication that the death was unnatural in nature, and not require a physician's assistance or prescription.[2]

With its detailed descriptions of diverse suicide methods and specific endorsement of the plastic bag asphyxiation method, publication of Final Exit brought an easily understood and generally effective suicide method to the masses. The book was a commercial success, appearing on the New York Times bestseller list and selling more than 1.5 million copies in the decade following its publication. In 2007, Final Exit was named one of the 25 most influential books of the past quarter-century by book critics and editors of USA Today.[3]

Concerns that suicides in nonterminally ill depressed persons might follow exposure to methods elucidated in Final Exit were soon raised,[4] and dramatic increases in plastic bag asphyxial suicides were observed in New York City[5] and the United States[6] in the year following publication of Final Exit. Investigators concluded that "most persons exposed to Final Exit were not terminally ill and had used it as a suicide manual ... (and that) it is likely that a psychiatric disorder would have been diagnosed in most of these people."[5 (p. 1509)]

Efforts by NuTech and others to develop a more effective suicide method and widely disseminate it to the public have continued to the present. In 2000, a supplement to Final Exit was published that presented the first description of helium-assisted plastic bag asphyxiation.[7] Advocates emphasized the enhanced lethality of this approach, reduction in time required for death to occur to less than 5 minutes, and elimination of the need for a sedative prescription. Proponents of the method also noted that materials needed to complete such suicides are readily accessible and that asphyxiation due to helium inhalation is often undetected by autopsy (where findings are typically nonspecific) or toxicological analysis (because special sampling and assay methods are required). Thus, such suicides are likely to remain undetected in cases where the helium delivery apparatus and plastic bag are removed before the death scene is examined and no other information is available implicating death by helium-assisted asphyxiation. Modifications of the helium method were published in 2002[8] and 2009,[9] a DVD including a step-by-step demonstration of the method is available for purchase,[10] and instructional videos depicting the method are accessible on the internet. A schematic of the helium delivery apparatus is presented in Figure 1.[9]

Given the recent development, broad dissemination, and notable lethality of helium-assisted suicide, we endeavored to better understand characteristics of suicides by this method. First, we reviewed findings of extant studies examining suicides by asphyxiation due to helium inhalation. Second, we report new findings from the largest series of these suicides heretofore examined. Results of this investigation may lead to improved identification of helium-assisted suicides by medical examiners, enhanced screening and prevention efforts on the part of physicians and other professionals treating individuals at risk for suicide, and shed new light on unintended deleterious consequences of widespread dissemination of detailed suicide methods to the general public.

MATERIALS AND METHODS

The current report presents findings from 2 related studies. The first is a review of published investigations of suicides by asphyxiation due to helium inhalation. The second is a case series of suicides by asphyxiation due to helium inhalation occurring in North Carolina between 2000 (the year in which the method was first described) and December 31, 2008.

Manuscript received January 19, 2010; accepted March 3, 2010.
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Supported by NIH grants DA15929, DA15556, DA021405 (M.O.H.) and DA007304 (M.T.H.).
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ISSN: 0195-7910/10/0000-0001
DOI: 10.1097/PAF.0b013e3181ed7a2d

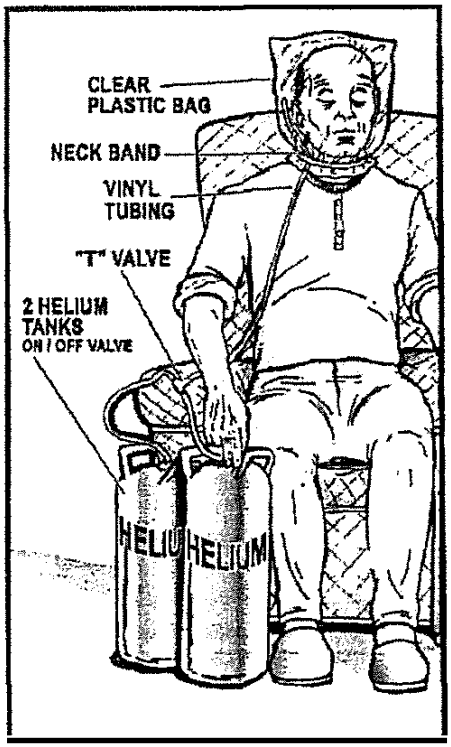

FIGURE 1. Schematic of plastic bag asphyxiation suicide using helium gas in final exit. Reprinted with permission from *Final Exit: The Practicalities of Self-deliverance and Assisted Suicide for the Dying.*[9] (p.4)

Identification of Published Reports

A broad search of the general medical literature was undertaken for any relevant reports addressing suicide by asphyxiation due to helium inhalation. This process entailed searching the PubMed database for the period January 1, 1957 to November 1, 2009 using the search phrase "suicide and helium." Seven pertinent records were identified as follows: 6 English-language case studies[11–16] and a Danish-language case study.[17] A search of EMBASE using the identical approach for the period January 1, 1988 to November 1, 2009 identified the same 7 reports. The 6 English-language reports relevant to this review were published between 2002 and 2007 and present a total of 14 cases.[11–16] The Danish study included a synoptic abstract in English indicating that the decedent was a 35-year-old man who had committed suicide with a plastic bag and helium using a "new and highly lethal technique."[17] The case reports included in this review constitute the entirety of published research on helium-assisted suicide and are presented in Table 1.

Identification of Suicides by Asphyxiation Due to Helium Inhalation in North Carolina

All deaths determined by the North Carolina Office of the Chief Medical Examiner (NCOCME) to be asphyxial suicides due to helium inhalation that occurred between January 1, 2000 and December 31, 2008, were included in this study. These suicides were identified through a search of the manner and cause of death fields of the electronic records maintained by the NCOCME. The presence of helium was confirmed by toxicological testing in 9 of 10 identified cases. Only the first reported case (ie, 2001) was not subjected to toxicological testing for helium. Specimens from suspected helium asphyxiation cases autopsied at the NCOCME are collected in 20 mL headspace vials. In some cases, given that one central laboratory conducts testing for all medical examiner cases in the state, blood samples are delivered to the NCOCME in standard collection vials. Immediately upon arrival, 5 mL of blood from the standard autopsy vial is transferred to a headspace vial for later analysis. Medical records associated with these deaths were manually reviewed and abstracted including the OCME Report of Investigation, State of North Carolina Death Certificate, Report of Autopsy, Toxicology Report, Case Encounter Form, Pathologist's Notes, and Supplemental Report of Cause of Death. On January 5, 2010, the University of North Carolina Institutional Review Board determined that the reported research does not require Institutional Review Board approval under pertinent federal regulations. Characteristics of the 10 cases identified are presented in Table 2.

RESULTS

Review of Published Cases

The first death attributed to suicide by asphyxiation due to helium inhalation reported in the medical literature occurred in September 2000,[11] shortly after the description of the method was published. Several investigators asserted that suicides by the helium method had not been seen in their localities prior to publication of the 2000 Supplement to Final Exit.[11,12,15,16]

The 14 decedents whose cases were presented in the 6 published reports ranged in age from 19 to 81 (M age = 50.0, SD = 21.8, median = 48.5). Between these extremes, decedents were approximately evenly divided between those in their 20s, 30s, 40s, 60s, and 70s. Medical and psychiatric histories were scant or entirely unreported for some cases, but revealed a history of depression, prior suicide attempt(s), paranoid schizophrenia, or some combination thereof in 4 (25.6%) cases. In 4 (25.6%) additional cases, psychiatric dysfunction may have contributed to the suicide, given that 3 of these decedents were determined to be in good health (ages 49, 49, and 76) and one mentioned the recent death of his wife as a reason for his suicide in a note left at the death scene. In 5 other cases (including 4 decedents in their 20s or 30s), no medical or psychiatric histories were reported. A terminal disease process was present in only 2 of 14 (14.3%) cases. In 2 (14.3%) additional cases involving men ages 71 and 78, "failing health" and "unspecified health problems" were possible contributing factors. Medical disorders were not implicated in 10 of 14 (71.4%) suicides.

In all reported cases, routine toxicological testing did not reveal the presence of helium and manner and cause of death determinations relied heavily on death scene investigations. Autopsy findings tended to be absent or nonspecific in the 12 cases that involved an autopsy.

In 8 cases (57.1%), a suicide note was found, and in 4 cases (28.6%) right-to-die literature was found at the death scene.

A number of helium delivery devices were employed. Five cases involved use of a mask; 4 of these cases were reported in 2002 or 2003, before plastic bag asphyxiation (without use of a mask) became preferred by advocates of the helium method.[8] Characteristics of the plastic tubing used, use of rubber bands and Velcro straps to secure plastic bags to the neck, types of helium canisters employed, and use of multiple plastic bags in 1 case were consistent with published descriptions of helium-assisted suicide.[8]

Characteristics of Suicides by Asphyxiation due to Helium Inhalation in North Carolina

Asphyxial suicides in North Carolina involving helium inhalation tended to occur almost exclusively in non-Hispanic, white

TABLE 1. Published Case Reports of Suicides by Asphyxia Due to Helium Inhalation

Authors/Date/ Location	Characteristics of Decedent	Medical/Psychiatric History	Helium-Delivery Apparatus	Death Scene	Autopsy Findings	Toxicology Findings
Ogden and Wooten (2002), South Carolina[11]	Woman, 60, white, suffering from adenoid cystic carcinoma with related eye involvement and diplopia. Death occurred 9/2000	History of depression and a prior suicide attempt. Unclear whether depression/suicide attempt antedated carcinoma diagnosis.	Found with surgical mask over face and clear plastic bag over head. Next to body was refillable industrial tank of helium. Clear plastic tube led from plastic bag to helium tank valve.	Decedent discovered on living room floor of home with suicide note and copy of her will. The book Final Exit, Final Exit videotape, and Spring 2000 Hemlock society newsletter were found on a nearby coffee table.	Does not appear an autopsy was conducted. It was noted at death scene that decedent's skin color was unremarkable and no external signs of poisoning were observed.	Blood/urine tests for medications and psychoactive substances were negative.
Gilson et al. (2003) Tucson, Arizona[12]	Cases 1 and 2: man, 49 and woman, 48, who were common-law married.	No specific information presented; decedents were reportedly in good health. Motivation for suicide unclear.	Each decedent had 3 plastic bags over their heads, which were secured by elastic straps around their necks.	Couple found lying supine by police on floor of master bedroom in their residence. Couples' attorney had called police after receiving a mailed suicide note. No right-to-die materials found.	Remarkable only for early decompositional changes.	Unremarkable for both decedents.
	Cases 3 and 4: husband, 78; wife, 76	Husband reportedly in "failing health" and "depressed"; wife in "good health" other than a recent minor elective surgery.	Both decedents were wearing filter cartridge-style masks attached to helium tanks with plastic tubing.	Couple found dead in bed by neighbor. Suicide notes were found close to bodies. Notes referring to the Hemlock society were found in apartment. No other right-to-die materials found.	External exams unremarkable. Internal exams not performed per family's wishes.	Negative for ethanol, medications, and illicit drugs for both decedents.
Gilson et al. (2003) Tucson, Arizona (continued)	Case 5: man, 81	Advanced squamous cell carcinoma of throat, cachectic.	Plastic bag over head with plastic tube running from inside plastic bag to helium tank.	Found by daughter in bed. Family unable to provide information as to whether "right-to-die" literature or suicide note were found at death scene.	Not clear that an autopsy was conducted.	Blood and urine tests were negative, but it was not clear what substances were assayed.
	Case 6: man, 71	Decedent mentioned unspecified health problems and the recent death of his wife as principal reasons for his suicide.	Plastic bag over head secured with elastic band and Velcro strap at neck. Plastic tube from helium tank connected to the mask inside plastic bag.	Found expired in chair in living room of home by police. A suicide note found, but no right-to-die literature.	External exam unremarkable except for decomposition.	Toxicology tests not performed due to decomposition.
	Case 7: man, 25	Medical history unknown; motivation for suicide unclear.	Plastic bag over head with plastic tube running from helium tank to bag with tube passing through a sink where warm water was running.	Found dead in empty bathtub of his apartment by landlord. Right-to-die literature and suicide note were not found.	Unremarkable except for decompositional changes.	Remarkable only for ethanol (234 mg/dL) in decomposition fluid.
Gallagher et al. (2003), Indiana[13]	Woman, 19, well-nourished	History of prior suicide attempts (number and nature not described). No description of medical history. Had searched methods of suicide on the internet.	Decedent wore air filter gas mask coated with a substance similar to correction fluid. A helium tank obtained from a local supply company was attached via clear plastic tubing to the mask. Duct tape sealed mask to skin of face covering nose and mouth.	Decedent found supine in backseat of car with helium tank on floor and valve between knees. Many signed suicide notes and a page from the "Church of Euthanasia" website entitled "How to kill yourself" were left in an envelope on the driver's seat. A hand-written map to a local general store was also found in the envelope with a list including tubing, mask and duct tape. A letter was found in decedent's residence describing where her body was located.	Conjunctival petechial hemorrhages bilaterally. Nares and oral cavity contained frothy white edema fluid. R lung = 670 g; L lung = 620 g. Lungs congested with severe pulmonary edema. No evidence of trauma, injury, or explanation for death other than helium inhalation.	Routine toxicology unremarkable. Presents a method by which specimens can be collected and analyzed for the presence of helium.
Auwaerter et al. (2007) Freiburg, Germany[14]	Man, 23	No information presented.	A helium gas canister was connected to a plastic bag with polypropylene tubing. The bag was over the decedent's head and affixed to neck with a rubber band.	Decedent was found dead in "lying" position in unidentified location. A nearly empty bottle of tequila, blister pack of travel sickness medication, and pack of Ibuprofen tablets were found.	Nonspecific findings included "an aqueous swelling of the brain and of the lungs and an acute hyperemia of the kidneys." No evidence of severe illness or injury.	Routine tests revealed a BAC of 0.9 mg/g; diphenhydramine in heart serum (0.81 μg/mL) and urine (2.2 μg/mL). Ibuprofen found in urine and gastric content. A positive test for helium by novel assay method was reported.

(*Continued*)

TABLE 1. *(Continued)*

Authors/Date/ Location	Characteristics of Decedent	Medical/Psychiatric History	Helium-Delivery Apparatus	Death Scene	Autopsy Findings	Toxicology Findings
Grassberger & Krauskopf (2007) Vienna, Austria[15]	Case 1: man, 28	History of paranoid schizophrenia; otherwise, no medical history reported.	Found with plastic bag over head sealed at neck with duct tape. A 10 L tank of party balloon helium was connected to the bag via plastic tubing.	Decedent found expired in his apartment reclining in a chair. Mouth contained frothy white edema fluid. A suicide note was left which named his mental illness as the primary reason for his suicide. No right-to-die literature found in domicile.	External exam unremarkable. Engorgement of right atrium and ventricle, pulmonary edema, and a few subpleural petechiae.	Blood/urine tests for 6 classes of illicit drugs were negative. Not clear whether ethanol was assayed.
	Case 2: man, 39	Not reported	Plastic tubing led from industrial helium tank into plastic mask.	Found expired in an empty bathtub wearing a plastic mask over face. Right-to-die literature and suicide note were found.	Autopsy remarkable. only for early decompositional changes.	Tests of decomposition fluid identified a BAC of 1 mg/L.
	Case 3: man, 39	Not reported.	Plastic bag over head connected via plastic tubing to a 10 L helium tank affixed to neck with rubber band.	Found supine on floor of his apartment with plastic bag over head. A suicide note was found.	External/internal exams unremarkable except for advanced decompositional changes.	Negative except for traces of benzodiazepines in urine.
Schon & Ketterer (2007) Bern, Switzerland[16]	Man, 64, white	Not reported	A gas canister labeled "helium" was found on a table at side of room opposite from where body was found. The helium canister was not connected to the 17 L blue plastic garbage bag that was found over the decedent's head. In addition to the plastic ribbon used to tie the bag, the decedent had inserted a rubber band into the bag's collar. The bag was secured tightly around decedent's neck.	Decedent found expired in hotel room lying supine on bed with garbage bag over head. No alcohol bottles, medications or drug paraphernalia were found. A rental receipt for the helium canister was found, but no suicide note or self-help materials. An inquiry at the decedent's home town revealed that another person in the area had committed suicide using the same method within the same week.	No external injuries/petechial hemorrhages found, except for a ligature mark impression attributed to a rubber band around neck. Nose, mouth, and airways filled with frothy reddish fluid. Lungs/brain edematous. Internal organs acutely congested. Pulmonary emphysema and hypertrophy/ dilation of right atrium/ventricle noted. No other potential causes of death were identified.	No obvious evidence of alcohol/drug abuse, but no toxicology assays performed.

TABLE 2. Characteristic of Suicides by Asphyxiation due to Helium Inhalation in North Carolina: 2000–2008

Year of Death	Characteristics of Decedent	Medical/Psychiatric History	Helium-Delivery Apparatus	Death Scene Description	Autopsy Findings	Toxicology Exam Findings
2001	Man, 47, never-married, white (non-Hispanic) graduate school education	Long history of depression treated by his physician. Depression listed as a contributing cause of suicide. Little information available about medical or psychiatric history or acute precipitants of suicide.	Plastic bag over head, secured with velcro tie around neck. Plastic tubing was taped to top of head, extended down left arm under shirt sleeve and exited at left cuff. The tubing was connected to a T-valve and attached to 2 helium tanks.	Found in living room of his home by a co-worker and police. Two bottles of temazepam and a will and suicide note found at scene.	Early decompositional changes noted at death scene; no autopsy conducted.	Trace levels of 7-aminoclonazepam, and temazepam (0.016 mg/L) were identified in a 1 mL sample of vitreous humor.
2003	Man, 31, married, white (non-Hispanic), 13 yr of education	Suicide note mentioned "chronic pain" as a reason for suicide. However, medical and psychiatric history are not known.	Clear blue, thin plastic bag over head secured with 2 large yellow rubber bands around neck. Clear plastic tube taped to inside of plastic bag, extending out of bag, looping around left arm and connected to helium tank.	Decedent found in his apartment. Had left a suicide note describing how he planned the suicide. No medications found in apartment.	Pathological diagnosis: bilateral pulmonary congestion. No significant external/internal injuries. Lungs: R lung: 750 g; L lung: 640 g. Parenchyma of both lungs show extensive congestion w/o obvious consolidation or focal lesions. Brain: 1500 g. Leptomeninges thin, delicate and congested. Cerebral hemispheres unremarkable w/mild generalized edema w/o evidence of herniation. Microscopic exams of lungs, kidneys, and brain show vascular congestion. No evidence of injury.	Two 8.0 mL aortic blood samples were positive for helium as was one lung sample. No ethanol detected in an 18.0 mL aortic blood sample.
2005	Man, 37, married, white (non-Hispanic); 16 yr of education	Medical and psychiatric history and acute precipitants of suicide are unclear.	Found with white plastic trash bag around head with tube hooked to helium tank valve at one end and the other end within the plastic bag. Tubing was connected to the helium tank with electrical tape. The bag was secured to neck with bag tie, which was knotted in a bow knot on right anterior neck. A clear vinyl plastic tube extended into the bag through a hole made in the rear of the bag space, held in place by black electrical tape.	Death occurred in motel. Decedent found supine in bed. Medications found at scene were an OTC sleep aid, Ibuprofen, and hydrocodone. Receipts from a local hardware store were found for helium tank, tubing, and tape No suicide note or right-to-die materials were found.	Pathological diagnoses: pulmonary vascular congestion and edema, slight diffuse cerebral swelling, moderate coronary atherosclerosis. R lung: 920 g; L lung 700 g. Lungs on section demonstrate marked vascular congestion Bronchial branches contain clear fluid and intra-alveolar edema. Brain: 1500g with mild diffuse swelling and narrowing of sulci. No evidence of acute trauma.	10 mL aortic blood sample revealed trace levels of cyclobenzaprine and propoxyphene and was positive (0.91 mg/L) for diphenhydramine. and helium. Diphenhydramine was believed to have contributed to the death. No ethanol or organic bases were identified.
2005	Man, 21, never married, white (non-Hispanic) 12 yr of education	History of symptoms, treatment, and hospitalization for paranoia/suicidal ideation. Not clear whether patient suffered from psychotic illness.	Plastic bag over head with elastic strap securing bag around neck. An empty helium canister found on floor beside decedent. A cylinder of helium and plastic tubing were found in decedent's bedroom closet.	Found in bedroom at parent's home sitting in chair. The following medications were found in home: Trazodone (100mg), Geodon (80mg), Risperdal (3mg), Trileptal (300mg), and Zoloft (50mg).	Pathological diagnosis: pulmonary vascular congestion and edema, cerebral edema, and early decompositional changes. R lung: 640 g; L lung: 590 g Brain: 1,500 g, microscopic lung sections show variable degrees of pulmonary vascular congestion and intra-alveolar hemorrhage.	Post-mortem exam revealed an ethanol level of .40 mg/dL and the presence of helium in 15.0 mL and 5.0 mL aortic blood samples, respectively.
2005	Man, 39, never married, white (non-Hispanic), 12 yr of education	No history of suicide attempts per family. Little information available about medical or psychiatric history and acute precipitants of suicide.	Found with plastic bag over head secured with a metal clip to hold bag tight around neck. Plastic tubing ran from a nearby helium tank to the back of the plastic bag. Duct tape covered front of bag and had 0.5 cm circular hole in it. Tube was connected to helium tank, which was turned on and near decedent's hand.	Found lying supine in bed at home by mother. No suicide note left, but insurance policy and will were found on coffee table.	Final anatomic diagnosis: congestion of lungs with early pulmonary edema. Brain: 1,325 g. Vessels over right hemisphere congested. R lung: 610 g; L lung: 560 g Lungs boggy with congestion. Microscopic sections show that alveolar spaces were partially filled with clear edema fluid.	Positive for helium in 4.0 mL subclavian vessel blood sample, but negative for ethanol in 17.0 mL subclavian blood sample.

(*Continued*)

TABLE 2. *(Continued)*

Year of Death	Characteristics of Decedent	Medical/Psychiatric History	Helium-Delivery Apparatus	Death Scene Description	Autopsy Findings	Toxicology Exam Findings
2005	Man, 34, unmarried, white (non-Hispanic); 9 yr of education	History of alcohol dependence and bipolar disorder. Prior psychiatric treatment for both disorders. Was living in car and taking Zoloft.	Had clear plastic bag over head with tubing connecting it to a helium tank. A velcro closure secured the bag around neck.	Found dead in driver's seat of a car parked in the yard of a relative's house. A picture of his girlfriend was found on dashboard.	Pathological diagnoses: pulmonary edema and vascular congestion; atherosclerotic coronary artery disease, focal, mild to moderate. R lung: 960 g; L lung 820 g. Lungs heavy and congested. Lung sections revealed areas of atelectasis, pulmonary edema, and collections of pigment-laden intra-alveolar macrophages.	20.0 mL and 6.0 mL aortic blood samples were positive for ethanol (70 mg/dL) and helium, respectively. Ethanol was listed as a contributing cause of suicide.
2006	Woman, 60, never married white (non-Hispanic), 12 yr of education	Obese (5'9", 303 lbs). No medical or psychiatric history information available except that EKG leads were found on right lower leg, left lower leg and left arm. No acute precipitants of suicide were identified.	Decedent had clear plastic bag over head with 1-2 inch plastic tubing attached to helium tank in back car seat and inside of plastic bag. A tan elastic band was used to secure bag to neck. The plastic tubing was taped to lower margin of plastic bag.	Decedent found in front passenger seat of car in motel parking lot where she had stayed. Letters to different people and "a very organized" suicide note were found in car. Note referred to pgs. 132–137 in Final Exit 3rd edition which describe helium-assisted suicide. Decedent had set e-mail to respond to messages with "Return to Sender due to Suicide."	Pathological diagnoses: Plastic bag over head with evidence of helium inhalation; pulmonary vascular congestion (R lung: 430 g; L lung: 400 g); decomposition. Sectioned lungs showed vascular congestion with patchy intra-alveolar edema. No evidence of acute trauma.	A 20-mL-blood sample from pleural cavity was positive for helium and ethanol (40 mg/dl). Elevated BAC may have been partially or totally due to decomposition.
2007	Man, 41, married (but recently separated from wife), white (non-Hispanic), 14 yr of education	Previously disabled in motor vehicle accident with neck and back injuries. Was reportedly depressed due to recent separation from wife and pending sale of home. Wife reported that decedent was taking prescribed antidepressants, Neurontin, Oxycontin, and Vicodin.	Clear blue plastic bag covered head and was wrapped with duct tape. Black tubing was connected at one end to the inside of bag and at the other end to a 65lb helium tank used to fill balloons for parties.	Found expired at home sitting in chair in basement. No suicide note left.	No autopsy.	A 13.0 mL subclavian blood sample was negative for ethanol, but positive for helium.
2007	Man, 45, never married, white (non-Hispanic)	History of alcohol and drug abuse and diabetes. Decedent has been very depressed per family's report. Family noted a history of social, medical and emotional problems. Was taking Coumadin, Clonidine, Aspirin, Verapamil, Atenolol, and Lovastatin.	Clear plastic bag was found over head. Two black tubes led from helium tank into the plastic bag. Had purchased these materials at local hardware store. The helium tank was from a party store balloon-filling kit.	Found sitting in chair in parent's home. Patient was pulseless and not breathing. The book Final Exit was lying open and face down on the bed. A suicide note was left describing how severely depressed the decedent had felt and apologizing for the suicide.	No autopsy, but blue nail beds and burst capillaries in lower legs bilaterally were observed at death scene.	19.0 mL subclavian blood sample was negative for ethanol and positive for helium.
2008	Man, 56, married, white (non-Hispanic), 12 yr of education	History of depression and substance abuse.	Decedent had a bag over his head with a tube attached to it and to a helium tank positioned on car passenger seat.	Found in car in garage at home by wife with car running and exhaust piped into the vehicle. A suicide note was found.	No autopsy.	18.0 mL subclavian blood sample was positive for helium and negative for ethanol. Carbon monoxide detected at <5.0% saturation.

OTC indicates over-the-counter; BAC, blood alcohol concentration; EKG, electrocardiogram.

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men who were relatively young (M age, 41.1; SD, 11.6; range, 21–60; median, 40.0). In 6 of 10 cases, decedents suffered from significant psychiatric dysfunction; in 3 of these 6 cases, psychiatric problems were present comorbidly with substance abuse. Medical histories identified chronic pain, disability, and chronic pain associated with injuries suffered in a motor vehicle accident, and diabetes (with probable coronary artery disease in 3 decedents). One decedent was found with electrocardiogram leads attached to her body, but autopsy and toxicological findings were negative for potential explanations for the death other than helium-assisted suicide. In none of the 10 cases were decedents suffering from terminal illness.

Helium delivery devices were consistent with those recommended in Final Exit (eg, use of T-valves, 2 helium tanks, Velcro and other neck fasteners), and all were associated with use of a plastic bag rather than mask.[8] In 5 cases, a suicide note was found; in 2 cases, a will was left; in 1 case, insurance papers were left; and in 2 cases, right-to-die materials were found.

Autopsies were performed in a majority of cases and typically revealed evidence of pulmonary vascular congestion and mild cerebral edema. Ethanol and diphenhydramine were considered contributing causes of death in 1 case each.

DISCUSSION

Despite reports identifying a plethora of prosuicide internet sites providing detailed instructions in methods of suicide including helium-assisted asphyxiation,[18] media accounts of helium-assisted suicides,[19–21] and the recent arrests of Final Exit Network members for allegedly assisting in asphyxial suicides involving helium,[22] scientific investigations of such suicides are largely absent from the medical literature. This dearth of information is unfortunate given the tragic consequences of such acts and because it is possible that suicides by the helium method are underestimated and increasingly common for reasons described later in the text.

The methods by which helium-assisted suicides are carried out have been carefully detailed and widely publicized and the approach is promoted as simple, painless, and quick.[8] Materials needed for helium-assisted suicides are easily obtained and inexpensive. One well-known internet vendor currently sells disposable helium tanks for less than $50, and reports that customers who bought helium tanks also often bought the book Final Exit.[23] Unless there is a high index of suspicion for helium involvement in a death, the death may be erroneously attributed to natural causes or underlying illness because standard toxicological assays are unlikely to detect helium and autopsy findings are generally nonspecific.[14,16] Standard toxicological assays using GC/MS employ helium as the carrier gas and therefore cannot detect helium unless another gas (eg, nitrogen) is substituted for the helium. Auwaeter et al[14] and Gallagher et al[13] developed useful methods of collecting, preserving, and analyzing gas samples taken from decedents' for qualitative detection of helium. In all North Carolina cases, helium-delivery devices were found at the death scene, and toxicological testing was conducted in 9 of 10 cases. However, it is possible that an unknown number of such suicides went undetected, if and when helium-delivery devices and plastic bags were removed from the death scene prior to investigation. The author of Final Exit states that a person may choose to leave right-to-die materials to be found to make an ethical statement that they are committing "rational suicide" or, conversely, make plans to have the helium delivery apparatus and plastic bag removed following their death if they prefer to keep the suicidal nature of the death concealed.[8] Toxicological testing for helium has been conducted at the NCOCME in suspected cases since 2003 by a novel testing procedure using a dual cell thermal conductivity detector.[24]

Of particular concern, are recent national reports of notable increases in the prevalence of suicide due to suffocation (a category that includes deaths by plastic bag asphyxiation with or without helium assistance as well as hanging and strangulation) since the 1990s and especially since 2000.[25–27] Such increases have been observed in respondents of widely varying ages, including adolescents, and both genders. Observers have noted that the reasons for these increases are poorly understood, that declining rates of suicide observed in the 1990s have been largely reversed, and that recent increases in suicides due to suffocation account for most of the recent overall increases in rates of suicide.[28] It is possible that greater awareness of the plastic bag asphyxiation method and the enhanced lethality of the method when used with helium may account for the significant increases in suicides due to suffocation reported since 2000.

Given the national growth in adolescent, young adult, and adult suffocation suicides since 2000,[25,26] and relatively young age, psychiatric dysfunction, and absence of terminal illness characteristic of many identified cases, it is possible that many persons committing suicide by the helium method are neither hopelessly nor terminally ill, but rather psychiatrically disordered. Although the author of Final Exit cautions readers to be certain they are hopelessly ill, and not just depressed and to talk to their doctor,[8] depressive illness and substance dependency often impair the very capacities required to make these assessments and undertake these actions.

Prospective studies are needed to better understand the prevalence, incidence, predictors, and characteristics of asphyxial suicides due to helium inhalation. It is important to learn more about decedents' medical and psychiatric histories and the circumstances in which depressed and/or suicidal persons encounter descriptions of the helium method (eg, internet demonstrations of the process). At present, professionals working with persons at risk for suicide should routinely assess whether patients have read or viewed instructional materials describing specific methods of suicide such as helium-assisted plastic bag asphyxiation. Inquiries of this nature do not increase subsequent risk for suicide and can provide critically important information to guide appropriate preventative actions where indicated.[29,30] Medical examiners should also increase their index of suspicion for suicides by asphyxiation associated with helium inhalation. Medical ethicists and the general public may also want to carefully weigh the unintended adverse consequences of widely disseminated suicide methods likely to appeal to some depressed persons (irrespective of their physical health status or age) against the putative benefits associated with making these methods more widely known and available.

ACKNOWLEDGMENTS

The authors thank P. Barnes, Administrative Services Manager, and other staff of the North Carolina Office of the Chief Medical Examiner for their assistance.

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Report on Study of Methods of Execution &
Recommendations for Procedures

Submitted by: Louisiana Department of Public Safety & Corrections

February 18, 2015

House Resolution 142 of the 2014 Regular Legislative Session was enrolled and signed by the Speaker of the House on June 5, 2014 to study and make recommendations relative to the different forms of execution and the methods of execution to determine the best practices for administering the death penalty in the most humane manner.

The Secretary of the Louisiana Department of Public Safety and Corrections, James Le Blanc, chaired this work and held an organizational meeting on July 22, 2014 to organize a study committee to conduct this work. At that time, he assigned the following individuals to serve on the committee:

Burl Cain, Warden, Louisiana State Penitentiary
William Kline, Executive Counsel, DPS&C Legal Department
Seth Smith, Chief of Operations, DPS&C Office of Adult Services
Stephanie LaMartinere, Assistant Warden, Louisiana State Penitentiary
Bruce Dodd, Deputy Warden, Louisiana State Penitentiary
James Hilburn, Attorney, Shows Cali & Walsh, LLP
Jeff Cody, Attorney, Shows Cali & Walsh, LLP
Angela Whittaker, Executive Mgmt Officer, DPS&C Secretary's Office

The committee met on the following dates:

August 11, 2014: Planning meeting to develop resource and research needs of the group.

September 2, 2014: Report and discussion on research findings.

October 31, 2014: Report and discussion regarding identifying experts and discussion on additional research compiled.

December 4, 2014: Report and discussion regarding research and protocol options and drafting the required written report.

January 8, 2015: Review of research and draft report and consensus on recommendations for protocol options.

January 22, 2015: Review and approval final report.

Background:

Capital punishment, or the death penalty, is a sentence used in the justice process whereby an offender is put to death as punishment for a crime he/she committed. The death penalty in the United States is a legal sentence and states determine whether the death penalty will be used as a form of punishment for crimes committed within their borders.

In Louisiana, the death penalty may be applied in cases involving first degree murder, a violation of La. R.S. 14:30, in circumstances such as:

(1) The murder was committed during the commission of or attempt of, a specified felony such as aggravated kidnapping, second degree kidnapping, aggravated escape, aggravated arson, aggravated rape, forcible rape, aggravated burglary, armed robbery, assault by drive-by shooting, first degree robbery, second degree robbery, simple robbery, terrorism, cruelty to juveniles, or second degree cruelty to juveniles.

(2) The murder was committed while the defendant was engaged in "ritualistic acts."

(3) The murder was committed for pecuniary gain or pursuant to an agreement that the defendant would receive something of value.

(4) The defendant caused or directed another to commit murder, or the defendant procured the commission of the offense by payment, promise of payment, or anything of pecuniary value.

(5) The defendant has been convicted of, or committed, a prior murder, a felony involving violence, or other serious felony.

(6) The capital offense was committed by a person who is incarcerated, has escaped, is on probation, is in jail, or is under a sentence of imprisonment.

(7) The defendant was a drug dealer or has prior convictions involving the distribution of a controlled substance.

(8) The victim was under the age of 12 years.

(9) The victim was 65 years or older.

(10) The victim was a fireman, peace officer, or correctional officer engaged in his lawful duties.

(11) The victim was a witness in a prosecution against the defendant, gave material assistance to the state in any investigation or prosecution of the defendant, or was an eyewitness to a crime alleged to have been committed by the defendant or possessed other material evidence against the defendant.

(12) The murder was especially heinous, atrocious, cruel or depraved (or involved torture).

Before a jury may impose the death penalty it must consider whether there were any mitigating circumstances against imposing the death penalty. Louisiana Code of Criminal Procedure Art. 905.5 provides for the following mitigating circumstances:

(a) The offender has no significant prior history of criminal activity;

(b) The offense was committed while the offender was under the influence of extreme mental or emotional disturbance;

(c) The offense was committed while the offender was under the influence or under the domination of another person;

(d) The offense was committed under circumstances which the offender reasonably believed to provide a moral justification or extenuation for his conduct;

(e) At the time of the offense the capacity of the offender to appreciate the criminality of his conduct or to conform his conduct to the requirements of law was impaired as a result of mental disease or defect or intoxication;

(f) The youth of the offender at the time of the offense;

(g) The offender was a principal whose participation was relatively minor;

(h) Any other relevant mitigating circumstance.

Pursuant to La. R.S. 15:569 and 570, every sentence of death executed on or after September 15, 1991, shall be by lethal injection, that is, by the intravenous injection of a substance or substances in a lethal quantity into the body of the offender until such person is dead.

Including Louisiana, there are currently 34 states that authorize the death penalty. Most all of these states have adopted lethal injection as the primary means of implementing the death penalty. While 18 of those states have solely authorized lethal injection as the execution method, the rest of the states that impose the death penalty have also set forth alternative methods of execution such as electrocution, lethal gas, hanging, and the use of firing squads. The methods of execution for each such state are set forth in the chart below.

Research from Other Capital Punishment States:

State	Lethal Injection	Electrocution	Gas Chamber	Hanging	Firing Squad	Methods and Alternatives	Lethal Injection Drugs
Alabama	x	x				Lethal injection, unless inmate affirmatively selects electrocution	500 mg - midazolam hydrochloride; 600 mg - rocuronium bromide; 240 milliequivalents - potassium chloride
Arizona	x		x			Lethal injection; inmate sentenced on or before 11/15/92 may choose lethal injection or lethal gas	midazlam/ hydromorphone
Arkansas	x	x				Lethal injection, but electrocution if lethal injection declared unconstitutional	Statute specifies a barbituate preceded by a benzodiazepine
California	x		x			Lethal gas or lethal injection may be chosen by inmate; if inmate fails to choose either method, then lethal injection	
Colorado	x					Lethal injection	Statute specifies sodium thiopental or equivalent
Connecticut	x					Lethal injection	
Delaware	x					Lethal injection	
Florida	x	x				Lethal injection, unless inmate affirmatively selects electrocution; if both deemed unconstitutional, then any constitutional method	
Georgia	x					Lethal injection	
Idaho	x					Lethal injection	
Indiana	x					Lethal injection	
Kansas	x					Lethal injection	
Kentucky	x	x				Lethal injection; inmates sentenced on or before 3/31/98 may choose lethal injection or electrocution	

State	Lethal Injection	Electrocution	Gas Chamber	Hanging	Firing Squad	Methods and Alternatives	Lethal Injection Drugs
Louisiana	x					Lethal injection	midazlam/hydromorphone
Mississippi	x					Lethal injection	Statute specifies an ultra short-acting barbituate in combination with a paralytic agent
Missouri	x		x			Lethal gas or lethal injection	
Montana	x					Lethal injection	Statute specifies an ultra-fast-acting barbituate in combination with a chemical paralytic agent
Nebraska	x					Lethal injection	
Nevada	x					Lethal injection	
New Hampshire	x			x		Lethal injection; but may be by hanging if lethal injection deemed "impractical"	Statute specifies an ultrashort-acting barbituate in combination with a chemical paralytic agent
New Mexico	x					Lethal injection, but only for crimes committed prior to July 1, 2009; otherwise, capital punishment repealed	
North Carolina	x					Lethal injection	
Ohio	x					Lethal injection	midazlam/ hydromorphone
Oklahoma	x	x			x	Lethal injection; but electrocution if lethal injection held unconstitutional; if both lethal injection and electrocution held unconstitutional, then firing squad	midazlam/ hydromorphone

State	Lethal Injection	Electrocution	Gas Chamber	Hanging	Firing Squad	Methods and Alternatives	Lethal Injection Drugs
Oregon	x					Lethal injection	Statute specifies an ultra-short-acting barbituate in combination with a chemical paralytic agent and potassium chloride
Pennsylvania	x					Lethal injection	Statute specifies an ultrashort-acting barbituate in combination with chemical paralytic agents
South Carolina	x	x				Electrocution, but inmate may choose lethal injection; if fails to choose either, then lethal injection; but if convicted prior to date of statute, then electrocution unless chooses lethal injection; if lethal injection held unconstitutional, then electrocution	
South Dakota	x					Lethal injection	
Tennessee	x	x				Lethal injection; but offender, whose capital offense occurred prior to 1/1/99, may choose electrocution; if those methods deemed unconstitutional, then use any constitutional method	
Texas	x					Lethal injection	
Utah	x				x	Lethal injection; but firing squad if court determines inmate has a right to this alternative; if lethal injection is held unconstitutional, then firing squad	Statute specifies that one of the intravenous injections shall be sodium thipoental or equivalent

State	Lethal Injection	Electrocution	Gas Chamber	Hanging	Firing Squad	Methods and Alternatives	Lethal Injection Drugs
Virginia	x	x				Inmate may choose lethal injection or electrocution; if refuses to choose, then lethal injection	
Washington	x			x		Lethal injection, unless inmate chooses hanging	
Wyoming	x		x		*	Lethal injection; if lethal injection is held unconstitutional, then lethal gas. *Wyoming Senate recently approved legislation that allows for the use of a firing squad. Concurrence is pending by the House.	Statute specifies an ultra-short-acting barbituate, alone or in combination with a chemical paralytic agent and potassium chloride

It may be noted that the basis for utilizing a particular method of execution is not necessarily uniform among the states that offer more than one execution method. In some states, lethal injection is the primary execution method unless it should be declared unconstitutional, in which case the statute next provides for an alternate method, or a series of alternate methods in the event a successive method should be deemed unconstitutional. In other states, the condemned inmate is actually given a choice between lethal injection and another alternate method of execution.

In Louisiana, between 1919 and May 21, 1957, executions were conducted by the local parish law authorities. Prior to August 6, 1941, the penalty in Louisiana was carried out by hanging. The last hanging in Louisiana was on March 7, 1941. Between August 6, 1941 and June 9, 1961, executions were performed by electrocution in the electric chair. Between 1941 and 1957, a portable electric chair was transported from parish to parish in order that the death penalty could be administered in the parish where the crime was committed. After 1957, the State became responsible for administering the death penalty. Prior the reinstatement of capital punishment, the last death in the electric chair was on June 9, 1961.

In 1967, there was a rising tide of litigation against the death penalty. Federal courts suspended all executions pending a final decision by the U.S. Supreme Court. In 1972, the U.S. Supreme Court struck down all capital punishment laws as unconstitutional. All individuals under death sentenced at that time were re-sentenced to life in prison.

Effective October 1, 1976, the new Louisiana death penalty statute was adopted. The state's death penalty law was again revised in 1978, specifying that the sentencing judge must sign the death warrant rather than the governor. Capital punishment was reinstated in Louisiana on June 29, 1979.

In 1990, the legislature approved the use of lethal injection for those sentenced after January 1, 1991. In 1991, the legislature provided that every death sentence executed after September 15, 1991 would be by lethal injection. Since the reinstatement of the death penalty in 1979, there have been 28 executions performed, 20 by electrocution and 8 by lethal injection. The last one was on January 7, 2010.

The death penalty has risen to the forefront of national headlines recently due to the shortage of drugs historically used in the lethal injection process. States continuing to carry out executions have been forced to obtain drugs from other sources or substitute drugs normally used in the process. The alternatives have provided inmates with new grounds for appeal as they request transparency regarding execution methods.

To date, Louisiana has 85 offenders in custody who have been sentenced to death.

Study:

This study was conducted by reviewing available scientific, technical and safety literature related to various methods of execution. It is not intended to express an opinion about Louisiana's law for administration of capital punishment.

Lethal Injection Protocols:

Through February 2011, Louisiana had in place a three drug protocol which included 3 gm sodium thiopental, 50 mg pancuronium bromide and 240 meq potassium chloride.

In February 2011, after lawsuits, international trade restrictions and raw materials shortages complicated the market for drugs used in executions and the lack of availability of sodium thiopental, a decision was made to modify the three 3 drug protocol to use pentobarbital in lieu of sodium thiopental. This decision was based on experiences in Oklahoma using pentobarbital and the use of it being upheld in the United State District Court in the Western District of Oklahoma. Base on the change, the protocol then called for 1 gm of Pentobarbitol, 50 mg pancuronium bromide and 240 meq potassium chloride.

In January 2014, the protocol was again updated to provide two options for lethal injection. They are:

A) 5 gm of Pentobarbital or
B) 10 mg of Midazolam and 40 mg of Hydromorphone

Recommended Protocols:

A. Lethal Injection

We are recommending for consideration a lethal injection protocol that calls for the use of a one drug protocol utilizing 5 gm of Pentobarbital injected intravenously (IVP). This protocol has been used in numerous states, including Texas, as a one drug method. The availability of this drug to Departments of Corrections is however severely hampered and there could be issues obtaining a supply of Pentobarbitol or any other drug to be used for lethal injection. Drug suppliers have refused to sell drugs to the prison systems for use in executions and other entities have refused to sell to Louisiana DOC. It is this committees understanding that suppliers have threatened providers with no longer supplying the drugs to their businesses if they in turn sell to correctional agencies for the purpose of lethal injection. As a result, suppliers fear the backlash of bad publicity to their businesses if involved in providing the drugs to correctional agencies.

This committee also recommends reconsideration of a bill that combines the language from the original and amended versions of House Bill 328 of the 2014 Legislative Session authored by Representative Lopinto. The attached draft legislation (Appendix A) amending LA R.S. 15:569 outlines what is needed to allow for the recommendations within this report and will provide for the confidentiality of information related to the execution of a death sentence. The amended version of the prior bill stated that "The name, address, qualifications, and other identifying information of any person or entity that manufactures, compounds, prescribed, dispenses, supplies or administers the drugs or supplies utilized in an execution shall be confidential, shall not be subject to disclosure, and shall not be admissible as evidence or discoverable in any action of an kind in any court or before any tribunal, board, agency, or person. The same confidentiality and protection shall also apply to any person who participates in an execution or performs any ancillary function related to an execution and shall include information contained in any department records, including electronic records, that would identify any such person." Such legislation would provide some security to those tasked to and involved in carrying out the state's order to execute an individual as punishment for a qualifying crime.

It should also be noted that the U.S. Supreme Court will consider in April whether a multi-drug protocol used in recent lethal injections in other states violates the Constitution with regard to cruel and unusual punishment.

B. Induced Hypoxia via Nitrogen

It is the recommendation of this study group that hypoxia induced by the inhalation of nitrogen be considered for adoption as an alternative method of administering capital punishment in the State of Louisiana.

It is important to note that the recommendation would induce hypoxia, which is a deficiency of oxygen reaching the tissues of the body. In nitrogen induced hypoxia, there is no buildup of carbon dioxide in the bloodstream so the subject passes out when the blood oxygen falls too low. The research reviewed suggests that this method would be the most humane method and would not result in discomfort or cruel and unusual punishment to the subject.

Though the exact protocol and nitrogen delivery device have not been finalized, it has been determined that a Gas Chamber would not be used. Options for the nitrogen delivery device include a mask or a device similar to an oxygen tent house (small clear oxygen tent covering only the head and neck area). Research as to the best method of delivery is ongoing.

Oklahoma has recently filed similar legislation to allow for induced hypoxia (refer to Appendix B). Also, you will find attached the Executive Summary (Appendix C) of the research conducted in Oklahoma that supports this method as a humane method which does not require the assistance of licensed medical professionals. We have also attached the documents (Appendix D) which make up the research used in Oklahoma by this committee in developing this recommendation. This method is believed to be simple to administer and nitrogen is readily available.

Conclusion:

This committee submits this study response to House Resolution 142 of the 2014 Regular Legislative Session to make recommendations to consider relative to the different forms of execution and the methods of execution upon agreement that the above considerations represent the best practices for administering the death penalty in the most humane manner. There are two sides to the debate on the death penalty. Proponents believe that the death penalty reduces crime and provides safe communities, while also honoring the victim and those left behind who grieve a loss. Opponents believe that the cost of capital punishment doesn't justify the outcome, that it does not deter crime, and that there are social injustices that are not addressed that make justice system inequitable. As a whole, this committee takes no stand on either side of this debate, but submits this response based on the request for this study and the research and materials available to the group.

We close reminding readers that many are directly impacted by the process of capital punishment: the victim, the victim's friends and family; law enforcement; the judiciary, the prosecutor, the defense attorney, the jurors, the public, the offender, the offender's family, and the staff tasked to carry out the protocol, to name just a few. We understand that the decision to act on these recommendations for consideration is an enormous task before you that cannot be taken lightly. We trust that we have provided the information you needed to consider Louisiana's options.

Amendment to LSA-R.S. 15:569

Appendix A

**Delete current Sections A and B; rewrite statute to read as follows:

Section 1. R.S. 15:569 is hereby amended to read as follows:

§569. Place for execution of death sentence; manner of execution; confidentiality

Every sentence of death executed in this state on or after August 1, 2015, shall be conducted by either of the following methods:

(1) Lethal injection, which is the intravenous injection of a substance or substances in a lethal quantity into the body of a person convicted until such person is dead. Execution by lethal injection shall be permitted in accordance with procedures developed by the department.

(2) Induced hypoxia via nitrogen or an inert gas, which is the administration of gas in a lethal quantity upon the body of a person convicted until such person is dead. Execution by nitrogen or inert gas shall be permitted in accordance with procedures developed by the department.

A. The method of execution shall be chosen by the secretary of the department based upon the availability of the department to administer the lethal injection or induced hypoxia.

B. Every sentence of death imposed in this state shall be executed at the Louisiana State Penitentiary at Angola. Every execution shall be made in a room entirely cut off from view of all except those permitted by law to be in that room.

C. No licensed health care professional shall be compelled to administer the lethal injection or induced hypoxia.

D. The name, address, qualifications, and other indentifying information of any person or entity that manufactures, compounds, prescribes, dispenses, supplies, or administers the drugs or supplies utilized in an execution shall be confidential, shall not be subject to disclosure, and shall not be admissible as evidence or discoverable in any action of any kind in any court or before any tribunal, board, agency, or person. The same confidentiality and protection shall also apply to any person who participates in an execution or performs any ancillary function related to an execution and shall include information contained in any department records, including electronic records, that would identify any such person.

E. The provisions of the Administrative Procedure Act, R.S. 49:950, et seq., shall not apply to the procedures and policies concerning the process for implementing a sentence of death.

Appendix B

STATE OF OKLAHOI

1st Session of the 55th Legislature (2015)

HOUSE BILL 1879 By: Christian

AS INTRODUCED

An Act relating to criminal procedure; amending 22 O.S. 2011, Section 1014, which relates to the manner of inflicting punishment of death; providing alternative method for inflicting punishment of death; and providing an effective date.

BE IT ENACTED BY THE PEOPLE OF THE STATE OF OKLAHOMA:

SECTION 1. AMENDATORY 22 O.S. 2011, Section 1014, is amended to read as follows:

Section 1014. A. The punishment of death shall be carried out by the administration of a lethal quantity of a drug or drugs until death is pronounced by a licensed physician according to accepted standards of medical practice.

B. If the execution of the sentence of death as provided in subsection A of this section is held unconstitutional by an appellate court of competent jurisdiction or is otherwise unavailable, then the sentence of death shall be carried out by nitrogen hypoxia.

C. If the execution of the sentence of death as provided in ~~subsection~~ subsections A and B of this section is held unconstitutional by an appellate court of competent jurisdiction or is otherwise unavailable, then the sentence of death shall be carried out by electrocution.

~~C.~~ D. If the execution of the sentence of death as provided in subsections A ~~and~~, B and C of this section is held unconstitutional by an appellate court of competent jurisdiction or is otherwise unavailable, then the sentence of death shall be carried out by firing squad.

SECTION 2. This act shall become effective November 1, 2015.

55-1-6354 GRS 01/20/15

PROVINCE OF ONTARIO

CITY OF BURLINGTON

AFFIDAVIT OF LARRY D. SASICH, PharmD, MPH, FASHP

Comes now the Affiant, Larry D. Sasich, who, being first duly sworn by an officer authorized by law to administer oaths, deposes and states as follows:

1. My name is Larry Sasich, PharmD, MPH, FASHP. I am over the age of twenty-one and competent to testify to the truth of the matters contained herein. The factual statements I make in this affidavit are true and correct to the best of my knowledge and experience. The opinions I express in this statement are made to a reasonable degree of scientific certainty.

2. I am a Consultant specializing in drug safety and efficacy issues. My background, experience and qualifications, in part, include:

   a. Serving as a consultant to the Saudi Food and Drug Authority, Riyadh, Saudi Arabia.

   b. Serving as Chairperson of the Department of Pharmacy Practice at the LECOM School of Pharmacy in Erie, Pennsylvania, from 2007 to 2009;

   c. Serving as a consultant to Public Citizen Health Research Group, Washington, D.C., and

   d. Serving as a Consumer Representative on the Science Board of Food and Drug Administration's, an advisory committee to the FDA Commissioner.

3. I have a Masters in Public Health, Epidemiology and Public Policy from George Washington University and a Doctorate of Pharmacy from University of the Pacific. I have completed a residency in nuclear pharmacy from the University of New Mexico. I have also been elected a Fellow in the American Society of Health-System Pharmacists (FASHP). I have also been appointed on the Science Board to the Commissioner of the Food and Drug Administration.

4. I have also authored publications and/or presented analysis on drug safety issues. A complete list of my publications and presentations are listed in my Curriculum Vitae, which is appended to this statement.

5. I have previously been qualified in Mr. Warren Hill's case by the Fulton County Superior Court as an expert in pharmacy, public health, compounding pharmacies and drug safety, and Food and Drug Administration standards and, in that capacity, testified via affidavit and live testimony in the case about the use and practice of compounding pharmacies in the United States and, specifically, the many risks associated with the use of compounded drugs in lethal injections.

6. I have reviewed materials provided by the Office of the Georgia Attorney General and Georgia Department of Corrections (DOC) in response to a request by the Georgia Resource Center for information pertaining to the DOC's

lethal injection protocol and lethal injection drugs. I am aware that Georgia law shields from public scrutiny the identity of the manufacturer of lethal drugs, any middlemen or supply chain handlers, prescribing or other physicians involved in the execution process, pharmacists, compounding pharmacies, and so on. I have also reviewed the Georgia Supreme Court's recent opinion in *Owens, et al. v. Hill*, Supreme Court Case No. S14A0092, 2014 Ga. LEXIS 400 (May 19, 2014), which involves this case.

7. I have been asked by Mr. Hill's counsel to offer supplemental testimony to address some of the Georgia Supreme Court's assumptions, as set forth in the *Hill* opinion, about the level of risk associated with using compounded drugs to implement judicial lethal injections. Some of the information set forth below may be redundant of my previous testimony, but I reiterate this information to provide context.

I. The Risks of Using Compounded Drugs

8. The oversight of compounding pharmacies in the United States at this time is at best haphazard. That the FDA reports serious issues with some compounding pharmacies[1] does not indicate that compounding pharmacies as an

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[1] *See infra* note 3 and Attachments A, B, and C.

industry are subject to consistent, meaningful regulation by the FDA. To the contrary, given the FDA's limited oversight over compounding pharmacies, many instances of noncompliance with GMP guidelines likely go undetected and/or unreported.

9. As I testified previously, it is essential that compounding pharmacies use ingredients manufactured by FDA-registered and inspected manufacturers in order to ensure the quality of the final product. If poor quality ingredients are used, even the best compounding practices will not build quality and suitability into the final product. To the contrary, the safe production of injectable pentobarbital, or other drugs compounded from a non-sterile Active Pharmaceutical Ingredient (API) is technologically too difficult to do outside of Food and Drug Administration ("FDA") regulated facilities that must comply with federal Good Manufacturing Practice ("GMP") guidelines.

10. GMP guidelines are in place to eliminate the substantial risk of serious harm that results when API s and drugs are produced or compounded in the guidelines' absence. That is, the GMP guidelines are in place to prevent the preventable. APIs and drugs produced by manufacturers or compounding pharmacies that do not follow GMP guidelines pose a concrete, substantial risk of serious pain and suffering for those to whom the resulting drugs are administered.

Indeed, by definition, an API or drug produced outside compliance with GMP guidelines is adulterated.[2]

11. In Mr. Hill's case, there is no evidence that the pentobarbital selected for use in the non-traditional compounding of that drug for lethal injection has been produced in an FDA-registered and inspected facility. The API used in compounding pharmacies may come from the grey market, having been produced in non-FDA-registered, non-FDA inspected facilities. The ability to trace raw APIs used in compounding back to the original manufacturers for information on quality, packaging, storage, shipment conditions and chains of custody from a chemical's cradle to grave is incredibly difficult.

12. APIs often come from plants in China or India, which may or may not be registered with or have records of inspection by the United States FDA. Plants

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[2] 21 U.S.C. § 351 (a)(2)(B) ("A drug or device shall be deemed to be adulterated . . . if it is a drug and the methods used in, or the facilitated or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drugs meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.") (internal citation removed). *See also* U.S. Dept. of Health and Human Services, FDA, and Center for Drug Evaluation and Research, *Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing Cross-Contamination*, (Current Good Manufacturing Practices, Apr. 2013), available at http://www.fda.gov/downloads/Drugs/Guidances/UCM246958.pdf.

in China have been identified in which pesticides are manufactured using the same equipment as is used to make APIs.

13. The use of non-sterile and potentially contaminated APIs creates a serious risk of harm, including reactions from bacterial, fungal and endotoxin contamination. The presence of adulterants or growing organisms (like bacteria and fungus) may also accelerate chemical degradation resulting in a product that is sub-potent. The presence of growing organisms may also alter the final pH, with the potential to create instability and/or incompatibility with human blood.

14. A larger than expected moisture content of APIs risks inaccurate weighing that may also result in a product that is sub-potent.

15. Counterfeit or substandard ingredients, and/or poor practice on the part of drug compounders, often results in drugs which are contaminated or sub-potent and which do not have the strength, quality or purity represented on their labeling. The harm associated with the use of such contaminated or sub-potent drugs is not speculative. Indeed, the risk is demonstrated and extremely high.[3]

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[3] *See, e.g.*, Attachment A – Form FDA-483 Inspection Report of Downing Labs (July 16, 2014) (stating that the "inspection revealed sterility failures in 19 lots of drug products intended to be sterile, endotoxin failures in three lots of drug products, and inadequate or no investigation of these failures"), also available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM405669.pdf;

16. Several studies, including a survey conducted by the FDA in 2001, have reported a high prevalence of quality problems with various compounded drugs, including sub-potency and contamination. A follow-up survey of compounded drug products was conducted by the FDA in 2006. The results showed that 33% of compounded drugs failed analytical testing using rigorously defensible testing methodology. Testing by the Missouri Board of Pharmacy, which is the only state that regularly tests compounded drugs, revealed that compounded drugs fail tests for potency and purity on average around 25% of the time, an unacceptable failure rate consistent with rates observed by FDA. This is an extremely high failure rate, further supported by recent FDA inspection observations related to absent or limited sampling and testing of compounded drug products that would serve to identify substandard products prior to distribution.

Attachment B – FDA Warning Letter to Grandpa's Compounding Pharmacy, Inc. (May 2, 2014) (warning that the pharmacy "poses a significant contamination risk" as a result of "serious deficiencies in [its] practices for producing sterile drug products and flaws in the design of [its] aseptic processing areas."), also available at http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2014/ucm396239.htm; Attachment C – FDA Warning Letter to Sichuan Pharmaceutical Co., Ltd. (September 9, 2011) (identifying "significant deviations from Current Good Manufacturing Practice . . . for the manufacture of APIs," including a "failure to have appropriate procedures in place to prevent cross-contamination."), also available at http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm272791.htm.

17. Pharmacies compounding injectable pentobarbital, or other compounded drugs, may purchase APIs, of unknown quality from an unknown source. The Certificates of Analysis that accompany the APIs to the compounding pharmacy are of unknown origin and may be produced by unknown contract-testing laboratories whose competence has been questioned.

18. Compounded injectable pentobarbital, or other compounded drugs, may contain endotoxins which can induce an inflammatory response that manifests as a painful reaction, fever, and increased heart and respiratory rates that can cascade to organ failure and a painful death.[4] Contract-testing laboratories have failed to detect endotoxins in products they have tested.

19. Compounded drugs may have partial or complete lack of effect due to ingredient tampering or controlled drug diversion after analytical testing, circumstances that would be expected to prolong the execution process.

20. Compounded drugs that are super-potent may result in a person experiencing suffocation and gasping for breath.

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[4] *See* Attachment A and accompanying FDA Alert (warning that endotoxins like those found in samples at Downing Labs "cause a wide variety of serious reactions such as fever, shock, changes in blood pressure, and in other circulatory functions").

21. Compounded drugs contaminated by endotoxins or exotoxins will result in painful reactions.

22. Compounded drugs may be contaminated by solid particulate matter or precipitates, which are not necessarily visible to the naked eye or easily identifiable by the person preparing the compound. Compounded drugs that have solid particulate matter of any kind will contaminate the solution or precipitate out of solution during intravenous injection and present a substantial risk of pain and suffering upon injection of the solution.

23. Compounded drugs with improper pH levels can produce a burning sensation upon injection.

24. Because there is inadequate oversight of both compounding pharmacies and the contract-testing laboratories used by compounding pharmacies, the State of Georgia does not know with certainty what is contained in the pentobarbital sodium injection, or other compounded drugs, that will be injected into Mr. Hill.

II. The Use of Contaminated Pentobarbital in Prior Executions Illustrates the High Risk of Needless Suffering Posed by Use of Compounded Pentobarbital in Lethal Injections

25. As I read the Georgia Supreme Court's opinion in the *Hill* case, part of the basis of the decision to vitiate the temporary injunction was the conclusion

that the use of compounded pentobarbital posed an insignificant or completely speculative risk of pain and suffering in the executed inmate. However, in my opinion, recent executions demonstrate that this risk is not speculative, but rather very real and very significant.

26. For example, on January 9, 2014 Oklahoma prisoner Michael Lee Wilson was executed under a three-drug protocol that used a pentobarbital injection produced by an unknown compounding pharmacy. Media witnesses reported that within 20 seconds of receiving the injection, Mr. Wilson cried that he felt his "whole body burning."[5]

27. It is my opinion that Mr. Wilson's reaction is consistent with contaminated pentobarbital sodium injection. Because of common problems with safety procedures of compounded pharmacies and testing laboratories, and the lack of adequate oversight by federal and state authorities, the injection used in Mr. Wilson's execution could have contained cross-contaminates to which he was

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[5] Associated Press, *"I Feel My Whole Body Burning," Says Oklahoma Death Row Inmate During Execution*, Jan. 10, 2014, http://www.foxnews.com/us/2014/01/10/feel-my-whole-body-burning-says-oklahoma-death-row-inmate-during-execution/. *See also* Charlotte Alter, *Oklahoma Convict Who Felt "Body Burning" Executed With Controversial Drug*, TIME, Jan. 10, 2014, http://nation.time.com/2014/01/10/oklahoma-convict-who-felt-body-burning-executed-with-controversial-drug.

allergic; bacteria; and endotoxins. The injection could have had an altered pH due to contaminates. Additionally, because of this lack of oversight no one knows for sure what was injected into Mr. Wilson.

28. The October 15, 2012, South Dakota execution of Eric Robert used compounded pentobarbital. According to reports,[6] Mr. Robert appeared to clear his throat, gasped heavily and snored. Over a ten-minute period his skin turned a purplish hue. During the course of his execution, he opened his eyes and they remained open until his death. It took 20 minutes for the state to declare Mr. Robert dead. Mr. Robert's heart continued to beat ten minutes after he stopped breathing.

29. It is my opinion that the events observed during Mr. Robert's execution are consistent with the administration of a compounded drug that was contaminated or sub-potent.

30. If Georgia proceeds with the execution of Mr. Hill using compounded pentobarbital or some other compounded drug, Georgia will be injecting a drug of unknown composition into Mr. Hill, which is highly likely to be contaminated or

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[6] *See e.g.*, Dave Kolpack and Kristi Eaton, *S. Dakota Executes Inmate Who Killed Prison Guard*, Associated Press, October 16, 2012, http://bigstory.ap.org/article/sd-death-row-inmate-be-executed-monday-0.

whose quality is otherwise compromised. Doing so carries a substantial risk of causing Mr. Hill unnecessary and lingering pain and suffering.

FURTHER AFFIANT SAYETH NAUGHT,

LARRY D. SASICH

Sworn to and subscribed before me
this 24 day of July, 2014.

NOTARY PUBLIC

Attachment A

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
4040 North Central Expressway, Suite 300 Dallas, TX 75204 (214) 253-5200 Fax:(214) 253-5314 Industry Information: www.fda.gov/oc/industry	06/03/2014 - 07/16/2014* FEI NUMBER 3010087152

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Kristi A. Kubosh, Pharm. D., R.Ph., Pharmacist in Charge

FIRM NAME	STREET ADDRESS
Downing Labs, LLC	4001 McEwen Rd Suite 110
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Dallas, TX 75244-5020	Producer of Sterile Drug Products

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

There is a failure to thoroughly review the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

Specifically,

A. SOP #9.040 entitled, "Sterility Testing of a Finished Preparation" (Effective date: 6/2012) documents that an investigation should be conducted in the event that contamination is observed.

My review of approximately (b)(4) Logged Formula Worksheets for the period between 4/16/2013 and 6/23/2014 revealed that your firm had sterility or endotoxin failures for 22 different lots of drug product. In each case, the investigations were either absent or incomplete.

All lots which failed testing for sterility or endotoxin were destroyed with the exception of the following:

- Cyanocobalamin, lot #N04302014@14

Lot #N04302014@14 was originally (b) (4) on 5/2/14. Subsequent testing for sterility failed (Test dated 6/2/14) and the lot was re-sterilized by (b) (4) on 6/3/14. Subsequent testing for endotoxin and sterility met specifications. The lot is currently being held in inventory pending distribution.

- Folic Acid, lot #N04172014@20 (Production date: 4/30/14, BUD: 10/28/14)

Lot #N04172014@20 was (b) (4) on 4/30/14. Subsequent testing for sterility failed as noted on testing record dated 6/2/14. The lot is being held in quarantine pending destruction.

Each batch with the failed result is identified in the following table:

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Stephen D. Brown, Investigator Darla J. Christopher, Investigator	DATE ISSUED 07/16/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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Dallas, TX 75244-5020	Producer of Sterile Drug Products

Product	Lot #	Mfd. Date	BUD	Sterility Test Result/Day Positive	Organism(s)	Endotoxin Result/Date	Investigation
HCG 5 K Lyophilized 5000 U Powder Injectable	N05082014@30	5/9/14	12/12/14	Negative	N/A	Failed endotoxin (Result of 150.75EU/vial versus spec of (b)(4) /vial)	Yes
Cyanocobalamin 30 mL Buffered 1 mg/mL Injectable	N04302014@14	5/2/14	11/1/14	Positive/Day 14	*Afipia felis*	<0.05 EU/mL	No
Folic Acid 30 mL 10 mg/mL Injectable	N04172014@20	4/30/14	10/28/14	Positive/Day 12	*Afipia felis*	<5.00 EU/mL	No
HCG 5 K Lyophilized 5000 U Powder Injectable	N04082014@14	4/17/14	10/15/14	Positive/Day 5	*Staphylococcus haemolyticus*	4.50 EU/Vial	Yes
Cyanocobalamin 30 mL Buffered 1 mg/mL Injectable	N03272014@7	3/27/14	9/23/14	Positive/Day 4	*Afipia felis*	<0.05 EU/mL	No
Green Tea (EGCG) 10 mL 10 mg/mL Injectable	N01202014@8	2/10/14	8/9/14	Negative	N/A	Failed endotoxin (Result of 252.64 EU/ml)	Yes
L-Carnitine 30ml 500mg/ml	N12202013@8	1/29/14	7/28/14	Negative	N/A	Failed endotoxin (Result 476.19EU/ml versus spec of (b)(4) U/ml)	Yes
Terbutaline/ Betamethasone 5 mL 0.05/0.01 mg/mL Injectable	N12202013@4	12/23/13	6/22/14	Positive/Day 10	*Methylobacterium brachiatum*	Not tested	Yes
Procaine 30 mL 10% Inj	N12182013@1	12/19/13	6/18/14	Positive/Day 8	*Propionibacterium acnes*	Not tested	Yes
Methylcobalamin Buffered 30 mL 5 mg/mL Inj	N11042013@1	12/16/13	6/15/14	Positive/Day 5	*Staphylococcus epidermidis*	Not tested	Yes
Magnesium Chloride Hexahydrate 30 mL 200 mg/mL Injectable	N11042013@14	11/14/13	5/13/14	Positive/Day 6	*Staphylococcus epidermidis*	Not tested	Yes
DMPS B-Complex 10ml	N10172013@20	11/6/13	2/1/14	Positive/Day 4	*Bacillus amyloliquefaciens* *Methylotrophicus*	Not tested	Yes
Ascorbic Acid (Corn) 50 mL 500 mg/mL Injectable	N10172013@19	10/30/13	4/29/14	Positive/Day 13	*Propionibacterium acnes*	Not tested	Yes
Hyaluronidase 10 mL 150 U/mL Injectable	N09042013@14	10/15/13	1/31/14	Positive/Day 4	*Staphylococcus epidermidis*	Not tested	Yes
Dexpanthenol 30 mL 250 mg/mL Injectable	N09032013@14	9/3/13	2/2/14	Positive/Day 3	Not tested	Not tested	Yes
Calcium Gluconate 50 mL 5% Injectable	N08152013@20	8/22/13	2/23/14	Positive/Day 13	*Bacillus fastidiosus*, *Bacillus simplex*, *Nocardia nova*	Not tested	Yes

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EMPLOYEE(S) SIGNATURE
Stephen D. Brown, Investigator
Darla J. Christopher, Investigator

DATE ISSUED
07/16/2014

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Dallas, TX 75244-5020	Producer of Sterile Drug Products

Product	Lot #	Mfd. Date	BUD	Sterility Test Result/Day Positive	Organism(s)	Endotoxin Result/Date	Investigation
Riboflavin (R5P) 30 mL 10 mg/mL Inj	N08212013@5	8/21/13	2/17/14	Positive/ Day 5	*Cupriavidus metallidurans*	Not tested	Yes
TPM IV Base#2 Concentrate 50 mL SDV Inj	N07122013@14	8/19/13	1/8/14	Positive/Day 7	*Roseomonas mucosa*	Not tested	Yes
L-Glutathione for Inhalation 10 X 4 mL Soln for Neb	N08142013@3	8/14/13	2/10/14	Positive/ Day 3	*Staphylococcus epidermidis*	Not tested	Yes
Ascorbic Acid (Corn) 50 mL 500 mg/mL Injectable	N07172013@26	8/8/13	1/13/14	Positive/Day 12	*Propionibacterium acnes*	Not tested	Yes
Folic Acid 10 mL 5 mg/mL Injectable	N06112013@27	6/11/13	12/8/13	Positive/Day 2	*Delftia acidovorans*	Not tested	Yes
L-Proline 30 mL 50 mg/mL Injectable	N06052013@19	6/3/13	12/2/13	Positive/Day 10	*Corynebacterium afermentans lipophilum*	Not tested	Yes

Some examples where an investigation was absent include the following:

1. Cyanocobalamin 1mg/ml Buffered, lot #N04302014@14 (Production date: 5/2/14, Beyond Use Date: 11/1/14)

Your contract laboratory determined that this lot failed sterility and the contaminating organism was *Afipia felis*. No investigation was performed.

2. Folic Acid 10mg/ml, lot #N04172014@20 (Production date: 4/30/14, Beyond Use Date: 10/28/14)
Your contract laboratory determined that this lot failed sterility and the contaminating organism was *Afipia felis*. No investigation was performed.

3. Cyanocobalamin 1mg/ml Buffered, lot #N03272014@7 (Production date: 3/27/14, Beyond Use Date: 9/23/140
Your contract laboratory determined that this lot failed sterility and the contaminating organism was *Afipia felis*. No investigation was performed.

Some examples where an investigation was incomplete consist of the following:

1. Green Tea (EGCG) 10ml 10mg/ml Injectable, lot #N01202014@8 (Production date: 2/10/14, Beyond Use date: 8/9/14)

Lot #N01202014@8 failed the test for endotoxin with a result of 252.64 EU/ml as documented on a Certificate of Analysis dated 2/26/14 from the contract laboratory.

Your investigation identified the possible root causes as 1)(b) (4) 2) aseptic technique, or endotoxin in the API.

However, your firm's investigation was incomplete in that:

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Stephen D. Brown, Investigator Darla J. Christopher, Investigator	07/16/2014

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a. The raw material, EGCG, was identified as a possible source of endotoxin contamination but was never tested.

b. (b) (4) was identified as a possible source of the contamination but was not investigated.

c. Aseptic technique was also included as a possible source of the contamination but was not investigated.

d. There was no assessment of (b) (4) (glassware) which have not been validated.

2. L-Carnitine 500mg/ml for Injection, lot #N12202013@8 (Production date: 1/29/14, Beyond Use Date: 7/28/14)

Lot #N12202013@8 failed the test for endotoxin with a result of 476.19 EU/ml as documented on a Certificate of Analysis dated 3/19/14 from the contract laboratory.

Your investigation identified possible root causes as 1) presence of endotoxin or gram negative bacteria in the API, and 2) excessive time between preparation and (b) (4) .

Your firm's investigation was incomplete in that:

a. The testing of the raw material, L-Carnitine, which was identified as a possible source of contamination was not conducted.

b. Excessive time between preparation and (b) (4) was identified as a possible cause but was not investigated.

c. The investigation did not include an assessment of (b) (4) (glassware) which have not been validated.

d. The investigation did not extend to all impacted batches. Per your Pharmacist in Charge, the L-Carnitine, lot (b) (4) which was used in L-Carnitine, lot #N12202013@8 was also used in the product, Lipotocin Plus 10 ml for Injection, lot #N01042014@2 (Production date: 1/9/14 Beyond Use Date: 7/8/14) which was sent to consignees.

3. Human Chorionic Gonadotropin 5000IU Lyophilized, lot #N04082014@14 (Production date: 4/17/14, Beyond Use Date: 10/15/14)

Lot #N04082014@14 failed the test for sterility as documented on a Certificate of Analysis issued by the contract laboratory (Organism: *Staphylococcus haemolyticus).*

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4040 North Central Expressway, Suite 300 Dallas, TX 75204 (214) 253-5200 Fax:(214) 253-5314 Industry Information: www.fda.gov/oc/industry	06/03/2014 - 07/16/2014* FEI NUMBER 3010087152

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Kristi A. Kubosh, Pharm. D., R.Ph., Pharmacist In Charge

FIRM NAME	STREET ADDRESS
Downing Labs, LLC	4001 McEwen Rd Suite 110
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
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Your investigation identified aseptic technique by the technician as the probable root cause but failed to include an evaluation of the following areas:

(b) (4)
Room pressurization
Laminar flow operation
Assessment of container closure
Sanitization procedures (Room, equipment, product containers, etc.)
Evaluation of other lots compounded by the same technician

B. SOP #9.030 entitled, "Particulate Testing for Sterile Preparations" (Date: 1/2013) provides guidance for the evaluation of vials of sterile, injectable drug products for particulates. My review of (b) (4) lots of drug products manufactured between 4/16/2013 and 6/23//2014 revealed that at least 185 lots had fibers or particulates. No investigations have been conducted.

In each case, your firm conducted a 100% inspection by (b) (4) Vials identified as containing fibers and/or particulates were then removed and discarded. However, this method has not been shown effective to detect fibers or particulates in amber vials.

The remaining vials from each lot were then distributed to consignees. Some examples consist of the following:

- Methylcobalamin, lot #N01162014@21
- DMSO, lot #N01082014@1
- Cyanocobalamin, lot #N01062014@11

C. Investigations have not been conducted for sterile, injectable drug products which were rejected due to precipitation or particulates. Some examples consist of the following:

1. Thiamine HCl 30ml 100mg/ml Injectable, lot #N02212014@10 (Production date: 2/25/2014, BUD: 8/24/2014): Particulates
2. M.I.C.A. 126 50ml Preserved 25/50/50/5/50/25 mg/ml Injectable, lot #N12272013@6 (Production date: 1/2/2014, BUD: 7/1/2014): Precipitation

D. A "Sterilizer Test Report" dated 2/27/14 issued by (b) (4) indicated that a gram stain confirmed spore growth in one or more test strips and control strips for a test conducted on 2/19/14. No investigation was conducted.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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OBSERVATION 2

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established.

Specifically,

A) Media Fills

SOP #7.007.3 entitled, "Media Fill for High Risk Compounding " (Date: 4/17/14) documents, in part, that a total of (b) (4) ml vials (b) (4) for positive controls and (b)(4) for product) will be used to conduct media fills.

1) The media fills were not representative of actual production processes in that:

a. The media fills failed to simulate a lot with the maximum number of vials (i.e. Cyanocobalamin, lot #N04302014@14: (b) (4) vials)
b. The number and type of interventions was not included.
c. The aseptic assembly of equipment (e.g., at start-up, during processing) was not included.

2) The (b) (4) tubes of media used as positive controls with the media fills were not inoculated with a known number/type of organisms. Instead, the (b) (4) tubes were exposed to the environment (undefined), capped and then incubated for (b)(4) days.

3) Media fills for lyophilized products were not conducted (i.e. Human Chorionic Gonadotropin and Sermorelin)

B) (b) (4) validation

Your firm failed to validate the (b) (4) used for the sterilization of injectable drug products. Some examples of (b) (4) utilized by your firm consist of the following:

(b) (4)

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(b) (4)

My review of approximately (b) (4) production records for the period between 4/16/2013 and 6/23/2014 revealed that integrity testing was not documented as being performed on (b) (4) for approximately (b) (4) lots.

D) (b) (4) Sterilization

Your firm failed to validate the (b) (4) used to sterilize injectable drug products and drug product components such as vials and stoppers.

Your firm currently uses the following (b) (4) for the sterilization of drug products and components:

(b) (4)

Some examples of sterile, injectable drug products which were terminally sterilized include the following:

- DMSO 50 mL 99% Injectable, lot #N01082014@1 (Production date: 1/20/2014, Beyond Use Date: 7/19/2014)
- Hyaluronic Acid 10 mL X-Link 10 mg/mL Injectable, lot #N05092014@1 (Production Date: 5/12/2014 Beyond Use Date: 11/1/2014)
- Vitamin A 10 mL 50,000 IU/mL Injectable, lot #N04142014@8 (Production Date: 4/14/2014 Beyond Use Date: 10/11/2014)

In addition, your firm uses (b) (4) of drug products which are (b) (4). The (b) (4) does not meet the USP standards for (b) (4) and is not tested to ensure the absence of endotoxins.

E) Qualification of ISO 5 processing area modifications

Your firm failed to re-qualify the ISO 5 and 7 processing areas after major modifications to the areas. For example, on 4/7/14, your vendor conducted major repairs in the ISO 5 and ISO 7 areas to include the re-positioning of four HEPA filters in the ISO 5 area and re-location of the lyophilizer from the ISO 7 cleanroom to the ISO 5 area. There was no documentation to indicate that cleaning was performed in the controlled areas after the repairs were made.

A re-qualification of the ISO 5 and ISO 7 areas did not occur until 5/21/14. Between 4/7/14 and 6/2/14, your firm

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compounded approximately [redacted] lots of injectable drug products of which at least [redacted] have been distributed.

Some examples include the following:

- Lidocaine HCl 50ml 1% Injectable, lot #N 05122014@12, (Production date: 5/13/14 Beyond Use Date: 11/11/14)
- Procaine Potassium Buffered 50ml 2% Injectable, lot #N04142014@5 (Production date: 5/13/14, Beyond Use Date: 11/10/14)
- Magnesium Chloride Hexahydrate 50ml 200mg/ml Injectable, lot #N04302014@17 (Production date: 5/12/14 Beyond Use Date: 11/10/14)

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OBSERVATION 3

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

Specifically, environmental monitoring is not representative of the clean room environment during aseptic processing operations. For example,

A) Viable air sampling is performed in the ISO 5 and ISO 7 areas once every (b) (4) when the rooms are being re-certified by your outside contractor.

B) Surface samples are obtained randomly (b) (4) in the clean room. The areas to be sampled are not identified.

C) Routine monitoring for clean room personnel is performed once every (b) (4) and there is no monitoring of gowns,

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arms, face masks or other areas of the technician.

D) Growth promotion testing is not performed on incoming prepared media (i.e. (b) (4) [redacted]") used for environmental sampling.

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OBSERVATION 4

Aseptic processing areas are deficient regarding systems for maintaining any equipment used to control the aseptic conditions.

Specifically,

A. There is no assurance that the air quality inside the ISO 5 area is adequately maintained. Currently, the ISO 5 area is separated from the ISO 7 cleanroom by a plastic curtain which descends approximately 30" from the ceiling. The latest cleanroom qualification dated 5/21/14 failed to include documentation to demonstrate that laminarity can be adequately maintained between the ISO 5 and ISO 7 areas.

On 6/3/2014, we observed that the sides of the plastic curtain which enclose the ISO 5 area inside the ISO 7 cleanroom were absent. I was told by management that the sides were removed on 6/2/2014 based on recommendations from the HVAC vendor since they were opaque and needed to be clear. The ISO 5 area was not recertified after this modification.We also observed on 6/3/14 that the product, HCG K Lyophilized 5000 U Powder Injectable, lot #05232014@2, was being processed within the uncertified ISO 5 area.

In addition, your firm manufactured the following drug products on 6/19/2014 and 6/23/2014 using the uncertified ISO 5 area:

- AMP Buffered 10ml 25mg/ml Injectable, lot #06192014@3 (Production date: 6/19/14, BUD: 12/16/2014)
- Methylcobalamin Buffered 30ml 1mg/ml Injectable, lot #06172014@14 (Production date: 6/23/14, BUD: 12/21/2014)
- Magnesium Sulfate 50ml 50% Injectable, lot #06132014@9 (Production date: 6/23/14, BUD: 12/21/2014)

Each lot was (b) (4) [redacted] in the ISO 5 area and then (b) (4) [redacted]. The Pharmacist in Charge told me that the lots were (b) (4) [redacted] since the firm had identified rationale in literature. In addition, I was told that the ISO 5 area was uncertified and that the firm was only compounding products which could be (b) (4) [redacted]. The three lots are being held in quarantine pending the completion of testing for sterility and endotoxin.

B. Your firm checks and documents the differential pressure between the ISO 7 and ISO 8 areas (b) (4) [redacted]. There are no requirements for additional monitoring.

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OBSERVATION 5

Each batch of drug product purporting to be sterile and pyrogen-free is not laboratory tested to determine conformance to such requirements.

Specifically, my review of approximately (b) (4) lots manufactured between 4/16/2013 and 6/23/2014 revealed that endotoxin testing had not been performed for approximately 180 of the (b) (4) lots of injectable drug products distributed. Some examples where testing for endotoxin was not performed consist of the following:

- Taurine 30ml 50mg/ml, lot #N12182013@13 (Production date: 1/22/14, Beyond Use date: 7/21/14)
- Methylcobalamin Buffered 10ml 1mg/ml, lot #N01162014@20 (Production date: 1/23/14 Beyond Use date: 7/22/14)
- Thioctic Acid 30ml 25mg/ml, lot #N12202013@5 (Production date: 1/23/14 Beyond Use date: 7/19/14)

OBSERVATION 6

Equipment and utensils are not maintained at appropriate intervals to prevent malfunctions and contamination that would alter the safety, identity, strength, quality or purity of the drug product.

Specifically, your firm has never conducted preventive maintenance on the (b) (4) or lyophilizer used for the processing of injectable drug products. My review of the operators' manuals for the (b) (4) and one lyophilizer revealed that specific maintenance is required to ensure optimal operation. Some examples of the recommended maintenance consist of the following:

A. (b) (4)

The lyophilizer is used for the production of two products, HCG 5 K Lyophilized 5000 U Powder Injectable and Sermorelin /GHRP-6/GHRP-2 3/3/3 mg per vial Injectable. Some examples of lots distributed include the following:

- Sermorelin/GHRP-6/GHRP-2 3/3/3 mg per Vial Injectable, lot #N03112014@9 (Production Date: 3/11/2014 Beyond Use Date: 9/7/2014)
- HCG 5 K Lyophilized 5000 U Powder Injectable, lot #N03182014@10 (Production Date: 3/27/2014 Beyond Use Date:

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9/23/2014)

The operating manual recommends the following maintenance:

1. (b) (4) [redacted]

2. (b) (4) [redacted]

B. (b) (4) [redacted]

1. [redacted]

- (b) (4) [redacted]

- (b) (4) [redacted]

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OBSERVATION 7

Adequate lab facilities for testing and approval or rejection of drug products are not available to the quality control unit.

Specifically, your firm has not authorized your contract laboratory to conduct suitability testing for all drug products tested for sterility as confirmed by management. Review of approximately (b) (4) testing records for the period between 4/16/2013 and 6/23/14 revealed that at least 80% of the records included a statement from the contract laboratory documenting that the sterility test did not meet all the requirements for sampling and/or method suitability specified in USP <71>. Some examples consist of the following:

- L-Glutamine 30ml 30mg/ml Injectable, lot #N05122014@8 (Production date: 5/13/14, Beyond Use Date: 11/11/14)
- Hyaluronic Acid 10ml X-Link 10mg/ml Injectable, lot #N05092014@1 (Production date: 5/12/14 Beyond Use Date: 11/1/14)
- Procaine 50 ml Buffered 1% 10mg/ml Injectable, lot #N05082014@23, (Production date: 5/9/14, Beyond Use Date: 11/7/14)

OBSERVATION 8

There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

Specifically,

A. Your firm utilizes a (b) (4) (b) (4) for the lyophilization of injectable drug products. Your firm has failed to validate the different cycles used for the lyophilization of the drug products, Human Chorionic Gonadotropin Lyophilized 5,000 Units Powder and Sermorelin. Some examples of specific cycle parameters consist of the following:

Freezing	Duration	HCG (Human Chorionic Gonadotropin)	Sermorelin
(b) (4) (b) (4)			(b) (4) (b) (4)

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(b) (4)

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OBSERVATION 9

Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the room to produce aseptic conditions.

Specifically,

A. There is no documentation to indicate that the plastic curtain separating the ISO 5 and ISO 7 areas has ever been cleaned or sanitized.

B. Your firm has not conducted disinfectant effectiveness studies to demonstrate that the disinfectants used to clean the walls, floors, ceilings, and work surfaces in the ISO 5 and ISO 7 areas can sufficiently reduce bioburden. Currently, your firm utilizes the following disinfectants in the ISO 5 and ISO 7 areas:

(b) (4)

C. Your firm uses non-sterile wipes in the ISO 5 and ISO 7 areas for the cleaning and sanitization of surfaces.

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OBSERVATION 10

Clothing of personnel engaged in the manufacturing of drug products is not appropriate for the duties they perform.

Specifically, the goggles used by technicians in the ISO-5 clean room are not sterile and are not disinfected prior to use.

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OBSERVATION 11

There is no written testing program designed to assess the stability characteristics of drug products.

Specifically,

A) Your firm has no documentation to justify the Beyond Use Date of injectable drug products of 180 days. My review of approximately (b) (4) lots of drug products manufactured between 4/16/13 and 6/23/14 revealed that your firm produced approximately (b) (4) different sterile, injectable drug products with Beyond Use Dates (BUDs) up to 180 days, to include preserved and preservative free drug product units which are intended for single use but not labeled accordingly. For example,

- Phosphatidylcholine 50ml, 5/2.5% Injectable, lot #N05092014@8, BUD 180 days.
- Lipotocin 10 ml Injectable, lot #N04302014@8, BUD 180 days.

B) Your firm has not conducted anti-microbial effectiveness testing to determine whether Benzyl Alcohol, Methylparaben, or Benzalkonium Chloride effectively inhibit microbial growth in sterile injectable drug products through BUD. My review of approximately (b) (4) lots of sterile drug products for the period between 4/16/2013 and 6/23/2014 revealed that your firm manufactured drug products containing these preservatives with BUDs of 180 days. For example,

- B12 3ml (Hydroxo 12.5mg/ml + Cyano 12.5mg/ml) 25mg/ml Injectable, lot #N05082014@22 (BUD: 180 days) Contains: Benzyl Alcohol
- Biotin 30 ml (Preserved) 10mg/ml Injectable, lot #N01282014@10 (BUD 180 days) Contains: Methylparaben
- Acetyl-L-Carnosine Eye Drop 15ml Modified 5% Ophthalmic, lot #N03282014@7 (BUD 180 days) Contains: Benzalkonium Chloride

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OBSERVATION 12

Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the identity and strength of each active ingredient prior to release.

Specifically, your firm has not conducted potency testing for any drug products manufactured and distributed. My review of approximately (b) (4) lots of sterile drug products manufactured between 4/16/2013 and 6/23/2014 revealed that potency testing had not been conducted for any lots.

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OBSERVATION 13

Master production and control records lack complete manufacturing and control instructions.

Specifically, your firm does not consistently document the model/lot number of the (b) (4) used in the sterilization of injectable drug products. For example, Lipotocin 10ml for Injection, lot #N04302014@18 (Production date: 5/5/14, Beyond Use Date: 11/3/14).

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FDA alerts health care professionals not to use sterile drugs from Downing Labs (aka NuVision Pharmacy)

[7/18/2014] The U.S. Food and Drug Administration is alerting health care professionals and consumers not to use drugs marketed as sterile produced by Downing Labs LLC, also known as NuVision Pharmacy, in Dallas, as they may be contaminated.

Health care professionals should immediately check their medical supplies, quarantine any sterile drug products from NuVision, and not administer them to patients. Administration of a non-sterile drug product intended to be sterile may result in serious and potentially life-threatening infections or death.

NuVision's products were distributed nationwide. Most of the product labels include: NuVision Pharmacy, Dallas TX. 75244 1-800-914-7435.

FDA investigators inspected NuVision and observed insanitary conditions that result in a lack of sterility assurance of purportedly sterile drug products produced by the company, which puts patients at risk (Form FDA-483 issued July 16, 2014). The inspection revealed sterility failures in 19 lots of drug products intended to be sterile, endotoxin failures in three lots of drug products, and inadequate or no investigation of these failures. Endotoxins are substances found in certain bacteria that cause a wide variety of serious reactions such as fever, shock, changes in blood pressure, and in other circulatory functions.

Patients who have received any drug product produced by NuVision and have concerns should contact their health care professional.

FDA is not aware of recent reports of illness associated with the use of these products. FDA asks health care professionals and consumers to report adverse events or quality problems associated with the use of NuVision's products to FDA's MedWatch Adverse Event Reporting program by:

- Completing and submitting the report online at MedWatch Online Voluntary Reporting Form
- Downloading and completing the form (PDF - 1.22MB), then submitting it via fax at 1-800-FDA-0178

For more information:

- FDA press release, April 15, 2013: FDA issues alert about lack of sterility assurance of drug products from ApotheCure, Inc. and NuVision Pharmacy and of forthcoming recall
- FDA Form 483 issued April 16, 2013
- FDA press release, May 18, 2013: FDA expands alert to health care providers about lack of sterility assurance of all sterile drug products from NuVision Pharmacy
- FDA recall request, July 26, 2013
- FDA press release, Aug. 16, 2013: FDA reminds health care providers not to use sterile products from NuVision Pharmacy

Attachment B

Grandpa's Compounding Pharmacy, Inc. 5/2/14

Department of Health and Human Services

Public Health Service
Food and Drug Administration

San Francisco District
1431 Harbor Bay Parkway
Alameda, CA 94501-7070
Telephone (510) 337-6700

Warning Letter

WL: 423162

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

May 2, 2014

Daniel R. Wills
General Business Manager
Grandpa's Compounding Pharmacy, Inc.
7563 Green Valley Road
Placerville, CA 95667-3917

Dear Mr. Wills:

Between September 3, 2013 and September 10, 2013, U.S. Food and Drug Administration (FDA) investigators conducted an inspection of your facility, Grandpa's Compounding Pharmacy, Inc., 7563 Green Valley Road, Placerville, CA 95667-3917. During the inspection, FDA's investigators were accompanied by California State Board of Pharmacy (BOP) inspectors. At that time, the investigators noted that you were not receiving valid prescriptions for individually-identified patients for a portion of the drug products you were producing. In addition, the investigators observed serious deficiencies in your practices for producing sterile drug products and flaws in the design of your aseptic processing areas, which could lead to contamination of the products, potentially putting patients at risk. For example, we observed that the air supply duct work for the cleanroom consists of, in part, a **(b)(4)** held together, in part, with duct tape. We also observed that the cleanroom contained an in-wall air conditioner bringing outside air into the room where aseptic manipulations are occurring. These items are difficult to clean and could allow for air to enter the cleanroom that has unacceptable microbial and particulate levels. Furthermore, we observed operators with exposed wrist and forearm skin engaging in aseptic manipulations. In addition, we observed that your firm uses tap water and a**(b)(4)** to clean and depyrogenate containers and closures; these are not suitable to depyrogenate the containers and closures intended for injectable drug products. Therefore, your products may be produced in an environment that poses a significant contamination risk. These observations and others were noted on a Form FDA 483, issued on September 10, 2013. We acknowledge receipt of your firm's response to the Form FDA 483 dated September 20, 2013, in which your firm stated it would cease all sterile compounding.

Based on this inspection, it appears that you are producing drugs that violate the Federal Food, Drug, and Cosmetic Act (FDCA).

A. Compounded Drugs Under the FDCA

At the time FDA inspected your facility, there were conflicting judicial decisions regarding the applicability of section 503A of the FDCA [21 U.S.C. § 353a], which exempts compounded drugs from several key statutory requirements if certain conditions are met.[1] Nevertheless, receipt of valid prescriptions for individually-identified patients prior to distribution of compounded drugs was relevant for both section 503A of the FDCA and the agency's Compliance Policy Guide 460.200 on Pharmacy Compounding (CPG) (2002), which was then in effect (CPG) (2002).[2] During the inspection, investigators observed that your firm does not receive valid prescriptions for individually-identified patients for a portion of the drug products you produce. Based on this factor alone, those drugs were not entitled to the statutory exemptions for compounded drugs described in section 503A of the FDCA and did not qualify for the agency's exercise of enforcement discretion set forth in the CPG.[3]

Since FDA inspected your facility, Congress enacted and the President signed into law the Compounding Quality Act (CQA)[4], which amended FDCA section 503A by eliminating the advertising restrictions that had been the basis for conflicting judicial decisions. The CQA otherwise left section 503A intact, and so clarified that the remainder of section 503A, including the requirement of valid prescriptions for individually identified patients, is applicable in every federal judicial circuit. Accordingly, the drugs you compound without valid prescriptions for individually identified patients are not entitled to the exemptions in section 503A.[5]

In addition, we remind you that there are a number of other conditions that must be satisfied to qualify for the exemptions in section 503A of the FDCA.[6]

B. Violations of the FDCA

The drug products that you manufacture and distribute without valid prescriptions for individually-identified patients are misbranded drugs in violation of section 502(f)(1) [21 U.S.C. § 352(f)(1)] of the FDCA. In addition, your sterile drug products are prepared, packed, or held under insanitary conditions whereby they may have been contaminated with filth, or whereby they may have been rendered injurious to health. As such, all sterile products you manufacture are adulterated within the meaning of section 501(a)(2)(A) [21 U.S.C. § 351(a)(2)(A)] of the FDCA. Furthermore, because you manufacture and distribute drugs without valid prescriptions for individually-identified patients, the manufacture of those drugs is also subject to FDA's Current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations (CFR), Parts 210 and 211. FDA investigators observed significant CGMP violations at your facility, causing such drug product(s) to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA [21 U.S.C. § 351(a)(2)(B)].

Misbranded Drug Products

Because the drug products for which you have not obtained valid prescriptions for individually-identified patients are intended for conditions that are not amenable to self-diagnosis and treatment by individuals who are not medical practitioners, adequate directions cannot be written for them so that a layperson can use these drug products safely for their intended uses. Consequently, their labeling fails to bear adequate directions for their intended uses, causing them to be misbranded under section 502(f)(1) of the FDCA [21 U.S.C. § 352(f)(1)], and they are not exempt from the requirements of section 502(f)(1) of the FDCA (*see*, *e.g.*, 21 C.F.R. § 201.115). It is a prohibited act under section 301(k) of the FDCA [21 U.S.C. § 331(k)] to do any act with respect to a drug, if such act is done while the drug is held for sale after shipment in interstate commerce of the components used to make the drug and results in the drug being misbranded.

Adulteration Charges

Additionally, FDA investigators noted that your sterile drug products were prepared, packed, or held under insanitary conditions, whereby they may have become contaminated with filth or rendered injurious to health, causing your drug products to be adulterated under section 501(a)(2)(A) of the FDCA [21 U.S.C. § 351(a)(2)(A)]. Examples of these conditions include an air supply system that is composed of, in part, a **(b)(4)** held together, in part, with duct tape; an in-wall air conditioner; operators performing aseptic manipulations with exposed wrist and forearm skin; and the use of tap water and a **(b)(4)** to clean and depyrogenate containers and closures intended for injectable drug products.

FDA investigators also noted CGMP violations at your facility, causing the drug products for which you have not obtained valid prescriptions for individually-identified patients to be adulterated under section 501(a)(2)(B) of the FDCA [21 U.S.C. § 351(a)(2)(B)]. The violations include, for example:

1. Your firm failed to establish an adequate air supply filtered through high-efficiency particulate air filters under positive pressure in the aseptic processing areas (21 CFR 211.42(c)(10)(iii)).

2. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

3. Your firm failed to ensure that manufacturing personnel wear clothing appropriate to protect drug product from contamination (21 CFR 211.28(a)).

4. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv)).

5. Your firm does not have, for each batch of drug product purporting to be sterile and/or pyrogen-free, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product (21 CFR 211.167(a)).

It is a prohibited act under section 301(k) of the FDCA [21 U.S.C. § 331(k)] to do any act with respect to a drug, if such act is done while the drug is held for sale after shipment in interstate commerce of the components used to make the drug and results in the drug being adulterated.

C. Corrective Actions

We are aware that the California State BOP issued a Notice of Violation and Embargo Notice to your firm on September 6, 2013. Additionally, on September 10, 2013, the California State BOP issued another Embargo Notice to recall all sterile drug products due to a lack of viable sterility and endotoxin testing, ordered your firm to immediately cease and desist the compounding of injectable sterile drug products (effective until October 31, 2013), and cancelled your firm's sterile compounding license. In a letter to the BOP dated September 16, 2013 (and referenced in your response to the Form FDA 483 dated September 20, 2013), you agreed to voluntarily relinquish your State of California Sterile Compounding License (LSC 99109) to the BOP.

In your September 20, 2013 response to the Form FDA 483, you stated that you had decided at that time to no longer continue sterile compounding. In addition, you stated that your lawyer was "looking over the observations and may have a further response, but he is currently on vacation." No other responses from your firm have been received by FDA since that time. In your letter to the California State BOP dated September 16, 2013, you stated you would continue to compound products that do not require you to have the licensed sterile compounding permit, as well as all other operations as a retail pharmacy.

FDA strongly recommends that if you decide to resume production of sterile drugs, your management immediately undertake a comprehensive assessment of your manufacturing operations, including facility design, procedures, personnel, processes, materials, and systems. In particular, this review should assess your aseptic processing operations. A third party consultant with relevant sterile drug manufacturing expertise could be useful in conducting this comprehensive evaluation.

As noted above, your firm has manufactured and distributed drug products without valid prescriptions for individually-identified patients, and the manufacture of such drugs is subject to FDA's drug CGMP regulations, 21 CFR Parts 210 and 211. Before resuming such operations, you should fully implement corrective actions that meet the minimum requirements of 21 CFR Part 211 in order to provide assurance that the drug product(s) produced by your firm conform to the basic quality standards that ensure safety, identity, strength, quality, and purity.

In addition, if you resume sterile compounding, you should also correct the violations of FDCA section 502(f)(1) noted above.

D. Conclusion

The violations cited in this letter are not intended to be an all-inclusive statement of violations at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence or the occurrence of other violations. It is your responsibility to ensure that your firm complies with all requirements of federal law and FDA regulations.

If you decide to resume sterile drug operations, you should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice, including, without limitation, seizure and injunction.

Within fifteen working days of receipt of this letter, please notify this office in writing if you have taken specific steps to correct violations, or you may inform us that you do not intend to resume production of sterile drugs. If you intend to resume production of sterile drugs in the future, please include an explanation of each step being taken to prevent the recurrence of violations, as well as copies of related documentation. If you do not believe that the products discussed above are in violation of the FDCA, include your reasoning and any supporting information for our consideration. In addition to taking appropriate corrective actions, you should notify this office prior to resuming production of any sterile drugs in the future. Your written reply should be addressed to:

Lawton Lum
Director, Compliance Branch
U.S. Food and Drug Administration
1431 Harbor Bay Parkway
Alameda, CA 94502

If you have questions regarding any issues in this letter, please contact Mr. Russell Campbell, Compliance Officer, at 510-337-6861.

Sincerely,
/S/

Kathleen M. Lewis, J.D.
District Director

cc:
Virginia Herold, Executive Officer
California State Board of Pharmacy
1625 N Market Street
Sacramento, CA 95834

---

[1] *Compare Western States Med. Ctr. v. Shalala*, 238 F.3d 1090 (9th Cir. 2001) *with Medical Ctr. Pharm. v. Mukasey*, 536 F.3d 383 (5th Cir. 2008).

[2] The CPG set forth a non-exhaustive list of factors that FDA considered in determining whether to take enforcement action when the scope and nature of a pharmacy's activities raised concerns. This CPG has been withdrawn in light of new legislation. See below.

[3] *See* 21 U.S.C. § 353a(a) (granting compounded drugs statutory exemptions if, among other things, "the drug product is compounded for an identified individual patient based on the . . . receipt of a valid

prescription order or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient . . . ."); CPG at 2 ("FDA recognizes that pharmacists traditionally have extemporaneously compounded and manipulated reasonable quantities of human drugs upon receipt of a valid prescription for an individually-identified patient from a licensed practitioner. This traditional activity is not the subject of this guidance.").

[4] Drug Quality and Security Act, Public Law 113-54, 127 Stat. 587 (Nov. 27, 2013).

[5]The CQA contains a number of other provisions, including new exemptions and requirements for compounders seeking to operate as outsourcing facilities. A discussion of the CQA and the agency's plans to implement the new law may be found at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm.

[6] For example, section 503A also addresses anticipatory compounding, which includes compounding (not distribution) before receipt of a valid prescription order for an individual patient. We are not addressing anticipatory compounding here.

!

Attachment C

Sichuan Pharmaceutical Co., Ltd. 9/9/11

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring MD 20993

Warning Letter

VIA UPS MAIL

WL: 320-11-019

September 09, 2011

Mr. Wang Gouping
General Manager
Sichuan Pharmaceutical Co., Ltd.
No. 189 Hualong Road
Pengzhou, Sichuan, China 611930

Dear Mr. Gouping:

During our June 23 to 29, 2010 inspection of your active pharmaceutical ingredient (API) manufacturing facility, Sichuan Pharmaceutical Co., Ltd. located at No. 189 Hualong Road, Pengzhou, Sichuan, China, an investigator from the Food and Drug Administration (FDA) identified significant deviations from Current Good Manufacturing Practice (CGMP) for the manufacture of APIs. These deviations cause your API(s) to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 351(a)(2)(B)] in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

We have reviewed your firm's response of August 05, 2010 and December 13, 2010, and note that it lacks sufficient corrective actions.
Specific deviations observed during the inspection include, but are not limited, to the following:

1. Failure to have appropriate procedures in place to prevent cross-contamination.

   From September 2008 to July 2009 your firm manufactured **(b)(4)** API in workshop **(b)(4)**, which is adjacent to workshops **(b)(4)** and **(b)(4)** where you manufactured **(b)(4)** API and **(b)(4)** injection, respectively. However, you failed to have adequate controls and monitoring program to prevent cross-contamination between these adjacent workshops.

In addition, your firm manufactures a **(b)(4)** API (**(b)(4)** (API) in a facility that was previously used to manufacture **(b)(4)** without conducting adequate decontamination, renovation, and activation of the facility. Your firm has failed to conduct adequate assessment of the cross-contamination risks.

Please note that analytical testing of a product for possible contamination with **(b)(4)** is not sufficient to ensure adequate conditions for **(b)(4)** manufacture. In your response to this letter include your plans for decontamination, renovation, and reactivation (if appropriate) of your facility including the decontamination agent, decontamination plans, analytical methodology for environmental and product testing, and the data obtained to support the effectiveness of the decontamination plan.

The deviations detailed in this letter are not intended to be an all-inclusive statement of deviations that exist at your facility. You are responsible for investigating and determining the causes of the deviations identified above and for preventing their recurrence and the occurrence of other deviations. If you wish to continue to ship APIs to the United States, it is the responsibility of your firm to ensure compliance with all U.S. standards for CGMP and all applicable U.S. laws and regulations.

Additionally, your firm is neither registered nor has it listed every API in commercial distribution in the United States with FDA, as required by 21 C.F.R. § 207.40 and section 510(i) of the Act [21 U.S.C. § 360(i)]. Information on how to register and list is available at the following internet website:http://www.fda.gov/cder/drls/registration_listing.htm. You must complete the required registration and listing and provide evidence that you have fulfilled these requirements in your response to this letter.

Until all corrections have been completed and FDA has confirmed corrections of the deviations and your firm's compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as an API manufacturer. In addition, failure to correct these deviations may result in FDA refusing admission of articles manufactured at Sichuan Pharmaceutical Co., Ltd. located at No. 189 Hualong Road, Pengzhou, Sichuan, China into

the United States. The articles are subject to refusal of admission pursuant to section 801(a)(3) of the Act [21 U.S.C. § 381(a)(3)] in that the methods and controls used in their manufacture do not appear to conform to Current Good Manufacturing Practice within the meaning of section 501(a)(2)(B) of the Act [21 U.S.C. § 351(a)(2)(B)].

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct deviations. Include an explanation of each step being taken to prevent the recurrence of deviations and copies of supporting documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the date by which you will have completed the correction.

Additionally, your response should state if you no longer manufacture or distribute **(b)(4)** API and provide the date(s) and reason(s) you ceased production. Please identify your response with FEI # 3002808073.

If you have questions or concerns regarding this letter, contact Milva E. Meléndez, Compliance Officer, at the below address and telephone number.

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Manufacturing and Product Quality
Division of International Drug Quality
White Oak, Building 51
10903 New Hampshire Ave
Silver Spring, MD 20993
Tel: (301) 796-0662
Fax: (301) 847-8741

Sincerely,

/Steven Lynn/
Steven Lynn
Director
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

!

IN THE CIRCUIT COURT OF PULASKI COUNTY, ARKANSAS
FIFTH DIVISION

JASON MCGEHEE,
STACEY JOHNSON,
JACK JONES,
BRUCE WARD,
KENNETH WILLIAMS,
MARCEL WILLIAMS
ANDREW SASSER,
DON DAVIS, and
TERRICK NOONER,

Plaintiffs,

v.

RAY HOBBS, in his official capacity
Director, Arkansas Department of Correction, and
ARKANSAS DEPARTMENT OF CORRECTION,

Defendant.

AFFIDAVIT OF DAVID B. WAISEL, M.D.

1. My name is Dr. David Waisel and I am a practicing anesthesiologist at Boston Children's Hospital in Boston, MA, and an Associate Professor of Anaesthesia at Harvard Medical School. I received my Medical Degree from Medical College of Pennsylvania in 1989. I have been practicing clinical anesthesiology for over twenty years. Over the years, I have authored several articles pertaining to anesthesiology that were published in various publications.

2. Counsel for the plaintiffs in this case asked me to opine on the effects and uses of barbiturate and benzodiazepine drugs. I have consulted with counsel on a *pro bono* basis and am not being compensated for my work in this case.

3. Barbiturates are a class of drugs that act to depress a person's central nervous system. The clinical uses of barbiturates are wide ranging, from treating anxiety or insomnia symptoms to treating seizure disorders to anesthetizing patients for surgery.

4. The term barbiturate describes a number of different drugs. Barbiturates are classified depending on the length of time of the drug's onset and how long those effects last. Generally, barbiturates

can be classified as ultra-short-acting, short-acting, intermediate-acting, or long-acting. There is a substantial difference between the way an ultra-short-acting barbiturate acts in the body as compared to a long-acting barbiturate. For example, an ultra-short-acting barbiturate produces a rapid onset in the body (typically within seconds). Depending on the dosage, a person administered an ultra-short-acting barbiturate will lose consciousness within seconds. While ultra-short-acting barbiturates take effect rapidly upon intravenous administration, the drugs start to wear off relatively quickly. Comparatively, a long-acting barbiturate may take considerably longer to take effect in the body, as well as may stay in the body for a significantly longer time. So while "barbiturates" is a word to describe a type of drug, barbiturate drugs themselves are diverse and have different effects on the body.

5. The duration of a barbiturate, meaning how long the drug works in the body (as explained above), is measured in the "half-life" of the drug. The half-life of a drug is the period of time required for the body to reduce the amount of the drug in the body by one-half. The half-life of a drug is useful to determine how long it will take the body to process the drug out of its system. So for example, ultra-short-acting barbiturates will begin to work very quickly in the body and will leave the body quickly; long-acting barbiturates will take comparatively longer to take effect in the body and longer to leave the body.

6. Like barbiturates, benzodiazepines depress (or slow down) a person's central nervous system. Benzodiazepines specifically enhance the effect of the $GABA_A$ (gamma-aminobutyric acid) receptor in the brain, which affects the physical functioning of the brain and can cause sedation, induce sleep, inhibit anxiety, prevent seizures, or relax muscles. Benzodiazepines are like alcohol in that they both bind to the $GABA_A$ receptor and can produce a similar cognitive effect: feelings of sedation or relaxation, an altered consciousness, a lack of judgment or insight, or tiredness. Benzodiazepines are used frequently to treat anxiety and induce amnesia.

7. Depending on the dose given, benzodiazepines can produce paradoxical effects. A paradoxical effect (or reaction) is when a drug produces an effect that is opposite of what is expected. For example, a person administered a sedative to calm them down may respond with the paradoxical effect of causing the patient to become more anxious, more talkative, aggressive or violent.

8. Benzodiazepines may produce paradoxical reactions. Depending on the dose administered, some individuals administered a benzodiazepine show signs of agitation, excitement, acute anxiety, anger, impulsivity and gross motor and behavioral disturbances. The cause of these reactions are unclear, although several risk factors have been identified, including a history of alcoholism and psychiatric or personality disorders, especially disorders characterized by poor impulse control.

9. I hold these opinions to a reasonable degree of medical certainty.

Dated this 26 day of AUGUST, 2013.

David B. Waisel, MD.

Sworn to and subscribed before me on this 26th day of AUGUST, 2013.

Notary

REBECCA D. BRENNAN
Notary Public
Massachusetts
Commission Expires Aug 15, 2019

SWORN DECLARATION OF SPENCER J. HAHN

STATE OF ALABAMA)
)
COUNTY OF MONTGOMERY)

I, Spencer J. Hahn, a resident of Montgomery, Alabama, hereby declare, under penalty of perjury, the following:

1. I am an Assistant Federal Defender in the Capital Habeas Unit of the Federal Defenders for the Middle District of Alabama, in Montgomery, Alabama, where I have worked since October 1, 2014. I have been licensed to practice law since 2004.

2. Ron Smith designated me and our Executive Director, Christine Freeman, to witness his execution. This declaration contains my observations of what occurred immediately before, during, and after Ron's execution.

3. At approximately 10:20 p.m., Christine and I, along with members of the press (including Kent Faulk) who had been waiting in a van next to our transport car, were escorted into the witness room. While waiting, I had noticed two people in an Etowah County Medical Examiner vehicle; they remained outside.

4. I asked the corrections officer who drove us if anyone from the victim's family was present, and was told that someone was. Once inside the witness room, I heard a radio transmission that witnesses were being taken to room 8, followed by footsteps and the shadows of feet passing our (closed) door. Whoever was in room 8 was allowed to leave before we did, as I heard a similar radio transmission about room 8, and saw the reverse of what I saw after the first message. They left and entered through the other end of the hall from us and the press.

5. The Warden read the death warrant to Ron, offered him a chance to make any final statement ("No, ma'am"), and the Warden left the room.

6. Shortly thereafter, the second guard left the room, and the prison chaplain approached Ron, held his right hand, and kneeled in front of him for a minute or so. As the prison chaplain approached, Ron appeared to be mouthing, repeatedly, what I believe was the Lord's Prayer.

7. The midazolam began around 10:30 p.m. The first thing I noticed was that Ron ran his tongue around his lips several times, as if he had a dry mouth. Then, at 10:31:55 p.m. (according to the clock above his gurney) Ron began having difficulty breathing, including regular asthmatic-sounding barking coughs every ten seconds or so. He also lifted his head and looked around, moved his arms, clenched his left hand, and moved his lips in what appeared to be an attempt to say something. Ron's eyes never closed, and he moved and coughed regularly throughout approximately the next fifteen minutes.

8. Both before and after the first consciousness check, it was obvious Ron was still awake, as he was still moving his head, hands and arms, coughing, and attempting to speak. He reacted to the arm pinch by moving his arm toward his body (away from the source of pain).

9. Sometime before the administration of the second dose of midazolam, I heard raised voices coming from the Commissioner's room. Although I couldn't make out the words, the tone indicated panic or, at the very least, extreme stress.

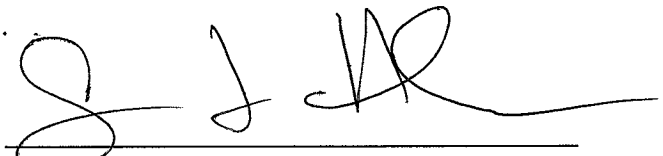
10. Ron again began to exhibit the signs he did after the first dose of midazolam. After several more minutes, a second consciousness check was done, during which Ron continued to move and his eyes remained open. While touching his left eyelid, the guard pushed it closed, but it opened as soon as he removed his finger.

11. Ron moved his right arm after the second consciousness check. Shortly thereafter, they must have administered the paralytic, as Ron's breathing became very shallow and he stopped moving. His eyes remained open, with the left eye opening further as his breathing became imperceptible.

12. The curtains were closed without anyone having approached Ron and, when I stood to leave, I, on my tiptoes, looked over the top of the curtain, and saw no signs of the EKG or anyone checking Ron. Leaving the building, I noticed that both members of the medical examiner's office were still in their truck.

I hereby declare, pursuant to 28 U.S.C. 1746, under penalty of perjury, that the foregoing is true and correct to the best of my knowledge and belief.

Dated this 13th day of December, 2016.



Spencer J. Hahn
Assistant Federal Defender

IN THE UNITED STATES COURT OF APPEALS
FOR THE EIGHTH CIRCUIT

No. 16-3072

In re: Missouri Department of Corrections, Petitioner

M7, Petitioner – Intervenor

Richard Jordan and Ricky Chase, Respondents.

On Petition for Writ of Mandamus to the United States District Court
for the Western District of Missouri – Jefferson City
(2:16-MC-09005)

RESPONDENTS' MOTION FOR LEAVE TO FILE TRANSCRIPT UNDER SEAL

James W. Craig
Emily M. Washington
Roderick & Solange MacArthur Justice Center
4400 S. Carrollton Avenue
New Orleans LA 70119
(504) 620-2259 (p)
(504) 208-3133 (f)
jim.craig@macarthurjustice.org
emily.washington@macarthurjustice.org

Attorneys for Respondents

RESPONDENTS' MOTION FOR LEAVE TO FILE TRANSCRIPT UNDER SEAL

Richard Jordan and Ricky Chase, Respondents in the above-captioned mandamus proceeding, move this Court for leave to file a portion of the transcript of the hearing before District Judge Bough under seal. The transcript, attached to the paper copy of this motion, is designated "Exhibit 4-B" in Respondents' pleadings in opposition to the petitions for mandamus and rehearing filed by the Missouri Department of Corrections ("MO-DOC") and M7. In support of this motion, Respondents represent the following to the Court:

1. On July 1, 2016, the United States District Court for the Western District of Missouri conducted a hearing on MO-DOC's motion to quash a subpoena duces tecum and notice of deposition served upon MO-DOC by Respondents.

2. A portion of the hearing was sealed with only MO-DOC and Respondents' attorneys present in the courtroom.

3. On September 20, 2016, the district court entered a Protective Order sealing the transcript of the *in camera* portion of the July 1 hearing. Doc. 38, *Missouri Department of Corrections v. Jordan et al.*, case no. 2:16-mc-09005.

4. Under the terms of the Protective Order, the transcript of the *in camera* portion of the transcript can only be filed in the Eighth Circuit Court of Appeals under seal.

5. In addition to the sealed transcript, Respondents submit a brief Argument Regarding Matters in Sealed Transcript, setting forth the relevance of the sealed transcript to the issues before this Court.

6. Respondents believe that this Motion may be made publically available on PACER. See Local Rule 25A(g).

WHEREFORE, PREMISES CONSIDERED, Respondents request that this Court grant leave to file the sealed portion of the July 1 transcript and the Argument Regarding Matters in Sealed Transcript under seal.

Respectfully submitted,

/s/ James W. Craig
James W. Craig
Emily M. Washington
Roderick & Solange MacArthur Justice Center
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CERTIFICATE OF SERVICE

I hereby certify that I have served a copy of this Motion on all parties by electronic mail. This pleading is not filed via the Electronic Case Filing system of the United States Court of Appeals for the Eighth Circuit.

This, the 30th day of September, 2016.

/s/ James W. Craig

IN THE UNITED STATES COURT OF APPEALS
FOR THE EIGHTH CIRCUIT

No. 16-3072

In re: Missouri Department of Corrections, Petitioner

M7, Petitioner – Intervenor

Richard Jordan and Ricky Chase, Respondents.

On Petition for Writ of Mandamus to the United States District Court
for the Western District of Missouri – Jefferson City
(2:16-MC-09005)

RESPONDENTS' ARGUMENT REGARDING MATTERS IN SEALED TRANSCRIPT

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RESPONDENTS' ARGUMENT REGARDING MATTERS IN SEALED TRANSCRIPT

On July 1, 2016, the United States District Court for the Western District of Missouri conducted a hearing on MO-DOC's motion to quash a subpoena duces tecum and notice of deposition served upon MO-DOC by Respondents. A portion of the hearing was sealed with only MO-DOC and Respondents' attorneys present in the courtroom. The sealed transcript is designated as "Exhibit 4-B" in the Respondents' oppositions to the motions filed by the Missouri Department of Corrections ("MO-DOC") and M7, MO-DOC's anonymous drug vendor.

During the in camera portion of the hearing, counsel for MO-DOC discussed matters set forth in the privilege log which had been submitted to the district court ex parte. Respondents' counsel did not have access to the ex parte privilege log.

MO-DOC's counsel focused the Court's attention on Request No. 2 of the subpoena duces tecum under consideration in the district court. That request seeks production of "All drug labels and package inserts for any drug purchased or obtained by the Department, from 2010 to the present, for use in lethal injection executions."[1] MO-DOC counsel stated:

> I'm primarily focused on request number 2 for documents about pentobarbital . . . if identified whether or not there is a responsive document to that request, that answers the question of whether it is or is not manufactured or

[1] Exhibit 3 to Respondents' Opposition at 5.

> compounded pentobarbital because manufactured pentobarbital has that information, and compounded pentobarbital does not have a package insert.
>
> So by merely saying that there exists a document that proves it's manufactured or proves that it's compounded, that answers the question does Missouri use compounded or manufactured pentobarbital.[2]

Thereafter, the district court stated "there are three responses that list No. 2."[3] Counsel for MO-DOC agreed.[4]

Thus, there is evidence that at some point after 2010, MO-DOC purchased manufactured pentobarbital for use in lethal injection executions. All parties agree that pentobarbital can be purchased in one of two forms: either compounded by a licensed pharmacy from the active pharmaceutical ingredients for the chemical; or manufactured by a pharmaceutical company under FDA-approved and monitored practices. Akorn Pharmaceuticals is the sole licensed manufacturer of pentobarbital.[5] Akorn has instituted a policy restricting the sale of Nembutal to corrections departments for use in executions.[6]

The sale of manufactured pentobarbital by M7 or another vendor to MO-DOC would violate the property and contractual rights of Akorn to determine how its

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[2] Exhibit 4-B at 8-9.
[3] Id. at 10.
[4] Id.
[5] See Exhibit D (May 13, 2016 article) to Exhibit 15 (Declaration of Comptroller DiNapoli) to Respondent's Opposition.
[6] Exhibit B to Exhibit 15 to Respondents' Opposition.

product is used. For the reasons set forth in the Oppositions filed by Respondents in the public record, mandamus should be denied if this Court, or the district court, finds that MO-DOC and M7's attempt to safeguard the confidentiality of the identity of MO-DOC's lethal injection drug vendors would facilitate the violation of the rights of Akorn and its shareholders.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that I have served a copy of this Argument on all parties by electronic mail. This pleading is not filed via the Electronic Case Filing system of the United States Court of Appeals for the Eighth Circuit.

This, the 30th day of September, 2016.

/s/ James W. Craig

2015 Arkansas Laws Act 1096 (H.B. 1751)

ARKANSAS 2015 SESSION LAWS

90th GENERAL ASSEMBLY, REGULAR SESSION, 2015

Additions are indicated by **Text**; deletions by
~~Text~~ .
Vetoes are indicated by ~~Text~~ ;
stricken material by ~~**Text**~~ .

ACT 1096
H.B. 1751
CORRECTIONAL INSTITUTIONS—EXECUTIONS—LETHAL INJECTION

AN ACT CONCERNING THE ADMINISTRATION OF A LETHAL INJECTION AT THE DEPARTMENT OF CORRECTION; TO DECLARE AN EMERGENCY; AND FOR OTHER PURPOSES.

Subtitle

CONCERNING THE ADMINISTRATION OF A LETHAL INJECTION AT THE DEPARTMENT OF CORRECTION; AND TO DECLARE AN EMERGENCY.

BE IT ENACTED BY THE GENERAL ASSEMBLY OF THE STATE OF ARKANSAS:

SECTION 1. DO NOT CODIFY. **Legislative findings.**

(a) The laws of Arkansas impose the sentence of death for its most serious offenses. The General Assembly finds it necessary to provide a means of carrying out the sentence of death while also complying with the constitutional prohibition on cruel and unusual punishment.

(b) To address objections to the method of lethal injection previously provided by law and to address the problem of drug shortages, the General Assembly finds that it should adopt alternative methods of lethal injection to bring about the death of the condemned prisoner.

(c) The General Assembly finds that this act meets those goals and satisfies the separation-of-powers doctrine by setting forth the state's policy and the procedural guidelines for carrying out the sentence of death.

SECTION 2. Arkansas Code § 5–4–617 is amended to read as follows:

<< AR ST § 5–4–617 >>

5–4–617. Method of execution.

(a) The Department of Correction shall carry out the sentence of death by intravenous lethal injection of ~~*a barbiturate*~~ ***the drug or drugs described in subsection (c) of this section*** *in an amount sufficient to cause death.*

(b) The Director of the Department of Correction or his or her designee may order the dispensation and administration of the drug or drugs described in subsection (c) of this section for the purpose of carrying out the lethal-injection procedure, and a prescription is not required.

(c) The department shall select one (1) of the following options for a lethal-injection protocol, depending on the availability of the drugs:

(1) A barbiturate; or

(2) Midazolam, followed by vecuronium bromide, followed by potassium chloride.

(d) The drug or drugs described in subsection (c) of this section used to carry out the lethal injection shall be:

(1) Approved by the United States Food and Drug Administration and made by a manufacturer approved by the United States Food and Drug Administration;

(2) Obtained from a facility registered with the United States Food and Drug Administration; or

(3) Obtained from a compounding pharmacy that has been accredited by a national organization that accredits compounding pharmacies.

~~*(b) Before the intravenous lethal injection is administered, the condemned prisoner shall be intravenously administered a benzodiazepine.*~~

~~*(c)*~~ ***(e)*** *The drugs set forth in* ~~*subsections (a) and (b)*~~ ***subsection (c)*** *of this section shall be administered along with* ~~*any substances that the manufacturer has mixed with the drugs and*~~ *any additional substances, such as saline solution, called for in the* ~~*manufacturer's*~~ *instructions.*

~~*(d)*~~ ***(f)*** *Catheters, sterile intravenous solution, and other equipment used for the intravenous injection of the* ***drug or*** *drugs set forth in* ~~*subsections (a) and (b)*~~ ***subsection (c)*** *of this section shall be sterilized and prepared in a manner that is safe and commonly performed in connection with the intravenous administration of drugs of that type.*

~~*(e)*~~ ***(g)*** *The* ~~*Director of the Department of Correction*~~ ***director*** *shall develop logistical procedures necessary to carry out the sentence of death, including:*

(1) The following matters:

(A) Ensuring that the drugs and substances set forth in ~~*subsections (a) - (d) of*~~ *this section and other necessary supplies for the lethal injection are available for use on the scheduled date of the execution;*

(B) Conducting employee orientation of the lethal injection procedure before the day of the execution;

(C) ~~*Logistics*~~ ***Determining the logistics*** *of the viewing;*

(D) Coordinating with other governmental agencies involved with security and law enforcement;

(E) Transferring the condemned prisoner to the facility where the sentence of death will be carried out;

(F) Escorting the condemned prisoner from the holding cell to the execution chamber;

(G) ~~*The*~~ ***Determining the*** *identity, arrival, and departure of the persons involved with carrying out the sentence of death at the facility where the sentence of death will be carried out; and*

(H) Making arrangements for the disposition of the condemned prisoner's body and personal property; and

(2) The following matters pertaining to other logistical issues:

(A) Chaplaincy services;

(B) Visitation privileges;

*(C) Determining the condemned prisoner's death, which ~~must~~ **shall** be pronounced according to accepted medical standards; **and***

~~*(D) Confirming the type and concentration of the drugs and substances set forth in subsections (a)–(d) of this section when they have been received by the department; and*~~

*~~(E)~~ **(D)** Establishing a protocol for any necessary mixing or reconstitution of the drugs and substances set forth in ~~subsections (a)–(d) of~~ this section in accordance with the ~~manufacturer's~~ instructions.*

*~~(f)~~ **(h)** The procedures for carrying out the sentence of death and related matters are not subject to the Arkansas Administrative Procedure Act, § 25–15–201 et seq.*

*~~(g)~~ **(i)(1)** The procedures under subdivision ~~(e)(1)~~ **(g)(1)** of this section**,** ~~and~~ the implementation of the procedures under subdivision ~~(e)(1)~~ **(g)(1)** of this section**, and the identities of the entities and persons who participate in the execution process or administer the lethal injection** are not subject to disclosure under the Freedom of Information Act of 1967, § 25–19–101 et seq.*

(2) The department shall keep confidential all information that may identify or lead to the identification of:

(A) The entities and persons who participate in the execution process or administer the lethal injection; and

(B) The entities and persons who compound, test, sell, or supply the drug or drugs described in subsection (c) of this section, medical supplies, or medical equipment for the execution process.

(3) The department shall not disclose the information covered under this subsection in litigation without first applying to the court for a protective order regarding the information under this subsection.

(j) The department shall make available to the public any of the following information upon request, so long as the information that may be used to identify the compounding pharmacy, testing laboratory, seller, or supplier is redacted and maintained as confidential:

(1) Package inserts and labels, if the drug or drugs described in subsection (c) of this section have been made by a manufacturer approved by the United States Food and Drug Administration;

(2) Reports obtained from an independent testing laboratory; and

(3) The department's procedure for administering the drug or drugs described in subsection (c) of this section, including the contents of the lethal-injection drug box.

*~~(h)~~ **(k)** The department shall carry out the sentence of death by electrocution if **execution by lethal injection under** this section is invalidated by a final and unappealable court order.*

(l) Every person that procures, prepares, administers, monitors, or supervises the injection of a drug or drugs under this section has immunity under § 19–10–305.

SECTION 3. SEVERABILITY CLAUSE. ***If any provision of this act or its application to any person or circumstance is held invalid, the invalidity does not affect other provisions or applications of this act which can be given effect without the invalid provision or application, and to this end the provisions of this act are severable.***

SECTION 4. EMERGENCY CLAUSE. ***It is found and determined by the General Assembly of the State of Arkansas that the courts now require heightened legislative oversight and control over the procedures used in carrying out capital punishment. In addition, victims' families need assurance that capital sentences will be carried out in compliance with prevailing case law. Therefore, an emergency is declared to exist, and this act being immediately necessary for the preservation of the public peace, health, and safety shall become effective on:***

(1) The date of its approval by the Governor;

(2) If the bill is neither approved nor vetoed by the Governor, the expiration of the period of time during which the Governor may veto the bill; or

(3) If the bill is vetoed by the Governor and the veto is overridden, the date the last house overrides the veto.

lslHouse

APPROVED: 4/6/2015

End of Document

LETHAL INJECTION PROCEDURE (Attachment C)

SECTION I. General

1. The Deputy Director, or designee, is responsible for assuring that the chemicals for lethal injection, the gurney, straps, and other necessary items, are available for use on the scheduled date of execution. The Deputy Director, or the designee, shall be healthcare trained, educated, and/or experienced in matters related to the establishment and monitoring of IVs, the mixing and administration of the chemicals, and assessing the presence or absence of consciousness.

2. When the chemicals have been received, the Deputy Director, or the designee, shall verify as to type and concentration, and thereafter supervise any necessary mixing or reconstituting of the chemicals in such a manner as will meet the injection requirements (see Chart A) and in accordance with manufacturer's instructions. The mixed or reconstituted chemicals shall be transferred to an appropriate syringe(s) and thereafter placed in a designated Injection Drug Box. The box will be secured and conveyed to the Cummins Unit.

3. The Deputy Director, or designee, shall maintain physical custody of the Injection Drug Box and physically convey the box directly to the execution chamber for use. If not used, the Deputy Director, or designee, shall secure the Drug Box until used or destroyed.

4. Orientation of the executioner(s) to the Department's *Lethal Injection Procedure*, if needed, will be conducted prior to the day of the execution and provided by the Director and/or designee(s).

5. On the evening of the execution, the executioner(s) shall, under the supervision of the Director, or designee, enter the injection room prior to the scheduled time of the execution and shall immediately inventory the Injection Drug Box to ensure that all chemicals are accounted for and that the infusion device(s) are in readiness.

6. The execution gurney will be positioned in the death chamber so that the Deputy Director, or designee, and the executioner(s) can directly observe the condemned inmate's face and IV infusion site(s).

SECTION II. IV Set-Up Procedure

1. The Deputy Director, or designee, shall have an intravenous infusion device placed in each arm, or other standard anatomical venous point of entry, of the condemned inmate and a solution of N.S. (Normal Saline) available for an infusion medium. The individual(s) engaged in this activity will be referred to as the IV Team and shall be qualified as set forth in Section V.

2. An IV administration set shall be inserted into the outlet of the bag of N.S. IV solution. Two (2) IV bags will be set up in this manner.

3. The administration set tubing for each set-up will be connected to the receiving port of the three-way control devices; one left arm/side, the other for the right arm/side.

4. IV extension tubing will be connected to the discharge ports on the right/left three-way control devices and shall be thereafter connected to the applicable right and left IV insertion site(s). Extension tubing will be of sufficient length to accommodate the distance from control device to IV insertion site(s).

5. The tubing shall be cleared of air and made ready for use.

6. Intravenous catheters shall be initiated through standard procedure for such devices. Once the infusion of the IV solution has been assured, the IV devices shall be secured as appropriate.

7. At this point, the administration sets shall be running at a slow rate of flow (KVO), and ready for the insertion of syringes containing the chemicals. The Deputy Director, or designee, shall maintain observation of IV infusion(s) to ensure that the rate of flow is uninterrupted. NO FURTHER ACTION shall be taken until the prearranged signal to start the injection of chemicals is given by the Warden.

8. In the event that a patent intravenous infusion site cannot be established, the IV Team shall be directed by the Deputy Director, or designee, to evaluate other possible infusion sites. All effort will be made to establish two (2) unrelated intravenous infusion sites. If one (1) patent infusion site is established, and a second site proves to be a futile effort, the Deputy Director, or designee, may direct the IV Team to suspend further action to establish a second site and proceed with one site. In the case that no patent infusion site is established after reasonable attempts as determined by the IV Team, the Deputy Director, or designee, will direct the IV Team to suspend further action and thereafter summon trained, educated, and experienced person(s) necessary to establish a primary IV line as a peripheral line or as a central venous line.

EVERY EFFORT WILL BE EXTENDED TO THE CONDEMNED INMATE TO ENSURE THAT NO UNNECESSARY PAIN OR SUFFERING IS INFLICTED BY THE IV PROCEDURE. STANDARD PRACTICE OF USING A LOCAL ANESTHETIC (1% LIDOCAINE) WILL BE ACCOMMODATED AS NECESSARY.

SECTION III. Preparation of Chemicals

1. The Deputy Director, or the designee(s), and a member of the IV Team shall prepare the designated chemicals and syringes for a total of one (1) complete set of chemicals. One (1) complete set of syringes is used in the implementation of the death sentence and an additional complete set of the necessary chemicals shall be obtained and kept available. The specific chemical contained in each syringe will be identified with the following information as set forth in the chemical charts:

   a. Assigned number

   b. Chemical name

   c. Chemical amount

   d. Designated color

2. The quantities of chemicals prepared and administered shall not be changed in any manner without prior documented approval of the director.

3. All prepared chemicals shall be utilized or properly disposed of in a timely manner after the time designated for the execution to occur.

4. The chemical amounts as set forth in the Chemical Chart are designated for the execution of persons weighing 500 pound or less. The chemical amounts shall be reviewed and may be revised as necessary for an offender exceeding this body weight.

5. CHEMICAL CHART

   a. **CHART A**: Three (3) Drug Protocol with Midazolam, Vecuronium Bromide and Potassium Chloride

CHEMICAL CHART	
Syringe No.	**Label**
1A	250 mg midazolam, **GREEN**
2A	250 mg midazolam, **GREEN**
3A	60 ml saline, **BLACK**
4A	50 mg vecuronium bromide, **YELLOW**
5A	50 mg vecuronium bromide, **YELLOW**
6A	60 ml saline, **BLACK**
7A	120 mEq potassium chloride, **RED**
8A	120 mEq potassium chloride, **RED**
9A	60 ml saline, **BLACK**

(1) Syringes 1A and 2A shall each have a dose of 250 milligrams midazolam for a total dose of 500 milligrams. Each syringe containing midazolam shall have a **GREEN** label which contains the name of the chemical, the chemical amount and the designated syringe number.

(2) Syringes 4A and 5A shall each have a dose of 50 milligrams vecuronium bromide for a total dose of 100 milligrams. Each syringe containing the selected bromide shall have a **YELLOW** label which contains the name of the chemical, the chemical amount and the designated syringe number.

(3) Syringes 7A and 8A shall each contain 120 milliequivalents potassium chloride for a total dose of 240 milliequivalents. Each syringe containing potassium chloride shall have a **RED** label which contains the name of the chemical, the chemical amount and the designated syringe number.

(4) Syringes 3A, 6A, and 9A shall each contain 60 milliliters of saline solution. Each syringe shall have a **BLACK** label which contains the name of the solution, amount of solution, and the designated syringe number.

SECTION IV. Injection Procedure

1. The three-way control device facilitates the movement of infusion fluid from saline bag or infusion fluid with the chemicals from the syringes. A valve serves to direct which fluid source is entering the IV set up.

2. When the signal to commence is given by the Warden, the executioner(s) shall administer the chemicals in the order they appear in chart A under the direction of the Deputy Director, or designee, as follows:

   a. Syringe 1A shall be inserted into the designated chemical receiving port of the three-way control device.

   b. The flow of IV solution will be interrupted by moving the three-way valve assembly to allow the infusion of chemical from Syringe 1A.

   c. The contents of Syringe 1A shall commence with a steady even flow of the chemical and continue until the full dose of the chemical has been administered. Only the force necessary to activate the syringe plunger will be used.

   d. When the contents of Syringe 1A have been injected, the three-way valve assembly will be moved so as to shut off the chemical receiving port and resume infusion of IV solution.

e. Syringe 1A will be replaced by Syringe 2A and the procedure described in subparagraphs a-d for Syringe 1A will be repeated. This process will be repeated for all subsequent syringes.

f. Following the administration of syringe numbers 1A, 2A, and 3A, and after at least five (5) minutes have elapsed since commencing the administration of syringe 1A, the Deputy Director, or designee, will confirm the condemned inmate is unconscious by using all necessary and medically-appropriate methods. The Deputy Director, or designee, shall also confirm that the IV line(s) remains affixed and functioning properly.

g. Once the Deputy Director, or designee, determines that the condemned inmate is unconscious, the remaining chemicals will be administered in the order they appear in Chart A.

h. In the unlikely event that the Deputy Director, or designee, determines that the condemned inmate remains conscious following the administration of the chemicals in syringe numbers 1A, 2A, and 3A, the back-up syringes of the first chemical (Syringe 1B and 2B) and saline (Syringe 3B), shall be administered via the secondary or alternative IV line.

(1) Following the administration of syringe numbers 1B, 2B, and 3B, and after at least five (5) minutes have elapsed since commencing the administration of syringe 1B, the Deputy Director, or designee, will confirm the condemned inmate is unconscious by using all necessary and medically-appropriate methods. The Deputy Director, or designee, shall also confirm that the IV line(s) remains affixed and functioning properly.

(2) Once the Deputy Director, or designee, determines that the condemned inmate is unconscious, the remaining chemicals will be administered via the secondary or alternative IV line in the order they appear in Chart A.

i. Throughout the chemical infusion process, the Deputy Director, or designee, will closely monitor the infusion site for evidence of infiltrate, vein collapse, or other challenge to the patency of the infusion site.

(1) Should a problem be suspected, the Deputy Director, or designee, will direct reduction of chemical flow rate or redirect chemical to the secondary or alternative site.

(2) In the use of a singular infusion site pursuant to Section II (8), if the infusion site is suspected to be compromised, chemical flow rate will be reduced. If problem persists, the:

(a) injection procedure will cease;

(b) curtain to death chamber will close; and

(c) the IV Team summoned, and the infusion site problem corrected.

(3) If all efforts to re-establish patent infusion site fail, the Deputy Director, or designee, will direct the IV Team to suspend further action and trained, educated, and experienced person(s) necessary to establish a primary IV line as a peripheral line or as a central venous line will be summoned to facilitate an IV infusion site.

(4) When the infusion compromise is corrected, the IV Team and the summoned person(s) will be excused, the curtain reopened, and the lethal injection procedure continued.

Section V. IV Team Qualifications

Each member of the IV team shall have at least two (2) years of professional experience and certification or licensure in at least one of the following fields:

1. Emergency Medical Technician-Intermediate, or

2. Emergency Medical Technician-Paramedic, or

3. Nurse, or

4. Physician Assistant, or

5. Physician.

AMENDED SUBMISSION

THE PHARMACOLOGY OF ARKANSAS'S LETHAL INJECTION PROCEDURE: FACTS, INTERPRETATIONS, AND ALTERNATIVES

January 2, 2017

Researched and written by:
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Reason for an Amended Report

The reason for the submission of an amended report is the discovery of a calculation error in section 5C of the original report. This was a simple error which led to an initial calculation of a higher blood concentration of a 500 mg IV midazolam dose.

The original report stated as follows: "This study gave peak blood concentrations of nearly 120 ng/mL (nanogram per milliliter) after a 5 mg IV dose. It follows then that with a 500 mg IV dose, the initial amount after direct IV bolus infusion is 100 times of what occurred with the 5 mg dose, which gives an initial blood concentration of ***120,000 ng/mL*** of midazolam after a 500 mg IV dose." [p 23 in original report, calculation error in bold, italics]. 120 ng/mL times 100 equals **12,000 ng/mL** (not 120,000 ng/mL). This has been corrected in the present version in section 5Bii in the amended report on p. 29. Subsequent calculations were corrected accordingly to arrive at a new ceiling-effect dosage of 228 mg IV midazolam.

The discovery of the calculation error does not essentially alter the summary and conclusions of the original report: that Midazolam's ceiling-effect dosage is lower than the 500 mg dose in the State's lethal-injection protocol and that a 500 mg dose of Midazolam cannot be relied on to render someone unconscious and insensate to the noxious stimuli that will occur from the application of the remaining drugs in the Arkansas lethal injection protocol.

Sections

1. Introduction

A. Author Qualifications

I am a full-time faculty member in the department of Pharmacology and Physiology at the College of Osteopathic Medicine, a unit of the Oklahoma State University, Center for Health Sciences campus in Tulsa, Oklahoma.

After receiving my Ph.D. in Pharmacology from the Mayo Clinic, in Rochester, Minnesota, I completed a 2 year postdoctoral fellowship at the University of Minnesota Medical School in Minneapolis, Minnesota, and secured a position as an Assistant Professor of Pharmacology with my present employer in 1990. I advanced through the academic ranks to Associate Professor of Pharmacology in 1993, and Professor of Pharmacology in 2000.

Besides my regular duties of teaching medical students, pursuing research and scholarly activities, and serving on college committees, I work part-time as a litigation consultant/expert witness on cases involving pharmacological issues. I have consulted in both civil and criminal cases, working with both the prosecution or plaintiff and the defendant.

With regard to the pharmacological issues of lethal injection, I have worked as a consultant with the state as well as with attorneys representing condemned inmates.

My *curriculum vitae* (CV) is attached as Appendix A to this report.

B. Materials Considered

Attorney Josh Lee, who retained me to study Arkansas's lethal injection procedures, provided me with several documents that I reviewed and relied upon in preparing this Expert Report. These materials were: (1) an email from Deputy Attorney General David Curran, to which was appended redacted package inserts and labels for the drugs that Arkansas intends to use in its execution procedure; (2) an email from Assistant Attorney General Jennifer Merritt, to which was appended a document titled "Lethal Injection Procedure (Attachment C)"; and (3) Arkansas's 2015 lethal injection statute, Ark. Code Ann. § 5-4-617 (2015). In addition to the above materials provided by Mr. Lee, I also considered pharmacological textbooks, reviews, and research studies (listed in Section 8, below), as well as *Baze v. Rees*, 128 S. Ct. 1520 (2008), and *Glossip v. Gross*, 135 S. Ct. 2726 (2015), which set the standard for when a lethal injection procedure may be said to violate the federal ban on cruel and unusual punishment. After Mr. Josh Lee left the Federal Public Defenders Office, my work as a pharmacology consultant continued with Mr. John C. Williams in the same office. Before submitting this amended report, I reviewed the Arkansas Supreme Court's opinion in *Kelley v. Johnson*, 2016 Ark. 268, and portions of the briefing in that case.

C. Brief Description of Arkansas's Execution Protocol

The execution procedure appended to the email from Deputy Attorney General Jennifer Merritt is a three-drug lethal injection protocol. First, the prisoner is to be injected with 500 mg. of the drug Midazolam. Next, after waiting five minutes, a member of the execution team ostensibly "confirm[s] the condemned inmate is unconscious," using unspecified methods. Then, the prisoner is to be injected with 100 mg (milligrams) of the muscle-paralytic drug, vecuronium bromide. Finally, the prisoner is to be injected with 240 mEq (milli-equivalents) of the heart-stopping drug, potassium chloride.

D. Referral Questions

Mr. Lee asked me to offer my expert opinion on several issues. First, Mr. Lee asked me to discuss the pharmacology of all the different drugs authorized by Arkansas's lethal injection statute, i.e., barbiturates, Midazolam, vecuronium bromide, and potassium chloride—with particular attention to any similarities and differences between barbiturates and Midazolam. Second, Mr. Lee asked for my opinion on whether Arkansas's chosen lethal injection procedure (Midazolam, followed by vecuronium bromide, and potassium) is sure or very likely to cause serious pain and suffering. Third, Mr. Lee asked me to address whether alternative execution procedures would significantly reduce the risk of pain and suffering and, if they would, to describe some of those procedures.

A thorough discussion of these issues follows. A summary of my opinions on the referred questions can be found in Section 7 of this Report.

2. Midazolam and Fast-Acting Barbiturates are Fundamentally Different Drugs

A. Pharmacological Equivalency and Pharmacological Substitution

Each drug has a unique chemical (atomic) structure and exerts a unique profile of pharmacological effects. Drugs are classified both by their chemical structures and by their therapeutic uses. Drugs that have very similar chemical structures are grouped together based on that structure. Drugs that have similar therapeutic uses are also grouped together by their therapeutic or pharmacological effects.

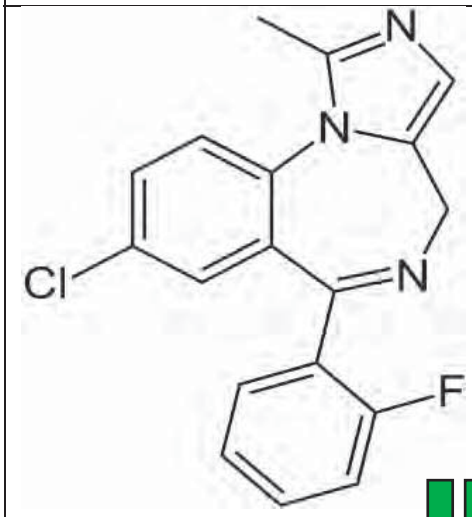
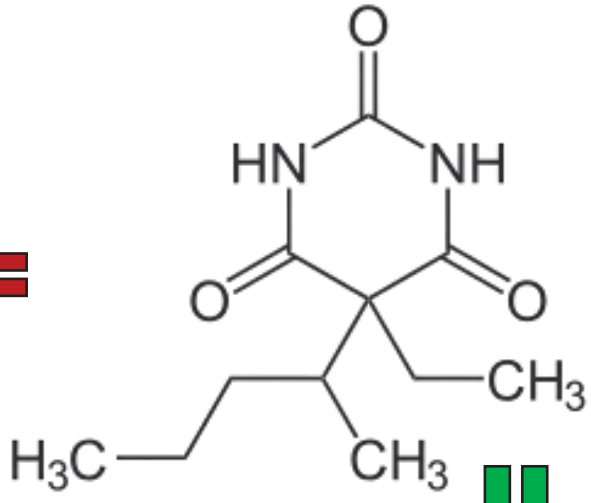
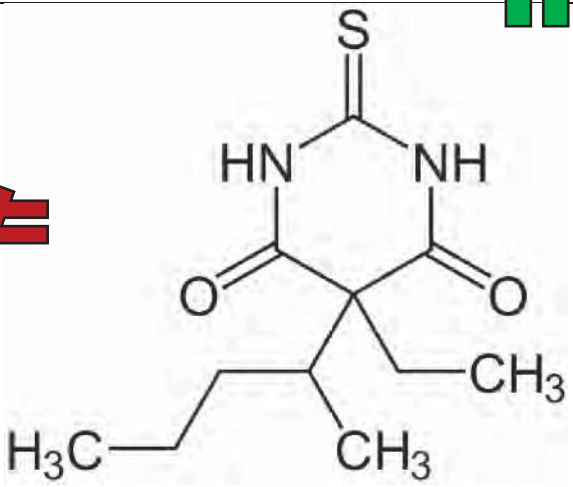
Pharmacological equivalency is present when two or more drugs exhibit the same or closely similar pharmacological properties. It is a working principle used by physicians who often substitute drugs due to drug allergies or for reasons of cost. Pharmacological equivalency is also the guiding principle for the FDA to accept a generic version of the same branded drug (e.g. Walgreen's ibuprofen, the generic form, is *pharmacologically equivalent* to Advil®, the branded formulation of ibuprofen. See *Meredith 2003, Borgheini 2003*).

Pharmacological substitution is the act of using one drug in the place of another. It is axiomatic that in order to maintain the same pharmacological and therapeutic effect of two drugs, the drug that is substituted must have pharmacological equivalency to the new drug.

There is no question that midazolam and fast-acting barbiturates (such as thiopental or pentobarbital) are different drugs. The key question in substituting drugs for lethal injection is one of a pharmacological nature: Does midazolam have *pharmacological equivalency* to fast-acting barbiturates such that a valid pharmacological substitution can be made? Pharmacological equivalency between midazolam, a benzodiazepine, and fast-acting barbiturates, is examined herein with respect to **pharmacological classification by chemical (atomic) structure, mechanisms of action, partial and full effects of these agents and the 'ceiling effect', therapeutic uses, and DEA scheduling of these agents.**

B. Pharmacological Classification of Midazolam and Fast-Acting Barbiturates

Table 1. Visual comparison of benzodiazepine and barbiturate chemical structures.

BENZODIAZEPINES	**BARBITURATES**
	
Midazolam (Versed®)	Pentobarbital (Nembutal®)
	
Diazepam (Valium®)	Thiopental (Pentothal®)

Midazolam belongs to the class of drugs called benzodiazepines whereas drugs like pentobarbital and thiopental are members of the barbiturate class of drugs (*Brenner and Stevens, 2013*). The

chemical structure of midazolam and pentobarbital are shown in the first row of Table 1 above to provide an accessible first exposure to the differences between the two drugs. The untrained eye clearly recognizes that midazolam and pentobarbital do not have similar structures and are not close analogs. The second row in Table 1 shows examples of other drugs from the same class of drugs as midazolam and pentobarbital. Most notably, at the center of the benzodiazepines there is 7-sided ring with two nitrogen atoms (N) attached to a 6-sided ring with one chloride atom (Cl). Quite differently, the two barbiturates do not contain such a core structure and instead consist of a single 6-sided ring containing two nitrogen atoms. The non-expert can see that the benzodiazepine, midazolam, is similar to diazepam (Valium®), and the barbiturate, pentobarbital (Nembutal®), is a close analog of thiopental (Pentothal®). There is an irrefutable difference between midazolam and fast-acting barbiturates at the atomic level.

In summary, Table 1 shows that that there is no chemical, structural **pharmacological equivalency between midazolam and fast-acting barbiturates.** However, Table 1 does show that the substitution of thiopental with pentobarbital (from one fast-acting barbiturate to another fast-acting barbiturate) does meet the test for pharmacological equivalency by chemical structure.

C. Mechanism of Action of Midazolam and Fast-Acting Barbiturates

The pharmacology of drugs ranges from effects on the whole organism, to effects on specific tissues or organs, down to the actual mechanism of action at the molecular level. For many drugs, the action at the molecular level can be traced upward to the effect on the whole organism, yielding a nearly complete description of drug action.

Starting at the molecular level, both midazolam and pentobarbital act on the $GABA_A$ receptor-chloride ion channel complex (henceforth $GABA_A$ receptor). GABA is the acronym for gamma-aminobutyric acid, an inhibitory neurotransmitter in the brain that is the natural activator of $GABA_A$ receptors (*Sigel and Steinmann 2012, Sieghart 2015*). When inhibitory neurons of the brain release GABA onto other brain neurons, the recipient neurons are inhibited and become more quiescent. This is an ongoing neurotransmitter action, occurring without the presence of any drugs or exogenous substances in the brain. The $GABA_A$ receptor is shaped like a funnel with a lid on it. When GABA binds to the receptor, the lid opens and chloride ions rush from the outside of the neuron to the inside. The chloride ions rushing inside the neuron causes the neuron to decrease its electrical activity.

Benzodiazepines act at the $GABA_A$ receptor on brain neurons where GABA itself acts (*Chang et al. 1981, Sigel and Barnard 1984*) but at a different molecular site than GABA on the $GABA_A$ receptor (*Cromer et al. 2002, Ernst et al. 2003*). Midazolam and all benzodiazepines do not increase the synthesis of the inhibitory neurotransmitter GABA but enhance the effect of GABA at the $GABA_A$ receptor (*Greenblatt et al. 1983*). GABA must be released by inhibitory neurons and be acting on the $GABA_A$ receptor at the same time as the benzodiazepine for drugs like midazolam to enhance GABA inhibition (*D'Hulst et al. 2009, Sieghart et al. 2012*). GABA acts on the receptor and opens the lid to the chloride ion channel (funnel) and midazolam increases the frequency that the lid opens (*Study and Barker 1981, Rogers et al. 1994*). In that way,

midazolam helps GABA have a greater inhibitory effect. However without GABA present, midazolam does little to the $GABA_A$ receptor.

Barbiturates such as pentobarbital also act at the $GABA_A$ receptor on brain neurons where GABA itself acts (*Olsen and Snowman 1982, Greenfield LJ 2013*). Barbiturates bind to a different spot on the $GABA_A$ receptors than benzodiazepines (*Cestari et al. 1996*). Unlike midazolam, pentobarbital and other barbiturates enhance GABA inhibition by increasing the time that the ion channel lid remains in the open position (*Study and Barker 1981*). Contrary to the mechanism of action of midazolam, pentobarbital, like all barbiturates, can cause neuronal inhibition even when GABA is not present (*Mathers and Barker 1980, Jackson et al. 1982*). Barbiturates therefore can open the lid on the ion channel by themselves and keep it open longer than benzodiazepines (*MacDonald et al. 1989, Sancar and Czajkowski 2011*). As a result, the flow of chloride ions into the neuron is not limited to enhancement only when GABA is present, but barbiturates can increase the rush of chloride ions into the neuron in the absence of GABA so that the activity of the neuron is completely shut down. Thus, barbiturates are more potent drugs at the $GABA_A$ receptor than benzodiazepines.

In summary, a large body of pharmacological research on the mechanisms of action of midazolam and fast-acting barbiturates **clearly demonstrates that benzodiazepines, like midazolam, and barbiturates, such as pentobarbital, do NOT exhibit pharmacological equivalency with regard to their detailed mechanism of action**. Compared to barbiturates, benzodiazepines bind to a different site on the $GABA_A$ receptor, need GABA to co-activate the $GABA_A$ receptor to work, and increase the frequency of the opening of the chloride ion channel, not the time it remains open.

D. The Pharmacology of the Partial Agonist, Midazolam, and the Full Agonists, Barbiturates

Most drugs that are used clinically do something to cells or neurons that they affect. They bind to (act on) a target receptor and the receptor does something, like open an ion channel. These types of drugs that do something are called agonists. Other types of clinically-used drugs, like the antihypertensive drugs called 'beta-blockers', bind to a receptor and prevent another substance from doing something. These drugs are called antagonists.

Agonists are further subdivided into partial agonists and full agonists. As their name suggests, full agonists produce a full pharmacological effect and partial agonists only produce a partial pharmacological effect. The difference between one drug being a partial agonist and another drug being a full agonist arises from the drugs' differing mechanism of action.

As noted above, midazolam, like all benzodiazepines, increases the frequency (not the duration) of ion channel opening only when GABA is present. As GABA is a neurotransmitter synthesized by inhibitory brain neurons, the amount of GABA released onto $GABA_A$ receptors is limited. Because midazolam depends on the co-activation of GABA to produce its effects, midazolam's effects on the brain is therefore also limited. In this regard, **midazolam is a partial agonist**.

Barbiturates, to the contrary, do not need co-activation by GABA to produce their effects. Therefore, the neuronal inhibition produced by barbiturates is not limited. In this regard, **fast-acting barbiturates are full agonists**.

By definition, partial agonists will exhibit a 'ceiling effect' in which greater doses will not produce a greater pharmacological effect. The ceiling effect of benzodiazepines, and the lack of ceiling effect for barbiturates, is so well-accepted that many medical pharmacology textbooks contain a Figure illustrating this fact. Fig. 1 below shows one such example.

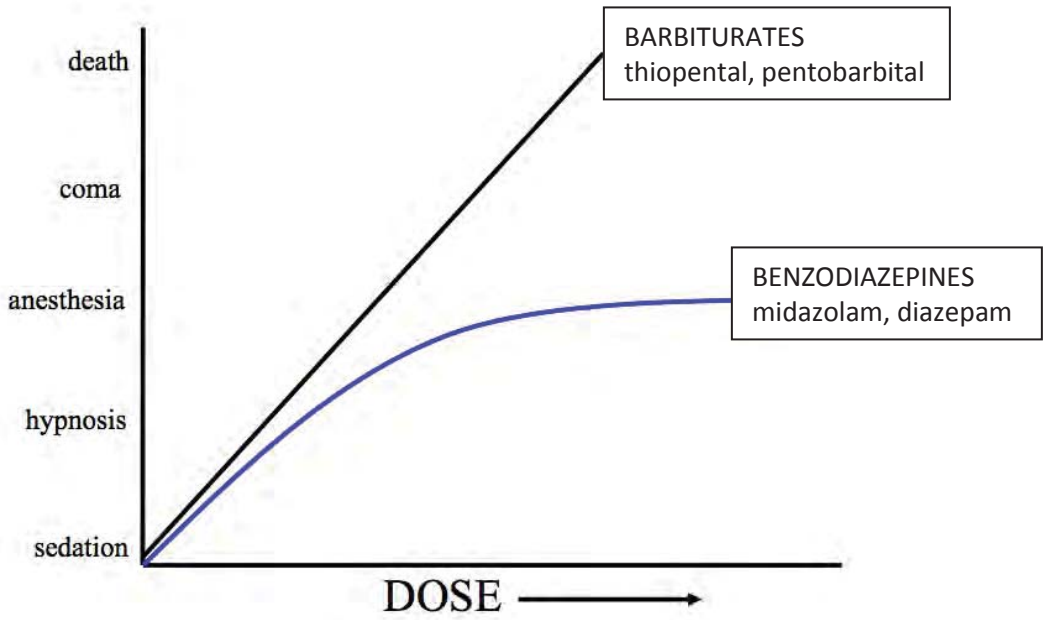


Fig. 1. Typical textbook example of a graph showing the differences between barbiturates (top line) and benzodiazepines (bottom line). The dose increases along the horizontal axis as you move to the right; the effects in humans increases as you move up the vertical axis. Note the **ceiling effect shown for benzodiazepines** versus the lack of ceiling effect for barbiturates. As the dose of benzodiazepine increases, a plateau ('ceiling') is reached before reliable general anesthesia is obtained. Increasing doses of barbiturates reliably produce anesthesia, coma, and death. Note: the term 'hypnosis' is medical terminology for 'sleep'. Adapted from *Brenner and Stevens 2013*.

In summary, **the fact that midazolam is a partial agonist, and that fast-acting barbiturates are full agonists, arises directly from their mechanisms of action, as barbiturates can act in the absence of GABA and increase the inhibition of brain neurons whereas midazolam and other benzodiazepines are limited with their effect only when GABA is present and thus cannot inhibit neurons as much as barbiturates. This pharmacological fact demonstrates that pharmacological equivalency is NOT met by substitution of a barbiturate with a benzodiazepine**. The ceiling effect of a midazolam and other benzodiazepines, and the lack of ceiling effect with the use of barbiturates, is beyond controversy and taught to all medical and pharmacology students.

E. Therapeutic Uses of Benzodiazepines and Barbiturates

The therapeutic use of a drug is a direct result of the drug's pharmacological properties, including, most importantly, a drug's mechanism of action. As noted above, while both benzodiazepines and barbiturates act on the $GABA_A$ receptor, they do so in very different ways. Because of the difference in their mechanism of action, the FDA approves benzodiazepines and barbiturates for difference therapeutic uses. Whereas barbiturates can be used as the sole agent for general anesthesia, benzodiazepines cannot.

i. The Anesthesia Continuum

Before examining the FDA-approved uses of midazolam, pentobarbital, and other agents, it is necessary to understand the terminology used in describing sedative and anesthetic effects. The authoritative professional organization for Anesthesiologists, the American Society for Anesthesiology (ASA), has published standards and definitions for the level of sedation and general anesthesia. There can be no question that these definitions serve as the foundation for any fact-finding. For this reason, the Continuum of Depth of Sedation Table from the ASA is presented below as Table 2 (next page).

There are four levels defined for the Continuum of Depth of Sedation. Of these four levels, there are three levels of sedation and only one level of general anesthesia (see Table 2, column headers). These are, in order of increasing depth of sedation, Minimum Sedation Anxiolysis, Moderate Sedation/Analgesia ("Conscious Sedation"'), Deep Sedation/Analgesia, and General Anesthesia.

Two important facts come from Table 2. First, there is only one level for complete anesthesia, called General Anesthesia. This is the level which renders the patient, or a condemned inmate, to a state of unconsciousness (stated in the text below the Table, underlined) and insensate to all conscious sensation including pain (in the Table itself, end of row one, under General Anesthesia, boxed). The other three levels of sedation are characterized by response to pain and drug-induced *depression* of consciousness *without loss* of consciousness. For this reason, it is clear that any drug used as the first drug in the Arkansas lethal injection protocol must produce a state of General Anesthesia.

Second, the specific use of the term 'General' in the name of the deepest level, 'General Anesthesia,' emphasizes overall brain-activity depression characterized by lack of pain sensation and unconsciousness. Use of the just the word 'anesthesia' does not mean 'general anesthesia.' As stated in the major authoritative pharmacology textbook, *Goodman and Gilman's The Pharmacological Basis of Therapeutics*:[1] "*The clinical literature often refers to the anesthetic effects and uses of certain benzodiazepines, but the drugs do not cause a true general anesthesia because awareness usually persists.*" It is clear that many uses of the word 'anesthesia' in the medical literature do not mean 'general anesthesia' and should not be interpreted as such unless there was loss of all sensation (including pain) and unconsciousness.

[1] Mihic SJ and Harris RA (2011) Chapter 17 Hypnotics and Sedatives, p 460, in Brunton LL et al. (Eds.), Goodman & Gilman's Pharmacological Basis of Therapeutics, Macmillan Co., New York, NY.

American Society of Anesthesiologists

CONTINUUM OF DEPTH OF SEDATION:
DEFINITION OF GENERAL ANESTHESIA AND LEVELS OF SEDATION/ANALGESIA*

Committee of Origin: Quality Management and Departmental Administration

(Approved by the ASA House of Delegates on October 13, 1999, and last amended on October 15, 2014)

	Minimal Sedation Anxiolysis	*Moderate Sedation/ Analgesia ("Conscious Sedation")*	*Deep Sedation/ Analgesia*	*General Anesthesia*
Responsiveness	Normal response to verbal stimulation	Purposeful** response to verbal or tactile stimulation	Purposeful** response following repeated or painful stimulation	Unarousable even with painful stimulus
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Spontaneous Ventilation	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular Function	Unaffected	Usually maintained	Usually maintained	May be impaired

Minimal Sedation (Anxiolysis) is a drug-induced state during which patients respond normally to verbal commands. Although cognitive function and physical coordination may be impaired, airway reflexes, and ventilatory and cardiovascular functions are unaffected.

Moderate Sedation/Analgesia ("Conscious Sedation") is a drug-induced depression of consciousness during which patients respond purposefully** to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained.

Deep Sedation/Analgesia is a drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully** following repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.

General Anesthesia is a drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, and positive pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired.

Because sedation is a continuum, it is not always possible to predict how an individual patient will respond. Hence, practitioners intending to produce a given level of sedation should be able to rescue*** patients whose level of sedation becomes deeper than initially intended. Individuals administering Moderate Sedation/Analgesia ("Conscious Sedation") should be able to rescue*** patients who enter a state of Deep Sedation/Analgesia, while those administering Deep Sedation/Analgesia should be able to rescue*** patients who enter a state of General Anesthesia.

** Reflex withdrawal from a painful stimulus is NOT considered a purposeful response.

*** Rescue of a patient from a deeper level of sedation than intended is an intervention by a practitioner proficient in airway management and advanced life support. The qualified practitioner corrects adverse physiologic consequences of the deeper-than-intended level of sedation (such as hypoventilation, hypoxia and hypotension) and returns the patient to the originally intended level of sedation. It is not appropriate to continue the procedure at an unintended level of sedation.

Table 2. Continuum of Depth of Sedation Table from the ASA [Emphasis added]

Instead of anesthesia, the term 'Moderate Sedation' or another one of the three sedation-level descriptors should be used, if loss of consciousness and insensibly to pain were not present. Textbooks or review articles that state that IV benzodiazepines can produce anesthesia mean that these agents, in general, can produce levels of sedation along the anesthesia scale (Table 2), not that they produce the specific, deepest level of anesthesia called General Anesthesia. Likewise, midazolam is sometimes referred to as 'an anesthetic' or able to produce 'anesthesia,' but this does not mean midazolam can produce 'general anesthesia'.

As shown in the next subsection, the FDA-approved indications (therapeutic uses) for midazolam do not include 'General Anesthesia' (Table 3). Section 5 below discusses clinical studies showing that midazolam is unable to produce a state of General Anesthesia.

ii. FDA-approved Labeling of Anesthetic Effects.

Table 3 below is a list of therapeutic uses for benzodiazepines and barbiturates. Entries marked with a 'YES' indicate that this class of drugs (benzodiazepine or barbiturate) is FDA-approved for this indication and list which particular drug(s) is approved for this therapeutic use.

Table 3. Comparison of therapeutic uses for five benzodiazepines and five barbiturates.

Therapeutic Use	**Benzodiazepines**	**Barbiturates**
Anxiety disorders	YES, alprazolam, diazepam, lorazepam	YES but only for 'sedation' with butabarbital
Panic Disorder	YES, alprazolam, clonazepam	NO
Acute Alcohol Withdrawal	YES, diazepam	NO
Skeletal Muscle Spasm	YES, diazepam	NO
Seizure Disorders	YES, clonazepam, diazepam	YES, pentobarbital (IV), phenobarbital (IV), thiopental (IV)
Preoperative Sedation	YES, midazolam (IM/IV)	YES, pentobarbital (IV), secobarbital
Outpatient Sedation	YES, midazolam (IV)	NO
Anesthesia Induction	YES, midazolam (IV)	YES, thiopental (IV)
Sole Anesthesia (brief)	NO	YES, thiopental (IV)
Sedation for Intubated Ptx	YES, midazolam (IV cont.)	NO
Co-Anesthesia (Adjunct)	YES, midazolam (IV)	YES, thiopental (IV)
Insomnia (short-term)	NO	YES, butabarbital, secobarbital, pentobarbital (IV)
Induce Coma in Brain Trauma	NO	YES, thiopental (IV)
Psychiatric Use (Narcoanalysis)	NO	YES, thiopental (IV)

Note: Benzodiazepine data of therapeutic uses are from the FDA-approved Prescribing Information labels of alprazolam (Xanax®), clonazepam (Klonopin®), diazepam (Valium®), lorazepam (Ativan®), and midazolam (Versed® injection). Barbiturate data are from current FDA-approved labels—for butabarbital (Butisol®), pentobarbital (Nembutal® injection), phenobarbital (Luminal®), secobarbital (Seconal®)—excepting the discontinued label for thiopental (Pentothal®), which is no longer marketed. All drug formulations are oral tablets except where noted; IV=intravenous, IM=intramuscular.

As shown in Table 3, there are 14 therapeutic uses for the benzodiazepine and barbiturate drugs. Among these 14 therapeutic uses, only 5 (or 35.7%) are common to both benzodiazepines and barbiturates. These shared indications are Anxiety Disorders, Seizure Disorders, Preoperative

Sedation, Anesthesia Induction, and Adjunct/Co-Anesthesia (used with a general anesthetic). It should be noted that benzodiazepines for the treatment of Anxiety Disorders have almost universally supplanted the older barbiturate drugs for this use (*Howie 1975*, *Pieters and Snelders 2007*). Five indications are for the use of benzodiazepines only; Panic Disorder; Acute Alcohol Withdrawal; Skeletal Muscle Spasms; Outpatient Sedation; and Sedation for Intubated Patients. Four indications are for the use of barbiturates only: Sole Anesthesia (for brief procedures); Insomnia (for short-term treatment of 2 weeks); Induce Coma in Brain Trauma; and Psychiatric Use (Narcoanalysis), *i.e.*, the limited and historical use of thiopental to get the therapy patient to talk, as in 'truth serum'.

Both midazolam and thiopental are indicated for use in Anesthetic Induction. Anesthetic Induction is a procedure to **start the anesthesia process**. Although midazolam is used for Anesthetic Induction, this use does not mean that midazolam can produce a state of General Anesthesia. Both midazolam and thiopental are indicated for use in Co-Anesthesia as adjunct anesthetics along with other agents. Use of midazolam as an adjunct agent in a Co-Anesthesia protocol does not indicate that midazolam by itself can produce a state of General Anesthesia.

Thiopental, **but not midazolam**, is indicated for Sole Anesthesia, for brief (15 minute) procedures. Thiopental, a barbiturate, is able to be used by itself to provide general anesthesia, but midazolam, like other benzodiazepines, is limited in its potency and cannot produce general anesthesia but only sedation.

Use of midazolam for Preoperative Sedation or Outpatient Sedation—both uses not reaching the level of General Anesthesia—is not germane to drug use for lethal injection. Likewise, use of midazolam to treat Anxiety disorders, Panic Disorder, Acute Alcohol Withdrawal, Skeletal Muscle Spasm, or Seizure Disorders is not pertinent to the production of General Anesthesia, the level of anesthesia needed to administer the second and third drugs used in Arkansas's lethal injection protocol without pain.

With regards to specific drugs, out of five indications for midazolam, midazolam shares only one therapeutic use with pentobarbital: Preoperative Sedation.

In sum, comparison of the FDA-approved labels for benzodiazepines and barbiturates—and more specifically for midazolam and pentobarbital—**demonstrates that pharmacological equivalency of barbiturates and benzodiazepines is NOT met considering the criteria of approved therapeutic uses.** Most importantly, midazolam is not approved for use as a Sole Anesthetic as it cannot produce General Anesthesia. In contrast, the barbiturate thiopental was approved as a Sole Anesthetic for brief procedures. Midazolam cannot produce General Anesthesia, whereas barbiturate drugs like pentobarbital and thiopental are more potent (with no ceiling effect) and can produce a state of General Anesthesia. Evidence supporting these facts is elaborated below in Section 5.

F. DEA Scheduling of Midazolam and Fast-Acting Barbiturates

Most prescription drugs are safe and without the potential for abuse and dependence. Thus, the vast majority of drugs prescribed by physicians do not come under the purview of the Drug Enforcement Administration (DEA). Drugs that pose a special danger of abuse or drug dependence are tightly regulated by the DEA and are called controlled substances.

Midazolam and barbiturates are controlled substances according to the DEA, as promulgated by the Controlled Substances Act of 1970. The DEA places dangerous drugs into five schedules, with Schedule I drugs having no approved medical use and being the most dangerous. Schedule II-V are drugs with medical uses but with decreasing danger of abuse and dependence. Midazolam, as with most of the other benzodiazepines like diazepam (Valium®) and lorazepam (Ativan®) are placed into Schedule IV. Fast-acting barbiturates are considered much more dangerous drugs to abuse so they are scheduled the highest level for drugs still used medically, as Schedule II controlled substances. This is evidence that midazolam is deemed safer to use by the DEA, with less evidence of abuse and drug dependence than fast-acting barbiturates. Simply put, the DEA decision to schedule midazolam and the fast-acting barbiturates differently **reflects the DEA finding that midazolam and fast-acting barbiturates do NOT exhibit pharmacological equivalency in causing drug dependence and abuse.**

G. Summary

Pharmacological equivalency between benzodiazepines and barbiturates, and more specifically between midazolam and fast-acting barbiturates, was investigated by examining key aspects of the pharmacology of the two drug classes. The findings from this section are:

i. There is no pharmacological equivalency between midazolam and fast-acting barbiturates using the criterion of chemical structures for benzodiazepines and barbiturates.

ii. There is no pharmacological equivalency when examining the different mechanisms of action of benzodiazepines (midazolam) and barbiturates (pentobarbital, thiopental).

iii. There is no pharmacological equivalency between the magnitude of pharmacological effects produced by benzodiazepines (partial agonists) and barbiturates (full agonists). In particular, it is well-known that midazolam has a ceiling effect that is not present barbiturates.

iv. There is no pharmacological equivalency when examining the different therapeutic uses of benzodiazepines and barbiturates, or between midazolam and fast-acting barbiturates. In particular, midazolam is does not produce General Anesthesia and could not be used as a Sole Anesthetic, whereas barbiturates are used as Sole Anesthetics and do produce General Anesthesia.

v. There is no pharmacological equivalency in the drug abuse and dependence properties of benzodiazepines and barbiturates as confirmed by the different scheduling of these drugs by the DEA.

3. Dosage and Characteristics of Pentobarbital Used in Lethal Injection

A. Therapeutic, Toxic, and Lethal Dosages of Intravenous (IV) Pentobarbital

Barbiturates are a class of sedative-hypnotic drugs, largely replaced in clinical therapeutics by the benzodiazepine class of sedative-hypnotics (*Brenner and Stevens 2013*). Examples of common barbiturate drugs are thiopental, pentobarbital, phenobarbital, and methohexital.

Nembutal® Sodium Solution (Pentobarbital Sodium for Injection, USP) is an FDA-approved drug formulation that is manufactured by Akorn, Inc. a subsidiary of Oak Pharmaceuticals, Inc., headquartered in Lake Forest, IL (*FDA 2015*). Its official indications are listed on the FDA label for use as: a. Sedatives; b. Hypnotics, for the short-term treatment of insomnia; c. Preanesthetics; and d. Anticonvulsant, in anesthetic doses, in the emergency control of certain acute convulsive episodes, *e.g.* status epilepticus (*Nembutal® Sodium Solution* Prescribing Information, Oak Pharmaceuticals). Pentobarbital sodium IV solution is also used 'off-label' for the induction and maintenance of coma to reduce intracranial pressure in brain-injured patients (*Woodcock et al. 1982*).

Clinical studies and forensic toxicology studies have determined the therapeutic, toxic, and lethal blood concentrations of pentobarbital (*Musshoff et al. 2004; Regenthal et al. 1999; Schulz et al. 2012; Winek et al. 2001*). These values are given in blood concentration ranges from the most recent paper, as shown in Table 4 below.

Table 4. Therapeutic, toxic, and lethal ranges of pentobarbital blood concentrations. Concentrations given in mg/L (milligram per Liter) which is equal to mcg/mL (microgram per milliLiter). Half-life (t1/2) is given in the last column and is the time in hours it takes for half the amount of drug to be cleared from the bloodstream. From Schulz et al. 2012.

Substance	Blood-plasma concentration (mg/L)			$t_{½}$ (h)
	therapeutic ("normal")	toxic (from)	comatose-fatal (from)	
Pentobarbital	1-5 (-10)	10-19	15-25	20-40

There are no clinical studies determining the lethal dose of IV pentobarbital sodium in humans for obvious reasons. However, the largest IV pentobarbital sodium dose ever administered to human volunteers is reported in an early pharmacokinetic study from the 1950s (*Brodie et al. 1953*). In two volunteers, 2.5 grams pentobarbital was injected IV over 50 minutes. While blood concentrations were not determined in these volunteers, the authors note that following these large doses of IV pentobarbital, the volunteers were deeply anesthetized and had to be put on a ventilator with oxygen "until spontaneous ventilation was deemed adequate." Such studies could not be performed today due to safety and ethical concerns, but it is clear that a 2.5 gram dose given IV was a lethal dose in these two individuals as it caused them to stop breathing on

their own. These volunteers would have died without the supportive measures of the artificial ventilator and oxygen supplementation.

The most straight-forward approach to determining the lethality of pentobarbital sodium used in lethal injection protocols is to pharmacologically model the blood concentrations of pentobarbital after a 5 gram IV bolus injection of pentobarbital sodium. Once a reasonable estimate is made of the pentobarbital blood concentrations after a 5 gram IV pentobarbital sodium dose, the blood levels obtained can be compared to lethal pentobarbital concentrations as shown in Table 4, above.

B. Blood Levels of 5 gram Pentobarbital after IV Bolus Dose in Humans

The study of drug movement after administration is called pharmacokinetics. The pharmacokinetics of pentobarbital sodium are characterized by a rapid distribution of pentobarbital throughout the body and into the brain. With direct IV administration, there is no absorption phase of the drug like when a pill is swallowed. For this reason, the peak blood concentration of IV pentobarbital is observed with the first time point of sampling after the IV bolus injection.

As mentioned above, there are no studies in the literature that give the blood concentrations of pentobarbital following a 5 gram IV dose, as this is higher than approved clinical doses. However, it is possible to examine the pentobarbital blood concentrations in humans from studies following the administration of lower doses of IV pentobarbital sodium. The data from these studies can then be used to model the blood concentrations of pentobarbital after a 5 gram IV dose.

In 1953, the first study of the fate of pentobarbital in humans estimated the peak amount of pentobarbital in the blood after IV bolus administration of 1 gram (= 1000 mg) pentobarbital sodium (*Brodie et al. 1953*). This study gave peak blood concentrations of about 25 mg/L after the IV dose. Twenty years later, the first study using modern techniques in pharmacokinetic analysis determined the blood concentration of pentobarbital after an IV dose of 50 mg pentobarbital sodium (*Smith et al. 1973*). These authors found that a 50 mg IV dose of pentobarbital gave an initial peak blood concentration of about 1.5 mg/L. In a second pharmacokinetic study of IV pentobarbital sodium, a 100 mg IV dose yielded an initial pentobarbital blood concentration of about 3.0 mg/L (*Ehrnebo 1974*). A figure from this second modern paper is included below (as Fig. 2, top of next page) to portray the pentobarbital blood concentration curve over time following IV administration.

Given that a 50 mg IV dose of pentobarbital gave an initial pentobarbital blood concentration of 1.5 mg/L and that a 100 mg IV dose of pentobarbital (Fig. 2, below) gave an initial pentobarbital blood concentration of 3.0 mg/L (i.e. doubling the IV dose, doubled the initial blood concentration) it follows that a 5,000 mg IV dose of pentobarbital would give an initial pentobarbital blood concentration of 150 mg/L. This is calculated from the fact that a 5,000 mg IV dose (= 5 grams) is 100 times greater than the 50 mg IV dose and 100 times 1.5 mg/L equals

150 mg/mL. By examining Table 4 above, this initial pentobarbital blood concentration of 150 mg/mL is 6 to 15 times greater than the lethal drug range listed as 10-25 mg/mL.

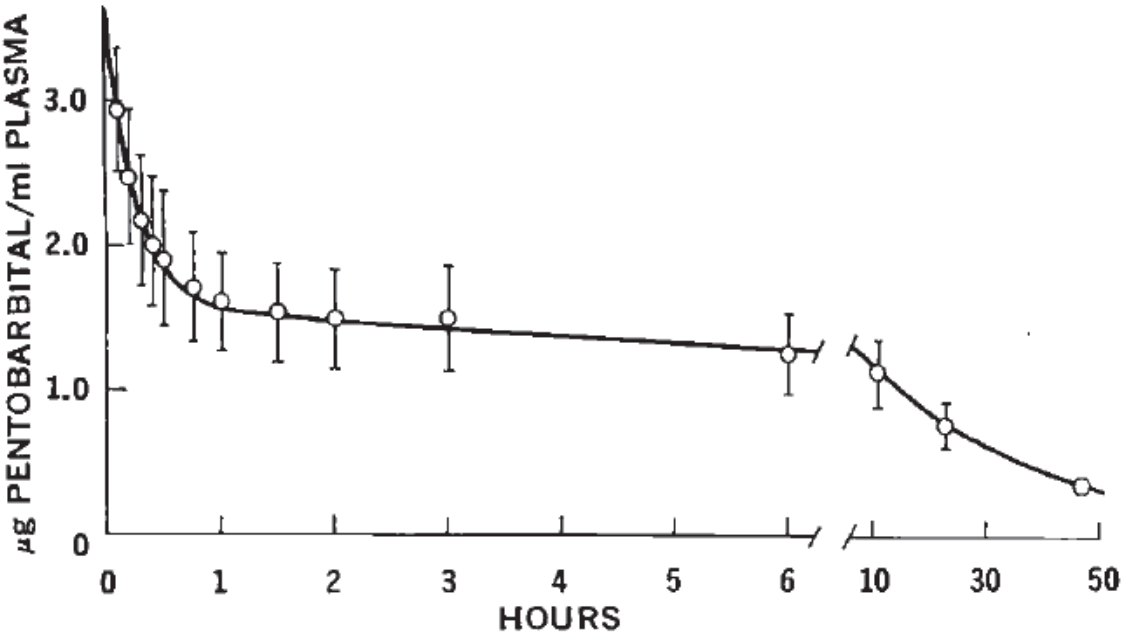


Fig. 2. Blood levels of pentobarbital following rapid IV injection of 100 mg to seven human subjects. Data points are the mean values of pentobarbital blood concentrations, plus and minus one standard deviation error bars. From *Ehrnebo 1974*. Note: µg/mL is equal to mg/L.

Given the above calculation that 5 grams of IV pentobarbital sodium yields an initial lethal blood concentration of 150 mg/L, the next determination is to model the fall of the pentobarbital blood concentration over time. It can be seen from Figure 2 above that the fall of pentobarbital blood concentrations occurs in two parts; the decrease in pentobarbital occurs more rapidly for the first hour, then the decrease slows down and changes slowly from the pentobarbital levels seen at one hour. The first rapid phase of the decrease in pentobarbital concentrations is due to the distribution of pentobarbital from the blood to the brain and other tissues. The second, slower phase in the decrease of pentobarbital is due to the elimination of pentobarbital from the blood by metabolism and excretion. The time it takes for the pentobarbital blood level to decrease by one-half is called the 'half-life' ($t_{1/2}$). The first rapid phase of pentobarbital decrease has a smaller half-life than the half-life of the second slower phase of pentobarbital decrease.

In order to determine the fall of pentobarbital concentrations over time, it is necessary to use the half-life data for IV pentobarbital from the pharmacokinetic studies cited above. Both of the modern pharmacokinetic studies of IV pentobarbital sodium show a rapid distribution of pentobarbital out of the blood of with a half-life of about 1 hour (*Ehrnebo 1974; Smith et al. 1973*) which lasts for about 2 hours, then a longer elimination half-life of about 22-50 hours. Using these half-life values, the pharmacokinetic modeling of a 5 gram (5000 mg) IV dose was done using an Excel® spreadsheet, as noted previously in the scientific literature (*Chamberlain 2003*).

The resulting graph of the decrease in pentobarbital blood levels after IV injection of 5 grams (5000 mg) is shown in Figure 3 below. This graph shows that with an initial blood concentration of 150 mg/L pentobarbital, the blood levels of pentobarbital decrease to 37.5 mg/L after 120 minutes. Within the first 5 minutes, the blood levels decrease to 141 mg/L (inset graph, Figure 3, below). Comparing these blood levels of pentobarbital with the lethal concentrations summarized in Table 4 above, after the first 5 minutes, the 5 gram IV dose of pentobarbital sodium yields blood levels of pentobarbital that are 5.6 to 14 times higher than lethal pentobarbital concentrations. After 120 minutes, the 5 gram dose gives blood levels that remain elevated above the lethal pentobarbital concentrations.

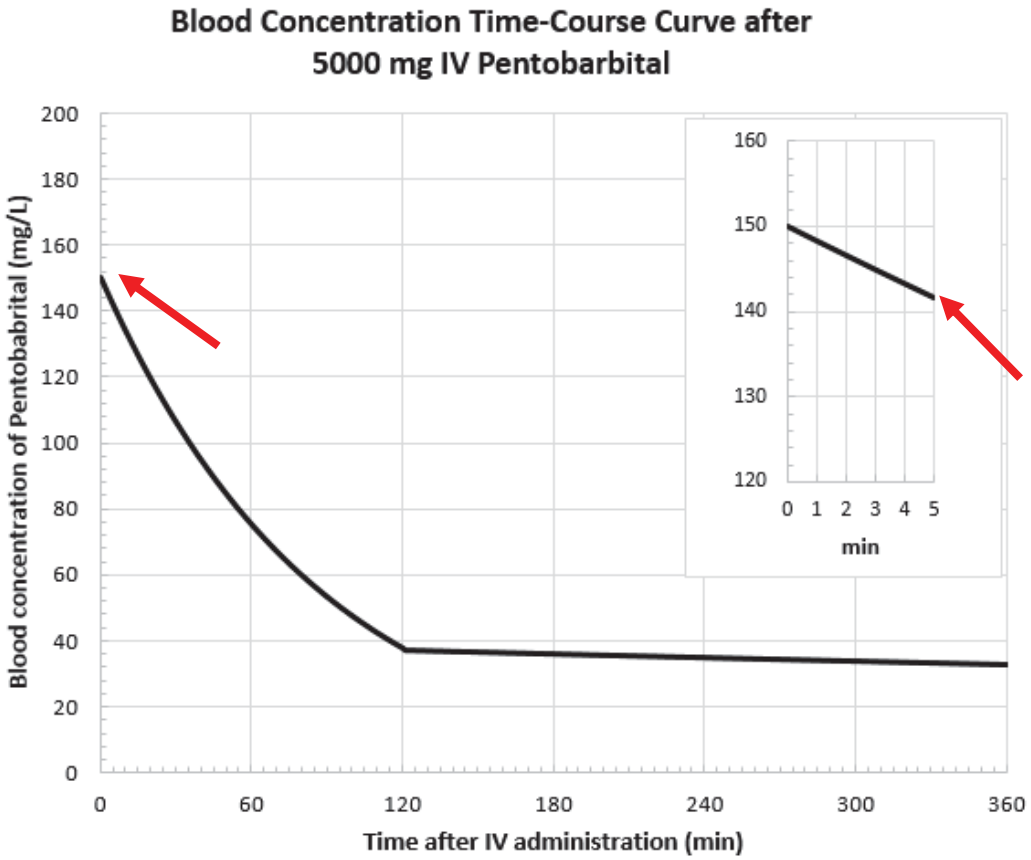


Fig. 3. Blood levels of pentobarbital following IV injection of 5 grams (5000 mg) as modeled by the best available data. The initial blood concentration was 150 mg/L (at left arrow). The rapid decrease (distribution phase) used a half-life of 60 min that lasted for 2 hours. The slower elimination phase used a half-life of 20 hours. Inset graph in upper right corner shows an enlargement of the first 5 minutes after IV injection (right arrow).

C. Differences Among Barbiturate Drugs

Barbiturate drugs were discovered and used to a great degree before the advent of the benzodiazepine drugs in the 1960s (*Harvey 1980*). All benzodiazepines have the same mechanism of action, which differs from barbiturates' mechanism of action (see Section 2C above). Barbiturate drugs potentiate and replace the action of GABA to greatly inhibit neurons, whereas benzodiazepines need GABA present to work and are limited in their pharmacological effects (i.e. are partial agonists, see Section 2D).

The differences in various barbiturate drugs lie primarily in their pharmacokinetic characteristics, and are subclassified according to how long they exert their pharmacological effects. The barbiturates are also classified by their therapeutic effects, such that there are anesthetic barbiturates, such as thiopental, pentobarbital, amobarbital, and anticonvulsant barbiturates, such as mephobarbital and phenobarbital (*Macdonald and Barker 1979*).

Barbiturates also differ by their individual chemical nature, most importantly in a term called lipophilicity. Lipophilicity, which means 'fat-loving,' describes a physical characteristic of drugs that correlates with how rapidly a drug can cross from the bloodstream to the brain. Rapid-onset, ultrashort-acting anesthetic barbiturates, like amobarbital and pentobarbital, are more lipophilic than anticonvulsant barbiturates like mephobarbital or phenobarbital (*Toon and Rowland 1983*). Because of this, the highly lipophilic barbiturates (amobarbital and pentobarbital) have a faster onset of action, usually within 30 seconds to 1 minute after an IV bolus dose (*Sessions et al. 1954*).

Finally, the barbiturates differ in terms of their potency: anesthetic barbiturates (pentobarbital and amobarbital) are more potent in their inhibition of brain neurons than anticonvulsant barbiturates like mephobarbital and phenobarbital (*Macdonald and Barker 1979*).

The pharmacological differences between barbiturates precludes a substitution of pentobarbital with any other barbiturate except another fast-acting barbiturate.

D. Summary

The findings from this section are:

i. The normal therapeutic blood concentration of pentobarbital ranges from 1-10 mg/L. Toxic blood concentrations of pentobarbital range from 10-19 mg/L and lethal concentrations of pentobarbital range from 15-21 mg/L and higher.

ii. A 5 gram IV bolus dose of pentobarbital sodium produces initial pentobarbital blood concentrations of about 150 mg/L, which is 6 to 15 times greater than the accepted lethal dose range. After 5 minutes, the blood concentration of pentobarbital is 5.6 to 14 times greater than the lethal blood concentrations of pentobarbital. After 2 hours, the blood concentration of pentobarbital remains above the lethal blood concentration range.

iii. All barbiturates share the same mechanism of action but differ in potency, time of onset, duration of action, and therapeutic indications. Only fast-acting barbiturates like thiopental or pentobarbital are suitable for use in lethal injection protocols.

4. Pharmacology of Vecuronium and Potassium Chloride

According to the Arkansas method-of-execution statute, § 5-4-617, the Director of the Arkansas Department of Corrections shall select one of the following options for a lethal injection protocol: a one-drug protocol using a barbiturate, or a three-drug protocol using midazolam, followed by vecuronium bromide, followed by potassium chloride. The pharmacology and mechanism of action of the first drug in the three-drug protocol, midazolam, was detailed above (Section 2) and the ceiling effect of midazolam is discussed below (Section 5). The second and third drugs listed in the Arkansas three-drug lethal protocol are vecuronium bromide, at a dose of 100 mg, and potassium chloride, at a dose of 240 mEq, which are discussed here.

A. Pharmacology and Clinical Effects of Vecuronium

Vecuronium, like pancuronium, is a drug classified as a neuromuscular blocker or simply called a paralytic drug. Neuromuscular blockers work by blocking the action of acetylcholine which is the neurotransmitter released from a nerve ending onto the muscle that causes the muscle to contract (*Hibbs and Zambon 2011*). Clinical uses of neuromuscular blockers are to provide muscle relaxation for endotracheal intubation, and to ensure patient immobility during surgery or mechanical ventilation (*Kovac 2009, Vecuronium Bromide for Injection Prescribing Information*). Vecuronium is a chemical analog to pancuronium and is about 1.5 to 1.75 times more potent than pancuronium (*Fahey et al. 1981*). Vecuronium has about the same onset time as pancuronium (within 5 minutes) but has a shorter duration of action, and produces no cardiovascular effects or changes in heart rate or blood pressure. With higher doses of vecuronium, the onset time can be reduced to 2.4 minutes (*Hilgenberg 1983*).

The clinical effects of vecuronium are shared by other neuromuscular blockers and include progressive loss of skeletal muscle contraction, first noted by drooping eyelids and muscle weakness (*Hibbs and Zambon 2011*). Motor weakness progresses eventually to a total flaccid paralysis. The small, quick muscles of the eyes, jaw, and larynx relax before those of the arms, legs, and trunk of the body. Finally, the intercostal muscles that expand the ribs and the diaphragm are paralyzed, and breathing ceases. Without intubation and mechanical ventilation, death ensues from a lack of oxygen (hypoxia).

There are a few studies of the effect of neuromuscular blockers given in human volunteers without an anesthetic agent. In a classic 1947 paper, a complete description of the effects of tubocurarine, an early neuromuscular blocker, on the central nervous system was examined (*Smith et al. 1947*). These researchers found that neuromuscular blockers had no effect on altering consciousness, or memory and had no analgesic effect. They concluded that these paralytic drugs should not be used alone as they may cause “serious psychic trauma.” A later study, using trained anesthesiologists and the researchers themselves, found that in these awake subjects vecuronium had no effect on consciousness and, like the earlier study by Smith

and colleagues, that the most distress came from a feeling of shortness of breath and 'air hunger,' even as they were artificially ventilated with supplemental oxygen at sufficient levels (*Topulos et al. 1993*). As early as 1950 clinicians realized that the use of paralytic drugs like vecuronium and pancuronium without adequate anesthesia leads to the possibility that a patient is awake but incapable of indicating distress or pain because of muscle paralysis (*Brice 1970*).

While these above studies were done on the researchers themselves, who were trained in the procedures and knew what to expect, most research on the adverse effects of vecuronium and other neuromuscular blockers comes from cases where conscious patients were completely paralyzed but unable to communicate with health care workers. In emergency care, patients who experienced paralysis without sedation or anesthesia reported dysphoria and severe pain (*Chong 2014*). Patients in intensive care units who were paralyzed with pancuronium because they were intubated and on mechanical ventilators, but were not sedated and were conscious, reported that they felt "buried alive"; some thought they were already dead (*Perry 1985*). Most of these patients said they would rather die than go through 4 days of being paralyzed while conscious again. A study of patients who emerged from anesthesia but were still paralyzed from neuromuscular blockers gave reports of panic, suffocation, and a feeling of already being dead (*Thomsen et al. 2015*). These experiences were horrific enough to trigger post-traumatic stress disorder (PTSD) in some unfortunate patients.

The above papers show that vecuronium or pancuronium, or any other paralytic drug, should only be used in patients that are anesthetized and unconscious. In documented cases where patients or experimental subjects were awake but paralyzed, intolerable and damaging experiences of pain, panic, and suffocation occurred.

B. Pharmacology and Clinical Effects of Potassium Chloride

Potassium chloride for injection is an electrolyte solution used for the treatment of hypokalemia, which means low blood-potassium levels (*Potassium Chloride for Injection Prescribing Information*). Hypokalemia can be life-threatening and can lead to dysfunction of excitable tissues such as cardiac, skeletal, and smooth muscle (*Kruse and Carlson 1990*). The low potassium of hypokalemia may result in muscular paralysis, respiratory failure, and cardiac abnormalities, which can be fatal.

Potassium chloride for injection is also used in late-term abortions of a fetus with genetic or severe, non-viable abnormalities (*Isada et al. 1992, Senat et al. 2002, Sfakianaki et al. 2014*). In these cases, potassium chloride is delivered directly into the fetal heart chamber or into the umbilical vein.

There are a few cases of high-dose potassium-chloride injection in awake patients, which only occurs as a result of an accident or intentional homicide in the hospital setting (*Wetherton et al. 2003*). The earliest report of an accidental high dose of IV potassium chloride due to improper mixing was in a male patient who immediately complained of a severe pain moving up his arm (above the site of the IV) and a ringing in his ears (*Lankton et al. 1973*). The patient then lost

consciousness, stopped breathing, and his heart stopped beating. Another case study in that same year reported that an IV infusion of potassium chloride produced severe pain at the site of the IV infusion (*Williams 1973*). In a forensic report of four IV potassium-chloride-induced deaths at hospital, one man who accidentally received a high-dose IV infusion of potassium chloride screamed out in pain (*Wetherton et al. 2003*). Potassium-chloride IV injections are also documented as a rare method of suicide in health care workers, but self-reports of the effects noted by these persons are unavailable (*Battefort et al. 2012, Bertol et al. 2012*).

The above studies show that IV administration of potassium chloride at high doses leads to severe pain in awake, unanesthetized patients.

C. Importance of Achieving General Anesthesia

In the case of lethal injection using a three-drug protocol, it is crucial to insure that the first drug achieves General Anesthesia because of the intolerable effects of the second drug (muscle paralytic) and third drug (potassium chloride).

Clinical experience with non-responsive patients shows that a cautious approach to the risk evaluation of midazolam's ability to produce General Anesthesia should be taken. Patients that are non-responsive are diagnosed of being in a vegetative state after repeated tests of consciousness show no evidence of sustained, reproducible, purposeful, or voluntary behavioral response to visual, auditory, tactile, or noxious stimuli (*MacDonald et al. 2015).* These tests in non-responsive patients are the same as tests used by anesthesiologists to detect the surgical plane of anesthesia. In the non-responsive patients, studies show that up to 43% of these patients that are diagnosed as vegetative are actually aware or conscious. Additionally, studies document that some patients are not unconscious even when strong general anesthetics, like pentobarbital or inhalation agents, are used. (*Escallier et al. 2014*) These findings mandate a conservative approach to questions of the first drug used in a three-drug lethal injection protocol. In other words, even under the best circumstances, clinicians assessing non-responsive patients and anesthesiologists inducing general anesthesia appear to get it wrong a significant percentage of the time and their patients are not unconscious (or anesthetized) as often as they think.

Because even trained anesthesiologists using powerful anesthetic drugs fail to detect awareness or consciousness a significant proportion of the time, the "consciousness check" articulated in Section IV.2.h(1) of Arkansas's lethal injection protocol does not provide any assurance that the condemned inmate will be sufficiently anesthetized or that he will not experience the pain and suffering caused by the second two drugs in Arkansas's protocol. According to Section 1.1 of the protocol, the "Deputy Director, or designee" who performs the consciousness check need not even be a physician or nurse, much less an anesthesiologist. Further, because it is pharmacologically impossible for midazolam to produce a state of General Anesthesia, as discussed above in Section 2 and further below in Section 5, any determination that the prisoner is unconscious when not in a state of General Anesthesia would by definition be erroneous.

D. Summary

i. Vecuronium administration produces paralysis of muscles, including muscles that promote breathing, preventing movement in patients undergoing surgery.

ii. Vecuronium administered to unanesthetized subjects in clinical studies gives rise to pain, panic, and suffocation, without a means to communicate this to others due to complete muscle paralysis.

iii. Potassium chloride is used to produce cardiac arrest (stop the heart) in the condemned inmate.

iv. Studies show that use of potassium chloride by IV injection in an awake and unanesthetized patient leads to severe pain radiating from the site of the IV infusion and cessation of breathing and heart function while conscious.

v. The condemned inmate must be in a state of General Anesthesia, noted by loss of consciousness and the inability to respond to a noxious stimulus, before the administration of vecuronium and potassium chloride.

5. Calculation of the 'Ceiling Effect' Dosage of Midazolam Used in Lethal Injection

This section discusses the concept of the "ceiling effect" in further detail. It calculates the ceiling-effect dose of midazolam using a methodology described below; it then discusses other clinical studies regarding midazolam's ceiling effect and their bearing on the calculation contained herein.

A. Introduction to the Issue of the 'Ceiling Effect' With an IV Bolus Dose of Midazolam

The 'ceiling effect' refers to the fact that greater doses of midazolam do not produce a greater pharmacological effect. The ceiling effect is well-known for midazolam and all similar drugs in the class called benzodiazepine sedative-hypnotics. By way of contrast, there is no ceiling effect seen with barbiturate sedative-hypnotics like thiopental and pentobarbital (see Section 2D above). The ceiling effect of midazolam and other benzodiazepines is not controversial and is portrayed in many introductory pharmacology textbooks (see Fig. 1 above).

As detailed in Section 2D above, benzodiazepines (including midazolam) act by enhancing the inhibitory effect of the neurotransmitter, GABA, on brain neurons. The decrease in neuronal activity produced by the inhibitory neurotransmitter, GABA, is not 'all or none'. GABA simply decreases the ongoing activity of neurons by a graded amount, depending on how much GABA is present. GABA is a limited resource in the brain, as it is made and released by inhibitory brain neurons, which are finite in number. Therefore midazolam is limited in its action by the amount of GABA present, whereas barbiturates are not limited by the amount of GABA present.

A little more pharmacology of benzodiazepines' mechanism of action and an analogy is needed. Midazolam and other benzodiazepines potentiate the binding of GABA at the $GABA_A$ receptor, but at a site different than where GABA binds. This is called allosteric modulation. To use an analogy, the allosteric action of midazolam might be thought of as a Boy Scout helping an elderly woman (GABA) across the street. The woman can cross the street without the Boy Scout (midazolam) but his presence and assistance helps the elderly woman move faster. Midazolam and other benzodiazepines can only enhance GABA action and have no inhibitory action on brain neurons on their own. By this allosteric mechanism of action, benzodiazepines have an innate 'ceiling effect' and can only produce sedation on a limited plateau. Using our analogy, the Boy Scout can move the elderly woman across the street only so fast, the act of getting the woman across the street is still limited by the ability of the woman to ambulate on her own two legs. There is a 'ceiling effect' in how fast the woman can cross the street, even if two or more Boy Scouts were to help her.

Most telling that midazolam has a ceiling effect is the lack of a fatal blood level range for midazolam in the latest compendium of therapeutic, toxic, and fatal blood levels of over 1,000 drugs (*Schulz et al. 2012*). **Table 5 below shows the blank space for the fatal blood levels of midazolam**. **There are few fatalities.**

Table 5. Therapeutic, toxic, and lethal ranges of pentobarbital and midazolam blood concentrations. Note the lack of fatal concentration ranges for midazolam. From Schulz et al. 2012.

Substance	Blood-plasma concentration (mg/L)			$t_{½}$ (h)
	therapeutic ("normal")	toxic (from)	comatose-fatal (from)	
Pentobarbital	1-5 (-10)	10-19	15-25	20-40
Midazolam	0.04-0.1 (-0.25)[134]	1-1.5		1.5-3[46]

B. Calculation of Ceiling Effect

This subsection calculates midazolam's ceiling effect using a modeling approach based on extrapolation from *in vitro* and cell-culture testing. The calculation considers that the Arkansas Lethal Injection Protocol employs two syringes with 250 mg midazolam each for a total of 500 mg. The State's procedure also states that "*after at least five (5) minutes have elapsed since commencing the administration of syringe 1A* [the first 250 mg midazolam syringe]*, the Deputy Director, or designee, will confirm the condemned inmate is unconscious by using all necessary and medically-appropriate methods."* Accordingly, the present subsection ultimately seeks to answer whether midazolam's ceiling effect is reached at or below (1) the brain concentration of midazolam produced immediately after the IV bolus administration[2] of a 500 mg midazolam dose and (2) the brain concentration 5 minutes after IV midazolam administration.

The first step of this modeling approach is to determine the concentration at which midazolam's ceiling effect occurs in studies done *in vitro* (using brain cells in a laboratory dish). Second, a calculation of the blood concentration of midazolam following a 500 mg IV bolus dose

[2] Bolus means a single IV injection all at one time as opposed to continuous infusion at a lower rate.

is made based on blood concentrations of midazolam following clinically-used doses. Third, based on the pharmacological data of midazolam crossing into the brain in preclinical studies, the extent of the 500 mg midazolam dose that enters the brain is calculated. Fourth, published studies are researched to calculate the concentration of midazolam in the brain after a 500 mg IV dose. Finally, by comparing the concentration of midazolam that produces a ceiling effect in studies done *in vitro* with the calculated concentration of midazolam in the human brain after a 500 mg dose, the ceiling-effect dose is calculated.

i. Ceiling Effect of Midazolam and Other Benzodiazepines Observed In Vitro

This subsection will highlight cell culture *in vitro* studies and preclinical (animals) studies from the medical literature that determined the ceiling effect of midazolam and other benzodiazepines. These studies will provide specific numerical values that can be used to model the concentration in the brain of a condemned inmate after a 500 mg IV dose of midazolam.

Table 6 below shows the threshold dose(s) that produced the observed ceiling effect in published studies of in vitro experiments. Most studies of diazepam show a ceiling effect threshold at 100 nM and all three studies of midazolam gave 100 nM as the concentration producing a ceiling effect.[3]

[3] Drug concentrations are measured with different units in different types of experiments or clinical studies. The in vitro studies presented in this subsection use Molar Concentration, which is basically a certain number of grams (1 Mole) in a liter of solution. 1 Mole of a drug in 1 Liter of solution gives a 1.0 M concentration. Then, using the metric system prefixes, we know that 1 M = 1000 mM (milli-Mole) which equals 1,000,000 µM (micro-Mole), which is equal to 1,000,000,000 nM (nano-Mole). For these types of studies, the drug solutions are mixed to make up different strengths, like 1 nM, 10 nM, 100 nM, and 1000 nM, and these different solutions are bathed on different sets of cells in a Petri dish and the pharmacological effects measured. The results shown below for the in vitro studies of benzodiazepine effects use drug solutions in the units of nM.

Other units are used in other studies below. Concentration of drug in blood is often given in ng/mL (nano-grams per milli-Liter). Again using the metric system prefixes, we know that 1 g (gram) equals 1000 mg (milli-grams) equals 1,000,000 µg (or mcg; micro-gram) equals 1,000,000,0000 ng (nano-gram). Finally, doses of drugs are administered on a per weight basis, such as 2 mg/kg, or as the same dose for everybody, such as 500 mg dose of midazolam administered intravenously (IV).

Table 6. Summary of selected studies showing ceiling effect of diazepam and midazolam

Benzodiazepine	Ceiling effect at:	Preparation	Reference
Diazepam	10 nM[a]	Cell culture (mouse spinal neurons)	*Skerritt and Macdonald (1984)*
Diazepam	100 nM	Cell culture (oocytes)	*Sigel and Baur (1988)*
Diazepam	50-100 nM	Cell culture (mouse spinal neurons)	*Rogers et al. (1994)*
Diazepam	100 nM	Cell culture (HEK cells)	*Li et al. (2013)*
Diazepam	100 nM	Cell culture (oocytes)	*Rüsch and Forman (2005)*
Midazolam	100 nM	Brain slices (rat)	*Rovira and Ben-Ari (1999)*
Midazolam	100-200 nM	Brain slices (rat)	*Bai et al. (2001)*
Midazolam	100 nM	Cell culture (oocytes)	*Rüsch and Forman (2005)*

[a] nM stands for 'nanomolar' which is a concentration term relating the number of drug molecules in a liter of solution.

A ceiling effect, which is really just a limit on the potency of a drug (see discussion of partial agonists in Section 2D), was noted with benzodiazepines, including diazepam (Valium®) and midazolam (Versed®), in the research studies that determined the mechanism of action for benzodiazepine drugs. Samples of figures from these original research papers are reproduced below (next two page) so that it will be obvious that a ceiling effect is documented and pervasive in the scientific and pharmacological literature.

Figures 4-7 on the next two pages show the actual graphs that confirm a ceiling effect for the benzodiazepines diazepam and midazolam from *in vitro* studies. The ceiling effect on these figures is denoted by a horizontal dashed blue line; this is the plateau that is reached where benzodiazepines given at higher concentrations do not produce greater effects.

Figure legends under the graphs further explain the graphs and the ceiling effect concentration. This is the lowest concentration of drug that produces the plateau effect or ceiling effect.

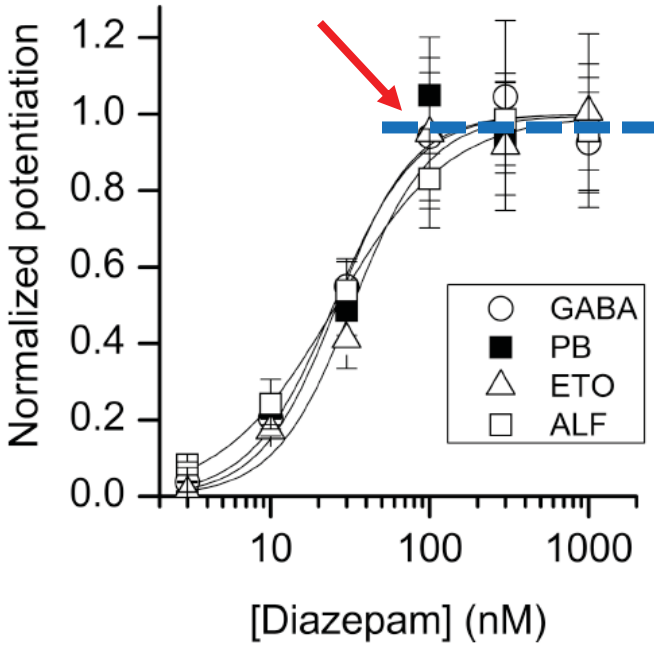


Fig. 4. Various doses of the benzodiazepine, Diazepam, were added with GABA (open circles) and other drugs and the current measured on the vertical scale (Y-axis). Arrow shows ceiling effect threshold at 100 nM. Horizontal dash line shows the ceiling effect. From Fig. 4 in *Li et al. 2013.*

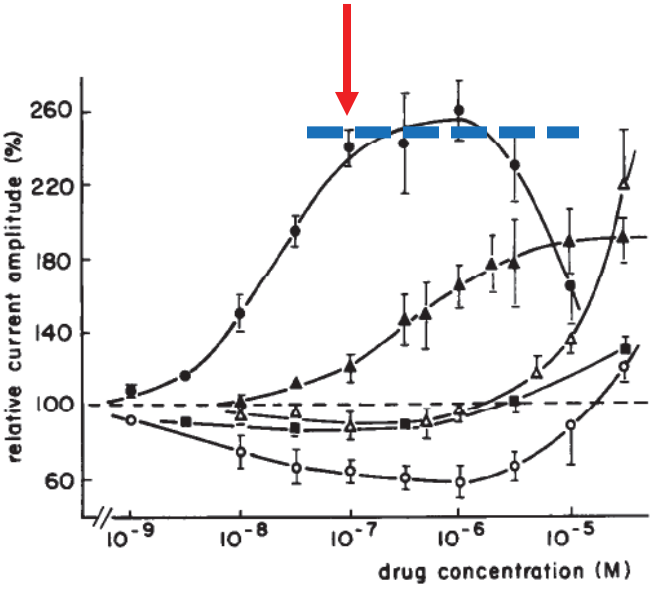


Fig. 5. Various doses of the benzodiazepine, Diazepam (closed circle, top curve) were applied to cells in the presence of GABA and the current measured on the vertical scale (Y-axis). Arrow shows ceiling effect threshold at 10^{-7} M which is equal to 100 nM. Horizontal dash line shows the ceiling effect. From Fig. 4 in *Sigel and Baur 1988.*

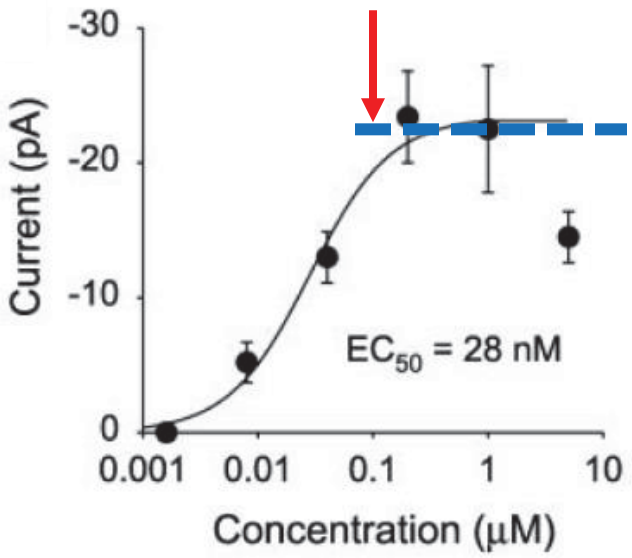


Fig. 6. Various doses of Midazolam (closed circle, top curve) along the horizontal scale (x-axis) were applied to cells in the presence of GABA and current measured on the vertical scale (Y-axis). Arrow shows ceiling effect threshold at 0.1 µM which is equal to 100 nM. Horizontal dash line shows ceiling effect. From Fig. 5B in *Bai et al. 2001.*

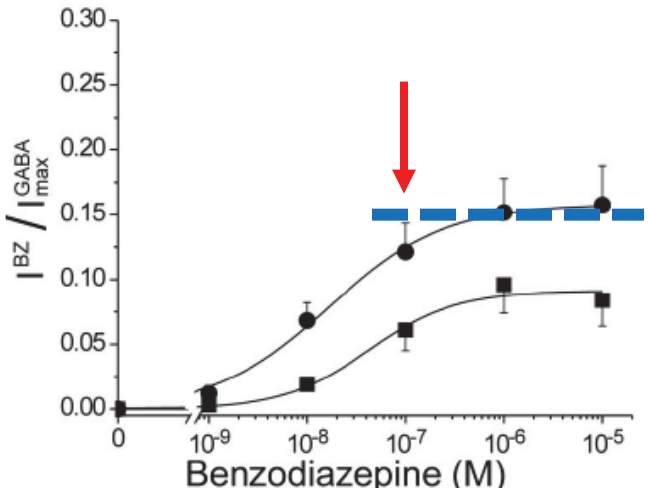


Fig. 7. Various doses of Midazolam (closed circle, top curve) or Diazepam (closed squares, bottom curve) along the horizontal scale (x-axis) were applied to cells in the presence of GABA and current measured on the vertical scale (Y-axis). Arrow shows ceiling effect threshold at 10^{-7} M which is equal to 100 nM. Horizontal dash line shows ceiling effect. From Fig 2A in *Rüsch and Forman 2005.*

ii. Blood Levels of 500 Mg Midazolam after IV Bolus Dose in Humans

As mentioned above, there are no studies in the literature that give the blood concentrations of midazolam following a 500 mg IV dose in humans, as this is higher than approved clinical doses. However, it is possible to review the blood concentrations in humans from studies examining the blood concentrations after clinical doses of IV midazolam. The data from these studies can then be used to model the blood concentrations of midazolam after a 500 mg IV dose.

A clinical study measured the peak amount of midazolam in the blood after IV bolus administration of 5 mg midazolam in eight healthy volunteers (*Schwagmeier et al. 1998*). This study gave peak blood concentrations of nearly 120 ng/mL (nanogram per milliliter) after a 5 mg IV dose. It follows then that with a 500 mg IV dose, the initial amount after direct IV bolus infusion is 100 times of what occurred with the 5 mg dose, which gives an initial blood concentration of 12,000 ng/mL of midazolam after a 500 mg IV dose.

A direct linear modeling of the 500 mg IV dose from the 5 mg dose is supported by other studies. In a more recent study using half of the above 5 mg IV dose, a 2.5 mg IV dose of midazolam, the peak blood concentration of 51.2 ng/mL which is about half the peak blood concentration seen in the above clinical study using a 5 mg IV dose of midazolam (*Veldhorst-Janssen et al. 2011*). Therefore it is not unreasonable to use this linear relationship to extrapolate as is done above

Given the estimate that the initial concentration of midazolam in the blood after a 500 mg IV bolus dose is 12,000 ng/mL, the next determination is to model the fall of midazolam blood concentration over time to determine the amount of midazolam that is available for transfer to the brain during the first 5 minutes. Five minutes is a crucial time point, as the Arkansas Department of Corrections Lethal Injection Procedure mandates that the offender being put to death will be checked for unconsciousness at least 5 minutes after the infusion of midazolam begins.

In order to determine the midazolam blood concentrations over time, it is necessary to have established pharmacokinetic data for IV midazolam. A key paper in this regard examined the pharmacokinetic data after dosing volunteers with 0.1 mg/kg midazolam IV infusions after 1 minute, 1 hour, and 3 hour lengths of infusion (*Greenblatt et al. 2004*). The dosing of midazolam with a 1 minute bolus infusion in this study comes closest to the method to be used by the Arkansas Department of Corrections (see above). Using these data from this study,[4] it was possible to model the blood concentration curve over time following the IV dose of 500 mg midazolam (see Fig. 8 next page). The modeling of the blood concentration curve following a 500 mg IV midazolam dose was done using an Excel spreadsheet, as noted in the scientific literature (*Chamberlain 2003*) and was done above in Section 3B.

[4] The Greenblatt study found that a midazolam IV dose given in 1 minute had a half-life of immediate distribution (t½ alpha) of 21 min and a half-life of elimination (t½ beta) of 171.6 minutes. These parameters were plugged into the spreadsheet formula to give the model data plotted in Fig. 8.

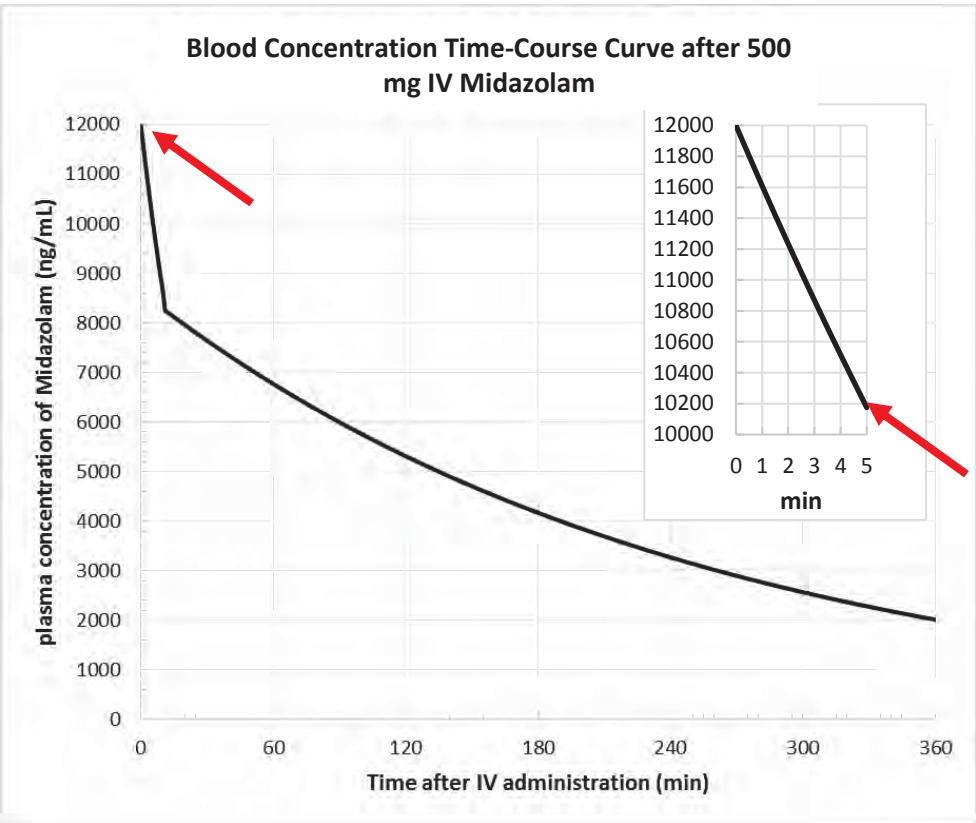


Fig. 8. Blood concentration curve following a single IV bolus dose of 500 mg midazolam. Inset shows the region of the plot from 0-5 minutes. See text for further details. Arrows denote the initial blood concentration of midazolam and midazolam concentration after 5 minutes (inset).

The key parameters calculated above are that following the 500 mg IV dose of midazolam, the initial highest concentration of midazolam is 12,000 ng/mL and after 5 minutes, the concentration of midazolam is 10,200 ng/mL.

iii. Extent of Midazolam Entering the Human Brain after an IV Bolus Dose

Studies that show the amount or extent of midazolam that enters the human brain would be best done by administering an IV dose in numerous people and then sampling brain tissue at various time points afterwards. These studies, of course, cannot be done. However, a number of preclinical studies in animals provide reliable data about the fraction of midazolam that crosses into the brain from the blood. These studies are reviewed next and will provide a value that can be used to determine the amount or extent of midazolam that enters the human brain after a 500 mg IV dose.

It should first be noted that drugs in the blood bind to blood proteins such as albumin and gamma-globulins and the amount of protein binding varies with each drug. This is important as only the free (unbound) drug is available to cross from the blood into the brain to exert its effect. Midazolam is a drug with high blood-protein binding, on the order of 94-97% (*Fragen*

1997). Using 95% as an estimate, this gives only 5% of the amount of midazolam in the blood available for crossing the blood-brain barrier and entering the brain. Taking this into account for the two key parameters of interest noted above, a 500 mg IV bolus of midazolam gives an initial free-drug blood concentration of 600 ng/mL (12,000 X 0.05) and a free-drug blood concentration at 5 minutes of 510 ng/mL (10,200 X 0.05).

Preclinical studies of the fraction of midazolam that enters the brain after an IV dose are done by sampling the cerebrospinal fluid (CSF) along with the blood at various times after midazolam administration (*Arendt et al. 1983, Jones et al. 1988*). The CSF is a good surrogate for the fluid surrounding the brain cells, as it is relatively protein-free so there is little to no binding of drugs to proteins like that which occurs in the blood. The CSF circulates around and through the brain and spinal cord, bathing these tissues (*Lin 2008*). Fig. 9 below shows the concentration of midazolam in the blood and in brain CSF at the same time points from the paper by *Arendt 1983*.

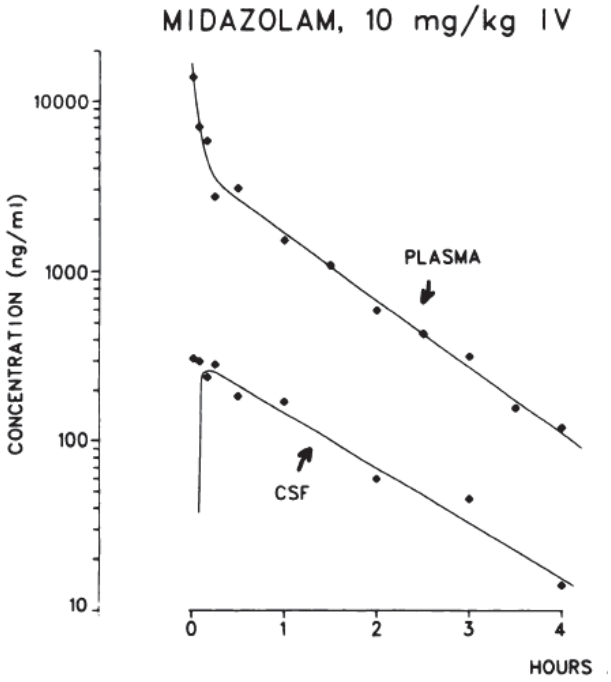


Fig. 9. Midazolam-concentrations curve in blood (plasma, top curve) and in brain CSF (bottom curve) after a single 10 mg/kg IV bolus dose. Note that the CSF concentration is much less than blood at all time points but mirrors the blood curve. From Fig. 2 (left panel) in *Arendt et al. (1983).*

The calculations performed in the study shown in Fig. 9 yielded a brain CSF/blood concentration ratio of 0.14 or 14% (*Arendt et al. 1983*). This ratio can be used in our determinations of brain concentration after 500 mg IV dose of midazolam to calculate that an initial blood concentration of 600 ng/mL midazolam equals 84 ng/mL in the brain (600 X 0.14) and at 5 minutes after start of infusion, the blood concentration of 510 ng/mL is equal to 71.4 ng/mL (510 X 0.14) in the brain.

iv. Dosage of IV Midazolam That Produces a Ceiling Effect in Humans

The above data gave the measurement of midazolam in blood in the units of ng/mL, or nanogram per milliliter, is a weight per volume measure, like mixing a teaspoon of salt in a glass of water). However, the existing data on the concentration of midazolam that produces a ceiling effect from *in vitro* studies reviewed above gave a value of 100 nM (nanomolar), which is in different units. The brain concentration of midazolam, as calculated in ng/mL above, must be converted to nanomolar terms to compare it with the existing *in vitro* data showing that midazolam's ceiling effect occurs at a midazolam concentration of 100 nM. This conversion is done by using the molecular weight of midazolam which gives the relationship between grams and moles.[5] For example, a concentration of midazolam of 32.6 ng/mL in the brain equals 100 nM in molar terms.

The calculated values of the brain concentrations of midazolam following a 500 mg IV dose gave an estimate of 84 ng/mL when the infusion begins and 71.4 ng/mL after 5 minutes elapsed from the start of the infusion. These two values expressed in nM are: 84 ng/mL = 257.9 nM and 71.4 ng/mL = 219.2 nM.

Given that midazolam shows ceiling effects at 100 nM concentration (see Table 6 above), the estimated initial brain concentration for midazolam using a 500 mg IV dose is about 2.6 times higher (at 257.9 nM) than the concentration of midazolam that produces a ceiling effect (100 nM). Five minutes[6] after the 500 mg IV midazolam administration, the brain concentrations for midazolam are estimated to be 219.2 nM or approximately double the ceiling effect concentration of 100 nM shown in preclinical studies (Table 6).

The midazolam dose that results in a 100 nM concentration of midazolam, the ceiling effect concentration, is obtained by using the values of brain concentration obtained with a 500 mg IV dose above after 5 minutes. A 500 mg IV dose gives a brain concentration of 219.2 nM after 5 minutes which is 2.192 times the ceiling effect concentration of 100 nM. Therefore, a dose that is 2.192 times less than 500 mg is 228 mg. Thus, a 228 mg IV dose of midazolam would be expected to reach the threshold concentration of midazolam to produce a ceiling effect after 5 minutes.

C. Comparison to clinical studies

Midazolam's anesthetic effects have also been studied in the clinical setting. This section provides an overview of bispectral analysis (BIS), reports results based on BIS, and discusses discrepancies between the ceiling effect calculated using the above modeling method and the ceiling effect noted in BIS-based studies.

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[5] Calculations were assisted by the Molar solution concentration calculator found at *www.physiologyweb.com.*

[6] Five minutes was chosen as the time point to examine as that is the time after midazolam administration that the first consciousness check is performed according to the Arkansas lethal injection protocol.

i. Bispectral Analysis (BIS)

Scientific models of consciousness rely on the measurement of activity in different areas of the brain and the known functions associated with them. When a general anesthetic is given, there is inhibition of the activity in the higher-order association areas of the brain more so than in the primary processing areas of the brain (*MacDonald et al. 2015*). Most telling, as patients come out of general anesthesia, there is dramatic and sudden activation of the higher-order association areas of the brain regions that correlates with patient responding to verbal commands (*Långsjö et al. 2012*). To a first approximation, consciousness is correlated to activity in brain-association areas and therefore unconsciousness is correlated to lack of activity in these brain association areas.

Researchers and clinicians have developed a way to measure the depth of general anesthesia using the technique of electroencephalograms (EEG). The EEG recordings are processed by the computer with a method called bispectral analysis, or BIS (*Escallier et al. 2014*). BIS gives a single number, on the scale from 100 (completely awake and alert) to 0 (coma and EEG burst suppression). BIS values are the most common objective means for assessing the effects of anesthetic agents, with lower values correlated to greater degrees of brain-activity depression.

Clinical signs of anesthesia correlate moderately well with BIS scores (*Weaver et al. 1970*). BIS values less than 60 are targeted during general anesthesia procedures as that is the depth of anesthesia associated with lack of awareness (*Weaver et al. 1970*). In this study, BIS values of 60 or less correlated with General Anesthesia, 65 with Deep Sedation and 80 to Moderate Sedation (see ASA table in section 2E above). Later studies have verified that a BIS value of 40-60 is considered to reflect the state of General Anesthesia (*Escallier et al. 2014*). For example, one study showed the BIS levels of patients who moved at skin incision (mean BIS value of 65) was greater than patients who did not move in response to skin incision (mean BIS value of 40) (*Johansen and Sebel 2000*).

Using thiopental doses to induce (but not maintain general anesthesia) gave BIS values as low as 60 (*Yoo et al. 2012*). Pentobarbital has decreased the depth of General Anesthesia in cases of intractable seizures to BIS values as low as 3 to induce barbiturate coma (*Jaggi et al. 2003*). These studies show that barbiturates are capable of reducing BIS levels consistent with General Anesthesia, and that high-dose administration of barbiturates can reduce cortical brain activity to near zero.

ii. Clinical studies of midazolam and BIS

Generally, midazolam is used as a premedicant before general anesthesia or for regional anesthesia (*Khanderia and Pandit 1987*). Midazolam is a less reliable induction agent than thiopental and induction of anesthesia using midazolam alone is unpredictable. Clinically, benzodiazepines such as midazolam are not used as much for anesthesia or induction of anesthesia but for conscious sedation (*Giovannitti and Trapp 1991*). Conscious sedation is a drug-induced state of relaxation where the patient remains conscious with reflexes intact and

little effect on cardiovascular or respiratory function (see ASA table in section 2E above). Midazolam is often used with an opioid analgesic in outpatient procedures such as colonoscopy and oral surgery.

Clinical studies examining the relationship of midazolam's BIS values to the level of sedation are considered first. BIS values of in the range of 77-92 were reported after repeated IV doses of midazolam in a surgical outpatient study (*Sandler 2000*). In surgery patients, the BIS threshold for responding to a verbal command after midazolam was 80, whereas patients did not respond to verbal command when a BIS score of 77 was observed (*Ibrahim et al. 2001*). In a clinical study using adult healthy volunteers, IV midazolam was infused until patients become unresponsive to mild prodding or shaking (*Lui et al. 1996*). Midazolam at total doses ranging from 4.5 to 20 mg IV decreased the BIS to a mean value of 69.

Clinical studies that show a ceiling effect of midazolam with regard to lowering the BIS values are described next. These studies noted that increasing doses of IV midazolam do not produce greater pharmacological effects in lowering the BIS values. One study noted that an IV midazolam dose of 0.3 mg/kg (25 mg for a typical 180 lb. adult) did not produce greater depression of the brain (as noted by the BIS value) than a dose of 0.2 mg/kg, or about 16 mg (*Miyake et al. 2010*). The authors note that a greater maximal effect was not seen in previous studies where IV midazolam showed a maximal dose of brain activity depression yielding a BIS value of 70, but not lower (*Ibrahim et al. 2002, Kuizenga et al. 2001*). These data suggest that a ceiling effect in humans occurs after an IV infusion dose of 25 mg.

The sedation that can be produced by midazolam, **and the lack of General Anesthesia at any dose**, is insufficient to render the prisoner insensate to the torturous effects of vecuronium bromide and potassium chloride. A prisoner sedated only with midazolam would be conscious of the suffocating effects of vecuronium bromide but, as a result of its paralytic properties, be unable to communicate his or her distress. The prisoner would also be subjected to the burning sensation of the 3rd drug, potassium chloride.

iii. Comparison between modeling and clinical studies

The dose of IV midazolam that produces a ceiling effect in clinical studies is lower (25 mg) than the theoretical ceiling-effect dose calculated above (228 mg). The difference in these results are not unexpected. The ceiling-effect dose of 25 mg comes from clinical studies examining midazolam's effects in patients. The calculated ceiling dose of 228 mg midazolam is mainly based on in vitro and preclinical studies. It is likely that that *in vitro* data using cell cultures are less sensitive to midazolam compared to the clinical effects of midazolam in patients.

Significantly, the ceiling effect of midazolam in the range of 25 to 228 mg IV means that increasing doses of midazolam do not produce increasing effects. The ceiling effect of midazolam is the reason why midazolam cannot produce the general anesthesia needed for a first drug in a three drug protocol.

D. Summary

The findings from this section are:

i. The ceiling effect of midazolam is a direct result of midazolam's mechanism of action. Pentobarbital and other barbiturates have a different mechanism of action and therefore do not exhibit a ceiling effect.

ii. Research done *in vitro* shows that the ceiling effect of midazolam occurs, under those conditions, at a concentration of 100 nM.

iii. An IV bolus dose of 500 mg midazolam produces a brain concentration that is 2 times higher than the concentration of midazolam that produces a ceiling effect at 5 minutes.

iv. An IV bolus dose of 228 mg midazolam is sufficient to reach the threshold of midazolam's ceiling effect at 5 minutes after administration. Amounts beyond that dose are not expected to produce a greater effect.

v. Clinical studies show that the ceiling effect of IV midazolam occur at infusion doses of about 25 mg. These studies show that greater midazolam doses do not produce greater depression of brain activity and cannot produce a state of General Anesthesia.

vi. Midazolam at a dose of 500 mg IV cannot be relied on to render someone sufficiently unconscious to block the noxious stimuli that will occur from the application of the remaining drugs in the protocol.

6. Pharmacological Considerations of Alternative One-Drug Protocols for Lethal Injections

Anesthetic Gases Produce General Anesthesia and Overdose Death

While IV anesthetics like thiopental, pentobarbital, or propofol are used to induce anesthesia, inhalational agents (gases) are generally used to maintain general anesthesia during surgical procedures (*Potyk 1998*). Halothane was the prototypical inhalational agent, but is no longer available in the U.S. due to a high incidence of hepatic toxicity with its use (*Rosenberg and Weaver 1991*). General anesthesia for most surgical operations is done using newer inhalational agents, like sevoflurane, desflurane, or isoflurane (*Ghatge et al. 2003*). Inhalational agents, like barbiturates, are potent activators of the $GABA_A$ receptor (*Franks and Lieb 1994*). Like barbiturates and unlike benzodiazepines, inhalational general anesthetics can produce their potent effects at the $GABA_A$ receptor with or without GABA present. Inhalational general anesthetics like sevoflurane, desflurane, and isoflurane also act on a number of other ion channels to shut down brain activity (*Franks 2006*).

Desflurane and isoflurane irritate the respiratory tract during induction of anesthesia, so they are used for maintaining general anesthesia once induction with another agent has occurred (*Rosenberg and Weaver 1991*). For that reason, only sevoflurane will be considered further in

this section. Sevoflurane is an ideal inhalational agent, as it can be also be used for induction of anesthesia and therefore substitute for an IV general anesthetic like thiopental, pentobarbital, or propofol (*Ghatke et al. 2003*). Sevoflurane is not pungent to the patient and produces a rapid onset of general anesthesia. A state of general anesthesia occurs within 2 minutes after administration of sevoflurane for induction and is quicker than after administration of isoflurane (*Ghatge et al. 2003, Sakai et al. 2005*).

As detailed in Section 5C above, a calculation based on the EEG activity (the BIS value) during administration of an anesthetic provides an objective measure of the level of sedation. A BIS value of 40-60 is considered to reflect the state of General Anesthesia (*Escallier et al. 2014*). Sevoflurane administration reliably produces a state of General Anesthesia and decreases BIS to values consistent with General Anesthesia or deeper, with BIS values as low as 10-20 (*Kreuer et al. 2008*). In a study of women undergoing C-section, sevoflurane decreased BIS to a mean value of 39 (*Zand et al. 2014*). For interventional radiology, BIS levels titrated to the range of 40-49 were needed to prevent movement of patients undergoing procedures with sevoflurane anesthesia (*Jung et al. 2015).*

Sevoflurane administration can lead to death by cardiac and respiratory depression, as shown by the forensic reports of cases involving sevoflurane overdose deaths (*Levine et al. 2007, Rosales et al. 2007*).

The procedures for administering an anesthetic gas requires less training than placement and delivery of a drug by IV. With sevoflurane, there is no need for IV access to induce anesthesia; sevoflurane is non-irritating and can be used directly for mask induction (*Sakai et al. 2005*). There is a cost for the equipment, and the anesthesia machine should include a waste gas scavenger system.[7] Because inhalational agents like sevoflurane are even more potent than barbiturates, they can be used in over-dosage as the sole lethal agent and would produce a rapid and painless death.

Equipment costs are relatively inexpensive, with used Anesthesia Machines, including sevoflurane and isoflurane vaporizers, available on Ebay and other medical-equipment-resale sites for around $2,000.[8] Newly manufactured machines may go for 3-5 times that cost depending on the model and features. Online training for personnel operating the Anesthesia Machines is available from manufacturers' websites.[9]

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[7] Examples of various waste gas scavenger systems are given in the 2013 white paper entitled "Management of Waste Anesthetic Gases" from the American Association of Nurse Anesthetists (AANA) available at: www.aana.com/resources2/professionalpractice/Documents/PPM%20Management%20Waste%20Gas.pdf

[8] Ebay Anesthesia Machines at: *www.ebay.com/bhp/anesthesia-machine*

[9] For example, at http://static.draeger.com/trainer/apollo/apollo_trainer/start.html#id=A1100

The inhalant drugs sevoflurane, desflurane, and isoflurane are commercially available in FDA-approved forms. Sevoflurane is available from Abbvie Pharmaceuticals in North Chicago, IL; Piramal Critical in Bethlehem, PA; Baxter Health Corporation in Deerfield, IL; Halocarbon Products in Peachtree Corners, GA; and Shanghai Hengrui, in Shanghai, China. Desflurane (Suprane®) is sold by Baxter Health Corporation of Round Lake, IL. Isoflurane (Forane®) is also available from Baxter Health Corporation and four other manufacturers.

In summary, FDA-approved, fast-acting inhalant anesthetics are commercially available, and a massive overdose of such drugs would produce a rapid and painless death.

7. Overall Summary and Conclusions

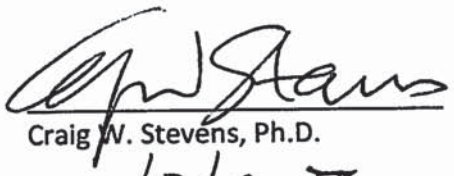
i. The State's decision to substitute midazolam for pentobarbital or thiopental as the first drug in the three-drug lethal injection protocol was made without sound medical or scientific reasoning or expert pharmacological advice. Pharmacological substitution is a legitimate method to provide equal pharmacological effects when one drug may no longer be available. For example, the muscle paralytic pancuronium, the second drug in the three-drug lethal injection protocol, can be substituted with the muscle paralytic vecuronium without violating pharmacological equivalency, as the two drugs are in the same drug class and have the same mechanism of action. Pancuronium and vecuronium have pharmacological equivalency.

However, it is not pharmacologically defensible to substitute barbiturates (like pentobarbital or thiopental) with the benzodiazepine midazolam, because no pharmacological equivalency exists. The final evidence of midazolam's non-equivalency with thiopental or pentobarbital is the fact that no state has attempted to use midazolam in a one-drug lethal injection protocol. If midazolam and pentobarbital (or thiopental) were pharmacologically equivalent, midazolam could be used as the sole agent in a one-drug lethal injection protocol using, as many states have done, using a single barbiturate drug, namely pentobarbital. **The lack of one-drug lethal injection protocols using midazolam by any State in the Union is a tacit admission that midazolam and pentobarbital (or thiopental) are not pharmacologically equivalent**.

ii. Because midazolam cannot induce General Anesthesia, a prisoner sedated with midazolam would consciously experience the suffocating effects of the vecuronium bromide and the burning pain of the potassium-chloride injection. The consciousness check specified by Arkansas's lethal injection protocol provides no protection; inasmuch as midazolam is pharmacologically incapable of providing adequate anesthesia, any determination that the prisoner is adequately anesthetized would necessarily be erroneous. As such, Arkansas's lethal injection protocol is sure or very likely to cause serious pain and suffering. Due to the paralytic effects of vecuroniun bromide, such serious pain and suffering would likely be invisible to observers of the execution procedure.

iii. A single-drug execution protocol would significantly reduce the risk of pain and suffering. FDA-approved, fast-acting inhalant anesthetics are commercially available and would produce a rapid and painless death.

I declare that I have examined this report and all statements contained herein, and to the best of my knowledge and belief, they are true, correct and complete. My opinions stated herein are based on high-level of scientific and medical certainty.



Craig W. Stevens, Ph.D.

1/3/2017

Date

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STATE OF OKLAHOMA)
) **SS**
COUNTY OF TULSA)

Now on this 3 day of January, 2017, Craig W. Stevens, a person whose identity was satisfactorily proven, appeared before me and, after first being placed under oath, did acknowledged his signature above to be his own voluntary act and deed, and affirmed that the facts contained herein were true.

Witness my hand and official seal

Robert A. Perry
Notary Official Signature

Robert A. Perry
Print Name

OFFICIAL SEAL
ROBERT A PERRY
NOTARY PUBLIC STATE OF OKLAHOMA
Commission # 08000041
My Commission Expires 12-20-2018

My Commission Expires 12/20/2018

No. 60CV-15-2921

IN THE CIRCUIT COURT OF PULASKI COUNTY, ARKANSAS
FIFTH DIVISION

STACEY JOHNSON, et al.

Plaintiffs,

v.

WENDY KELLEY, in her official capacity as
Director, Arkansas Department of Correction, and
ARKANSAS DEPARTMENT OF CORRECTION

Defendants.

AFFIDAVIT OF JONATHAN I. GRONER, M.D.

I, Jonathan I. Groner, M.D., do declare as follows:

1) I am a medical doctor and Professor of Clinical Surgery at The Ohio State University College of Medicine. I graduated from Northwestern University Medical School in 1984. I completed my residency in General Surgery at the Medical College of Wisconsin and in Pediatric Surgery at Nationwide Children's Hospital. I became licensed to practice medicine in the State of Ohio in 1992 and remain licensed to practice in Ohio. I was appointed to the faculty of The Ohio State University College of Medicine in 1994. I practice surgery and train medical students and residents in the practice of surgery. My

particular specialties include pediatric surgery, general surgery, and trauma surgery.

2) I hold a certification in General Surgery and Pediatric Surgery from the American Board of Surgery and have served as an Examiner for the American Board of Surgery's General Surgery Qualifying Examination. I also hold multiple certifications in advanced burn life support and in advanced trauma life support. I have served as the president of the Central Ohio Trauma Center and served on the Ohio Emergency Medical Services Board.

3) I have done extensive research in the areas of pediatric surgery, general surgery, and trauma surgery. My related research interests include the impact of trauma on minority children, firearm trauma, ATV injuries, child abuse, and physician participation in lethal injection. I have published multiple peer-reviewed articles on the administration of capital punishment by lethal injection. I am also the author of *The Hippocratic Paradox: the Role of the Medical Profession in Capital Punishment in the United States*, 35 FORDHAM URB. L.J. 883 (2008). In that article, I wrote that, assuming the shooters hit their mark (the heart), execution by firing squad would be "nearly instantaneous and painless." That is because the "[d]isruption of blood flow to the brain, which would result from lacerations to the heart by

multiple bullets, causes almost immediate loss of consciousness, resulting in rapid death with little or no pain."

4) Counsel for the Plaintiffs asked me to opine further upon the comments I made in the Fordham article. I hold all opinions expressed to a reasonable degree of medical certainty.

5) My analysis assumes the following execution procedure. This procedure is consistent with the procedure the State of Utah used in the 2010 execution of Ronnie Lee Gardner. I have reviewed the protocol Utah followed during that execution.

A. The inmate is placed in a chair and strapped into position so that he/she is not capable of moving. The chair and restraints allow maximum exposure of the chest (as the inmate sits in a straight, upright position).

B. A prison official examines the inmate and locates the position of the inmate's heart by physical exam (palpation of the chest for pulse) or the use of a stethoscope (point of loudest audible heartbeat).

C. The official pins a target to the inmate's clothing indicating the location of the inmate's heart.

D. Four to five law enforcement officers aim high-caliber, long-barreled weapons at the target at close range.

E. When the order is given, the officers fire their guns at the target on the inmate's chest.

6) This procedure will cause a nearly instantaneous death for the following reasons:

A. The location of the palpable heartbeat or the loudest audible heartbeat corresponds to the left ventricle, the largest pumping chamber of the heart. This is the chamber that pumps the blood out of the heart to the body.

B. A single bullet entering the left ventricle would tear a large hole in the left ventricle; multiple bullet holes would accelerate the process.

C. Blood that would normally flow out of the left ventricle into the aorta would immediately begin to flow out through the hole in the ventricle and fill the chest cavity with blood.

D. Cessation of blood flow in the aorta would cause immediate cessation of blood flow to the carotid arteries, which are the major blood supply to the brain.

E. Cessation of blood flow to the brain causes unconsciousness within seconds.

F. Death would follow soon after (3 to 4 minutes) from exsanguinating hemorrhage.

7) This swift death will also be painless. From my experience as a trauma surgeon, it is clear that patients with gunshot wounds to the heart with exsanguinating hemorrhage (loss of most of the blood volume) are unconscious and do not react to pain. In fact, the rescue maneuver for a person that has penetrating trauma to the heart who arrives at the emergency department with waning signs of life—in other words, someone who is bleeding to death from a hole in the heart—is to perform an "Emergency Department thoracotomy," meaning that the chest is cut open immediately in an attempt to repair the hole in the heart. This operation is done without anesthesia. It involves cutting through skin and muscle between the ribs on the left side under the nipple. The incision is usually at least 10-12 inches long. An instrument is used to spread the ribs apart allowing visualization of the heart and aorta. An attempt is made to repair the wound in the heart.

8) It is my opinion that Utah's execution of Ronnie Lee Gardner by firing squad caused a swift and painless death. The media reported that Mr. Gardner pushed his left arm forward "about 2 inches against the restraints," and "in that same motion, he closed his hand

and made a fist." *See* Nate Carlisle, *Firing Squad: An Eyewitness Account of Gardner's Execution*, Salt Lake Tribune, June 18, 2010, *available at* http://bit.ly/2eyfTND. This motion is consistent with reflex contractions following massive trauma to his left pectoralis muscle and ribs from the multiple high-velocity, large-caliber gunshot wounds. There was no report of verbal reaction, which is probably the most common manifestation of pain.

9) The current midazolam protocol has a far greater risk of causing pain and suffering compared to the firing squad. Midazolam is not a general anesthetic and, to my knowledge, is not used as a sole agent for any surgical procedure. The administration of drugs to cause respiratory arrest and cardiac arrest in an inmate medicated only with midazolam is far more likely to cause a painful death.

10) In sum, based on my medical expertise and my review of Utah's functioning firing-squad protocol, I reaffirm my earlier conclusion that execution by firing squad will cause rapid death with little to no pain.

JONATHAN I. GRONER, M.D.

11/29/2016

Date

State of Ohio)
)
County of Franklin)

Now, on this 29 day of November, 2016, Jonathan I. Groner, a person known to me (or whose identity was satisfactorily proven), appeared before me and, after first being placed under oath, did acknowledge his signature above to be his own voluntary act and deed, and affirmed that the facts contained herein are true.

Joyce A Blake
Notary Public
My commission expires:
8/23/2017

TMF 01/01.00 GENERAL PROVISIONS

TMF 01/01.01 Purpose of Technical Manual
TMF 01/01.02 Cross Reference
TMF 01/01.03 Policy
TMF 01/01.04 Definitions

TMF 01/01.00 GENERAL PROVISIONS

TMF 01/01.01 Purpose of Technical Manual

A. The purpose of this Technical Manual is to provide the Department's policies, procedures and post orders for planning and carrying out the sentence for the execution of a person convicted of a capital offense.

B. This chapter shall include policies and procedures related to:

1. planning and preparation;

2. execution of the sentence;

3. post-execution requirements and process;

4. security and control;

5. witnesses and official visitors

6. news media access limitations and briefing;

7. delays, stays, and commutations;

8. support services functions;

9. briefing and training; and

10. documentation, review and audit.

C. Post orders are included for the staff and others involved in the execution planning, implementation, documentation and review.

TMF 01/01.02 Cross Reference

A. Department Policies and Procedures Manuals

AGr05 Media Relations
FDr14 Inmate Property

B. Other Authority

UCA 77-19-6 Judgement of death-Warrant-Delivery of warrant-Determination of execution time.

UCA 77-19-10	Judgement of death-Location and procedures for execution.
UCA 77-19-11	Who may be present-Photographic and recording equipment.
UCA 77-19-12	Return upon death warrant.
UCA 26-4-6	Investigation of deaths by county attorney-Requests for autopsies.
UCA 26-4-7	Deaths over which medical examiner has jurisdiction.
BPPPM 3.12	Commutation Hearings for Death Penalty Cases

TMF 01/01.03 Policy

It is the policy of the Department that:

A. execution of persons sentenced to death under Utah law by a court of competent authority and jurisdiction be carried out in the legally prescribed manner;

B. the Department shall make every effort in the planning and preparation of the execution event to ensure that the execution process:

1. adheres to the intent of the law;

2. is handled in a manner which minimizes negative impact on the safety, security and operational integrity of the prison;

3. accommodates the need for public access to information concerning the event;

4. reasonably addresses the privacy interests of those persons for whom the law, Department policy or commonly-held principles of decency require such privacy;

5. provides sufficient staffing to ensure that unplanned problems can be accommodated and overcome;

6. prepares for stays of execution, commutations and other delays in the execution count-down;

7. provides an opportunity for interested persons to exercise their First

Amendment rights to demonstrate for or against capital punishment in a lawful manner;

8. ensures a firm and adequate response to unlawful civil disobedience, trespass, or other violations of the law by persons attempting to disrupt, prevent or other-wise frustrate the lawful process associated with the execution; and

9. anticipates and provides for sufficient support needs for the execution and the prison as a whole;

C. the Department shall arrest and encourage the prosecution of persons, including but not limited to, those who:

1. violate 77-19-11 UCA prohibitions against filming, taping, sketching, broadcasting or otherwise electronically documenting the death of the condemned;

2. trespass or otherwise enter upon prison property without proper permission and clearance from the Department;

3. participate in unlawful demonstrations;

4. unlawfully attempt to or disrupt, prevent or otherwise interfere with the execution;

5. being inmates, are involved in disruptive, assaultive or other proscribed behavior; or

6. unlawfully threaten, intimidate or terrorize persons involved in the execution process;

D. staff involved in the execution make every effort within the requirements and limits of these polices and procedures and the laws of the State of Utah to:

1. minimize the anxiety and negative impact of the execution on the victim's and inmate's family and friends witnessing the execution;

2. display appropriate levels of professionalism, restraint, and courtesy in interaction with witnesses, demonstrators, news media, and other non-staff persons during the execution process; and

3. not permit interactions, emotion or intimidation to prevent their proper handling of missions and duties;

E. the Department review the adequacy and/or the performance of:

1. the policies and procedures employed;

2. the Department staff members involved in the execution;

3. members of allied agencies assisting with the execution; and

4. statutes and other authority impacting the execution; and

F. the evaluation of each execution event be used to improve operational procedures for the future.

TMF 01/01.04 Definitions

allied agency	refers to another criminal justice agency
Attorney General's Office	staff at the Attorney General's Office or any designated contract attorney approved to carry out the responsibilities described in this technical manual
attorney of record	the condemned inmate's attorney and other assisting legal personnel

broadcast media	refers to radio and television media
civilians	any person not a member of the Department, allied law enforcement agency, nor mutual aid agencies
Command Post Director	the member who is assigned to supervise the command post functions and activities
commutation	the change from a greater to a lesser punishment after conviction
drug injection box	box or boxes each of which shall contain one complete set-up for lethal injection; with or without drugs
execution building	refers to the area containing the execution chamber
execution chamber	the immediate enclosed areas containing the condemned at the moment of execution

mutual aid	agencies or personnel that provide medical, fire suppression, and other support services to the Draper site
news magazines	magazines having a national circulation being sold by news stands to the general public and by mail circulation
news media	collectively refers to those involved with news gathering for newspapers, news magazines, radio, television or news services
news media members	persons over the age of eighteen who are primarily employed in the business of gathering or reporting news for newspapers, news magazines, national or international new services or radio or television stations licensed by the Federal Communications Commission
newspaper	for purposes of this chapter, the publication:

1. circulates among the general public;

2. publishes legal notices in the community in which it is located or the area to which it distributes; and

3. contains items of general interest to the public such as political, commercial, religious or social affairs

pardon	an act of grace by an appropriate authority exempting a person from punishment for a crime
press	refers to the print media; also see "news media", generally
reprieve	the temporary suspension of the execution
respite	see "reprieve"
security curtains	the curtains which cover the viewing room windows in the executionchamber
Warden	warden assigned to the Draper site
witness viewing	the areas from which the

area	execution is viewed by government witnesses, inmate's witnesses and news media witnesses

TMF 01/02.00 PRE-EXECUTION CHECKLIST

TMF 01/02.01 General Provisions
TMF 01/02.02 Prior to Receiving Death Warrant
TMF 01/02.03 Receipt of Death Warrant to Thirty Days Prior to Execution
TMF 01/02.04 Twenty-Nine to Fourteen Days Prior to the Execution
TMF 01/02.05 Thirteen to Seven Days Prior to Execution
TMF 01/02.06 Six to Three Days Prior to Execution
TMF 01/02.07

TMF 01/02.00 PRE-EXECUTION CHECKLIST

TMF 01/02.01 General Provisions

A. Purpose of Chapter

1. The purpose of this chapter is to provide a checklist of procedures and events which should occur between the issuing of the death warrant and 24 hours prior to the execution.

2. Full detail will not be provided for each procedure or event in this chapter. For detail, reference will be made to Chapter TMF 01/05 and other chapters where such detail may be found.

3. This chapter will be divided to cover the following time periods:

   a. prior to the death warrant being issued;

   b. issuing of death warrant to 30 days prior to the execution;

   c. 14 to 29 days prior to the execution;

   d. 7 to 13 days prior to the execution;

   e. 3 to 6 days prior to the execution; and

   f.

B. Policy

1. It is the policy of the Department that the count-down to the execution be completed in a systematic manner to ensure that all procedures and events which are necessary in the preparation of the execution are completed in a timely manner.

2. This count-down, though offering flexible application, should be observed and followed as written unless deviation or adjustment is required for carrying out the execution.

3. The Executive Director/designee may direct deviation from or adjustment to the policies and procedures in this manual at any time when necessary for the good of the Department's mission in carrying out the execution. Approval for the changes shall be documented in writing.

TMF 01/02.02 Prior to Receiving Death Warrant

A. Execution Planning Team

When it appears an execution is imminent, prior to the issuing of the death warrant, the Warden shall select an Execution Planning Team. The Team mayinclude:

1.

2.

3.

4.

5.

6.

7.

8.

9.

10.

11.

B. Involve Additional Planning Assistance

Other persons who may be invited to attend on a meeting-by-meeting basis, include:

1. a representative or representatives from the Attorney General's Office;

2. a representative from the office of the County Attorney which prosecuted the condemned;

3. a representative from the Board of Pardons and Parole;

4. representatives from the law enforcement agencies which investigated the case involving the condemned;

5. representatives from law enforcement and other allied agencies who may be asked to assist with various aspects of the execution; and

6. any other persons deemed necessary or appropriate by the Executive Director/designee, DIO Director or Warden.

C. Develop Assignments

When it is reasonable to believe a death warrant will be issued in the near future, the Execution Planning Team and those additional persons deemed appropriate shall meet to:

1. review the Execution Plan (TMF 01);

2. make assignments for the pending execution;

3. develop a schedule of events;

4. assign responsibilities related to revision of the Execution Plan, if needed; and

5. take any other steps necessary to prepare for the issuance of the

deathwarrant and begin the execution count down.

D. Identify Possible Execution Dates

1. The Execution Planning Team shall review the Department's schedule of events and identify favorable and unfavorable dates within the period of time in which the execution may be ordered.

2. Information concerning the Department's requests/concerns related to scheduling shall be communicated to the Attorney General's Office to be communicated to the sentencing court.

TMF 01/02.03 Receipt of Death Warrant to Thirty Days Prior to Execution

Upon receipt of a death warrant from a competent court, the following procedures shall be initiated and should be completed at least 30 days prior to execution.

A. Receipt of Death Warrant

1. Upon receipt of the death warrant and as soon as practical thereafter, a meeting of the Execution Planning Team shall be scheduled by the Warden.

2. The Execution Planning Team shall then coordinate the implementation of the procedures set forth in this technical manual under the direction of the Warden.

B. Time and Place of Execution

1. Date

The date for the execution shall be that day set by the sentencing judge.

2. Time

"The Department of Corrections shall determine the hour, within the appointed day, at which the judgment is executed." 77-19-6(3)

3. Location

C. Condemned Inmate's Choice of Witnesses

1. The condemned inmate shall be informed that he may designate religious representatives, friends, or relatives not exceeding a total of five in number to witness the execution. 77-19-11 (2) (d) UCA

2. Refer to TMF 01/07.

D. Disposition of Personal Property

1. The inmate shall be contacted for instructions concerning the disposition of his personal property.

2. Refer to TMF 01/05.06.

E. Disposition of Funds in Inmate's Account

1. The condemned shall be contacted for instructions concerning the disposition of the funds in any accounts controlled or administered by the prison or Department.

2. Refer to TMF 01/05.06 and TMF 01/05.07.

F. Organ Donation

Organ donation is not an option for condemned inmates.

G. Disposition of Body

1. The condemned shall be asked for instructions concerning the disposition of his remains following the execution.

2. Refer to TMF 01/05.08.

H. Designate Persons Required to Assist with Execution

1. Those persons necessary to carry out the execution shall be identified.

   a. The Executive Director/designee, DIO Director or Warden shall be responsible for identifying, selecting and obtaining the services of the executioners. See TMF 01/05.03 and TMF 01/05.04.

   b. The Public Affairs Director shall be responsible for coordinating the notification of the news media and selection of individual news media witnesses. See TMF 01.08.02.

   c. The Warden shall be responsible for designating those persons necessary to carry out and support the execution.

2. Redundancy in assignment may be developed for all vital or important positions. The Warden, DIO Director, and Executive Director/designee shall determine which positions require back-up and shall ensure adequate coverage is provided.

3. "Compensation for members of a firing squad or persons administering intravenous injections shall be in an amount determined by the director of the Division of Finance." 77-19-10 (4)UCA

   a. The Department shall negotiate with the executioners and Division of Finance the fee to be paid to the executioners.

b.

c.

I. Other Approved Witnesses

The Executive Director/designee shall designate other approved witnesses as outlined in TMF 01/07.03.

J. Contact with State Medical Examiner

1. Contact shall be made withthe State Medical Examiner to coordinate the Medical Examiner's role.

2. The Medical Examiner shall be requested to provide direction concerning:

a. transfer of custody of the executed inmate from the Warden to the Medical Examiner;

b.

c.

3. Refer to TMF 01/04.

K. Support Services

1. The Support Services Deputy Warden coordinates the functions of Support Services Section Personnel.

2. Support Services units shall include, but not be limited to:

a. the Food Services Unit (See TMF 01/05.19); and

b. the Maintenance Unit (See TMF 01/05.18).

L. The Correctional Medical Administrator coordinates functions of the Medical Unit personnel. (See TMF 01/05.18)

M. Brief Prison Administrators

1. It is necessary to maintain as nearly as possible a normal prison operation during the execution and the activities preceding and following the execution.

2. Prison administrators should be briefed as appropriate on plans for the execution, restrictions on access, crowd control, additional security procedures, etc., on an on-going basis.

3. Briefings should begin as soon as plans begin to evolve which will effect the general prison operation, and should continue until the operation returns to normal.

TMF 01/02.04 Twenty-Nine to Fourteen Days Prior to the Execution

A. Witnesses

1. The Executive Director/designee shall develop a final list of witnesses consistent with the requirements of 77-19-11 (2) and (3) UCA.

2. Any changes to the Government witness list shall be approved by the Executive Director.

3. Each witness shall be required to sign an agreement prior to being cleared and added to the witness list.

4. The Executive Director may make additions to the witness list when necessary.

5. Refer to TMF 01/05.05.

B. News Media

1. Witness requests shall be received and processed by the Public Affairs Office in accordance with TMF 01/08.02.

2. Alternate coverage/accommodations for members of the press selected to be present at alternate site shall be handled consistent with TMF 01/08.03.

C. Inmate Property and Accounts

1. Finalize arrangements for disposition of the condemned inmate's property and accounts 14 days prior to execution.

2. Refer to TMF 01/05.06 and TMF 01/05.07.

D. Disposition of Body

1. Finalize, if possible, decision concerning disposition of the body.

2. Refer to TMF 01/05.08.

E. Selection of Executioners

1. Finalize the selection of executioners and their back-ups.

2. Refer to TMF 01/05.03 and TMF 01/05.04.

F. Medical/Medical Examiner

1. Finalize arrangements for a physician consistent with 77-19-10UCA.

2.

3. Refer to TMF 01/05.08.

G. Practices and Rehearsals

1. Initiate practice sessions for persons involved in the various parts of the execution event.

2. Not all of the persons involved will practice together. Individual teams will practice as units, with inter-team practices scheduled, as necessary.

TMF 01/02.05 Thirteen to Seven to Days Prior to Execution

A. Inmate Property/Accounts

All paperwork on disposition of property and accounts should be completed at least seven days prior to the execution.

B. Disposition of Body
All paperwork should be completed at least seven days prior to the execution.

C. Food Services

1. At least seven days prior to execution, contact the condemned inmate to arrange last meal. TMF 01/05.18.

2. Determine with the Warden, Draper Site Security Deputy Warden, and Public Affairs Director what beverage and food service will be needed at the various locations where staff will be working.

D. Purchase of Substances to Be Used in Lethal Injection

1. Purchase substances to be used in the execution.

2. Refer to TMF 01/05.11.

E. Support Services

Finalize all arrangements involving the Support Services assistance with the Support Services Director.

F. Finalize all arrangements involving the Medical Section assistance with the Correctional Medical Administrator.

G. Allied Agencies

Finalize arrangements with allied agencies assisting with the execution.

TMF 01/02.06 Six to Three Days Prior to Execution

A. Witnesses

1. All witness agreements should be signed.

a. Copies shall be provided to the:

(1) Command Post Director; and

(2) Auditor-in-Charge.

b. Persons refusing to sign agreements shall not be permitted to attend.

2. Exceptions to the time requirements will permit delayed signing of agreements for witnesses coming in from out-of-state.

B. Brief Allied Agencies

1. Members of allied agencies who have not participated in practice sessions or have not otherwise been briefed previously, shall be briefed and their post or responsibilities explained.

2. Briefings will include a detailed review of the individual's post order.

C. Inmate Property and Accounts

1. Complete all unfinished paperwork and arrangements.

2. If the condemned fails to cooperate in these arrangements, he shall be notified

that the property and money will be disposed of according to state law, and Department policy.

D. Executioners

The Warden shall:

1.

2. ensure completion of all arrangements necessary for security of executioners and protection of their identities.

E. Equipment Check/Inventory

1.

2. Refer to TMF 01/05.10(Firing Squad) and 01/10.09 (Lethal Injection).

TMF 01/02.07

A. Observation Period

1.

2.

3. Refer to TMF 01/05.12.

B. Meeting of Execution Planning Team

The Team shall meet to examine preparation for the execution. The checklists shall be reviewed and immediate assignments made to bring all items current with the schedule of events.

Refer to TMF 01/02 pre-execution checklist
Refer to TMF 01/03 execution checklist
Refer to TMF 01/04 post execution procedure

C. Review of Procedures

Conduct final review of procedures.

D. Arrangements for Pickup of Executioners

1.

2.

E. Food Services

1. Verify last meal preparation.

2. Verify beverage/food preparations for working teams.

F. Communications

1. Verify installation of and test communications equipment for:

a.

b.

c. Information Center.

2. Refer to TMF 01/05.10.

G. Contact Support Agencies

1. Contact:

a. the Attorney General's Office;

b. the State Medical Examiner's Office;

c. allied law enforcement agencies; and

d. the Governor's Office.

2. Verify that each agency fully understands its role and is prepared to complete tasks.

H. Equipment Check

1. Complete pre-execution inventory and equipment check.

2. All systems should be tested.

TMF 01/03.00 EXECUTION CHECKLIST

TMF 01/03.01 General Provisions
TMF 01/03.02
TMF 01/03.03
TMF 01/03.04
TMF 01/03.05
TMF 01/03.06

TMF 01/03.00 EXECUTION CHECKLIST

TMF 01/03.01 General Provisions

A. Purpose of Chapter

1. The purpose of this chapter is to provide a checklist of procedures and events which should occur

2. Full detail will not be provided for each procedure or event in this chapter. For detail, reference will be made to Chapter TMF 01/05 and other chapters where such detail may be found.

B. Policy

1. It is the policy of the Department that the count-down to the execution be completed in a systematic manner to ensure that all procedures and events which are necessary to carry out the execution are completed in a carefully coordinated manner.

2. The execution shall be carried out in a manner consistent with state law.

TMF 01/03.02

A.

1.

2.

3. Refer to TMF 01/05.12.

B.

1.

2. Refer to TMF 01/05.12.

C. Inmate Communication

1.

2.

3.

4. Refer to TMF 01/05.12.

D. Food Services

1. The Warden/designee shall contact the condemned to make arrangements for the final three meals.

2. The final meal shall be served.

3. Refer to TMF 01/05.18.

E.

1.

a.

b.

c.

d.

2. Refer to TMF 01/03.03 and TMF 01/05.08.

F. Equipment Check

1.

2. Refer to TMF 01/05.10 and TMF 01/05.11.

TMF 01/03.03

A. Final Briefing

1.

2. The final briefing shall be attended by the Executive Director/designee, DIO Director, Warden, special teams and other persons specified by the Executive Director or Warden. The Warden shall conduct the meeting, with the Executive Director/designee and DIO Director providing policy decisions, as needed.

3. During the briefing, participants shall:

a. identify problems, develop solutions and specify time lines and approve modified policy changes;

b. provide status reports;

c. coordinate support services involvement; and

d. conduct final review of count down procedures.

B. Food Services

1. The condemned shall be fed at specifiedtimes

2.

3. Refer to TMF 01/05.18

C. Visits

1.

2.

D. Restricting Access to Prison Property

1.

a.

b.

c.

d.

e.

2.

a.

b.

3.

E.

1.

2.

3.

4.

TMF 01/03.04

A.

1.

a.

b.

c.

2.

a.

b.

c.

3.

a.

b.

c.

4.

a.

b.

B.

1.

2.

TMF 01/03.05

A. Pre-Execution Procedures

1. The Warden shall ensure that all count-down procedures for all required activities and actions are completed.

2. Immediate action to complete any unfinished required procedures shall be initiated.

B. Execution Site Teams Assemble

1.

2. The Tie-Down Teams and their back-ups will be positioned to await escort of the condemned to the execution chamber.

C. Contact with the Attorney General's Office

1.

a.

b.

(2)

2.

3.

a.

b.

4.

A. Communications with Attorney General's Office

Refer to TMF 01/03.05,C, above.

B. Final Sequence of Events: Preparation

1. Bringing Condemned Inmate to Execution Chamber

The condemned inmate shall be:

a. removed from the observation cell by the Tie-Down Team;

b. dressed in a clean jump suit (the color of the jump suit will be at the discretion of the Warden);

c.

d. escorted to the execution chamber.

2. Tie-Down Procedures

the condemned shall be tied down as explained in TMF 01/05.13(lethal injection) or TMF 01/05.14(firing squad).

3. Prepare Condemned Inmate for Execution

The condemned shall be readied for execution:

a. if lethal injection, by completing the I.V. set-up procedure (See TMF 01/05.15); or

b. if firing squad, by completing the firing squad set-up procedures (See TMF 01/05.16).

4. Admit Witnesses

a. Witnesses shall be admitted and escorted to assigned viewing areas.

b. The government witnesses shall enter first and shall be escorted to the government witness area. The escort shall remain with the witnesses.

c. Following the government witnesses, the authorized witnesses invited by the condemned, and the victim's witnesses shall be admitted and escorted to the designated witness area.

(1) If any of the condemned inmate's invited witnesses, or the victim's witnesses wish to be on-site but not actually witness the execution, accommodations may be made for them.

(2) The escort officers shall remain with the condemned inmate's witnesses and the victim's witnesses.

d. The last witnesses to be admitted shall be the news media representatives.

(1) The members of the news media selected to witness the execution shall be escorted to the designated witness room. They shall be separate from the condemned inmate's witnesses and the victim's witnesses. Escort officers shall remain with the news media witnesses and ensure their separation from the other visitors while at the execution site.

(2) The two pool photographers shall be escorted to a designated site, away from, and out of sight of, the execution chamber. They shall

be secured inside the designated site until after the execution and until such time that they are allowed to film the cleaned up execution chamber.

C. Final Sequence of Events: Execution

1. Staff Witness

a. Staff participating in the preparation for the execution shall exit the execution site.

b. Staff members remaining to participate in and observe the execution shall include the:

(1) Executive Director/designee;

(2) Executive Director's back-up;

(3) DIO Director;

(4) Warden;

(5) Executioners;

(6) Escort Officers; and

(7) other staff as designated by the Executive Director/designee, DIO Director, or Warden.

2. Count-Down

a. At the designated hour mandated for the execution, when everything is ready, the phone communication shall be terminated and the Executive Director/designee shall instruct the Warden to proceed with the execution.

b. The Warden and DIO Director shall pull open the curtains covering the witness room windows.

c. The Warden shall ask the condemned inmate if he has any last words or wishes to make a statement.

(1) The statement should not exceed two minutes.

(2) If the inmate uses foul language, the Warden should immediately proceed with the next step in the execution procedure.

(3) If the statement exceeds two minutes, the execution shall proceed without waiting for the conclusion of his remarks.

(4) Audio recording equipment may be used by the Department for the purpose of recording the defendant's last words. The Department shall permanently destroy the recording made under this subsection not later than 24 hours after the completion of the execution.

d.

e. The Executive Director/designee shall instruct the executioners in the case of death by injection, or the firing squad leader in the case of a firing squad execution to proceed with the execution:

(1) upon receiving the Warden's signal to proceed;

(2) after verifying the earliest legal execution time has passed; and

(3) if no instruction to halt has been received from the Attorney General's Office.

f. Following the instruction from the Executive Director/designee to execute the condemned inmate, the executioners shall immediately proceed with the execution as required in TMF 01/05.15(if by lethal injection) or TMF 01/05.16(if by firing squad).

q. If the execution is ordered delayed

the Executive Director shall instruct the executioners to step away from the execution equipment and shall notify them that the execution has been stayed or delayed. The procedures set forth under TMF 01/06 shall then be initiated.

TMF 01/04.00 POST-EXECUTION PROCEDURES

TMF 01/04.01 General Provisions
TMF 01/04.02 Certification of Death
TMF 01/04.03 Removing Witnesses from Execution Chamber
TMF 01/04.04 Removal of Executed Inmate
TMF 01/04.05 Removing Executioners from the Execution Area
TMF 01/04.06 Site Clean-Up
TMF 01/04.07 News Media Re-Entry to Execution Site
TMF 01/04.08 Returning to Standard Operation
TMF 01/04.09 Audit of Execution
TMF 01/04.10 Post-Execution Countdown Schedule

TMF 01/04.00 POST-EXECUTION PROCEDURES

TMF 01/04.01 General Provisions

A. Purpose of Chapter

The purpose of this chapter is:

1. to provide the procedures to be followed following the death by execution of the condemned inmate;

2. to identify the responsibilities for tasks to be completed; and

3. to provide for the transfer of the body of the condemned from the custody of the Department.

B. Policy

It is the policy of the Department that:

1. the witnesses to the execution shall be removed from the execution chamber for the news media witnesses who shall be removed to a secondary location until permitted to return for a filming opportunity in the execution chamber;

2. the condemned inmate shall be examined by a licensed physician following the administering of the fatal drugs or the first volley by the firing squad to ensure that death has occurred;

3. the physician, when satisfied that death has occurred, shall certify the condemned inmate dead;

4. following the certification of death, the body of the condemned shall be surrendered to the State Medical Examiner;

5. after removal of the body, the chamber shall be restored and the news media permitted to return to photograph the chamber;

6. after the chamber has been photographed, the news media shall be returned to the designated area to brief the other assembled members of the news media;

7.

8. the entire execution process will be reviewed and evaluated by the AuditBureau to permit a post-execution examination of the competence, efficiency and effectiveness of the execution procedures and staff (see TMF 01/20).

TMF 01/04.02 Certification of Death

A. After the drugs have been administered/or the execution completed by firing squad:

1. the Warden shall wait a maximum of three minutes;

2. the Warden shall then tell the DIO Director/designee to summon the attending physician to the condemned; and

3. the physician shall take the condemned's vital signs.

B. If there are signs of life, the physician shall wait beside the condemned and check the vital signs every 60 seconds until vital signs cease.

C. If execution is by firing squad, and if after a maximum of ten minutes from the first volley, there are still signs of life, the physician will inform the Warden. The Warden will then initiate the steps in TMF 01/05.16.

D. When no vital signs are detected, the physician shall certify death in keeping with standard medical practices.

TMF 01/04.03 Removing Witnesses from Execution Chamber

2. The Medical Examiner, or his designee, may issue the death certificate for deaths that occur at the prison. (UCA 26-4-7, 26-4-10)

TMF 01/04.05 Removing Executioners from the Execution Area

A.

B.

C.

TMF 01/04.06 Site Clean-Up

A. The injection team shall (if execution was by lethal injection):

1. use universal precautions and protective equipment to protect for blood or other potentially infectious materials;

2.

3.

4.

5.

B. The Tie-Down Team shall be responsible for:

1. using universal precautions and protective equipment to protect against blood and other potentially infectious material; and

A. After the certification of death by the physician, the curtains shall be closed by the Warden and DIO Director/designee and the witnesses shall be escorted from the witness viewing rooms

1.

2.

3.

4.

5.

B. The news media shall be escorted to an alternate location in the execution building until they can be returned for the filming opportunity after the execution chamber has been cleaned up.

C. The condemned inmate's witnesses, government witnesses, and the victim's witnesses shall be escorted to waiting transportation vehicles

D.

TMF 01/04.04 Removal of Executed Inmate

A. After the witnesses have been removed:

1. if the execution is by lethal injection, the IV should be cut by the executioners in order for the catheters to remain in the executed inmate's body; and

2.

B. The State Medical Examiner/designee shall be escorted into the death chamber

1. The State Medical Examiner has jurisdiction over all deaths that occur at the Utah State Prison. (UCA 26-4-7)

2. cleaning up the execution site, using universal precautions where appropriate.

TMF 01/04.07 News Media Re-Entry to Execution Site

A. After the site is restored and cleaned, the news media witnesses and pool photographers shall be escorted to the execution site.

B. The photographers shall be permitted to tape/photograph the site and observation cell (if approved by the Warden) as required in TMF 01/08.

C.

TMF 01/04.08 Returning to Standard Operation

A.

1.

2.

B.

C.

TMF 01/04.09 Review of Execution

Refer to TMF 01/20.

TMF 01/04.10 Post-Execution Countdown Schedule

See Exhibit 04-1 for the proposed schedule for the post-execution period.
(Sample for Lethal Injection)

Execution

_____
Date

0005 DIRECTOR/DESIGNEE GIVES WARDEN OK TO BEGIN EXECUTION
0005 TO 0006 CURTAINS PULLED
0006 TO 0008 LAST STATEMENT BY CONDEMNED
0008 SIGNAL BY WARDEN TO BEGIN EXECUTION
0023 SIGNAL BY EXECUTIONER THAT DRUGS HAVE BEEN ADMINISTERED
0024 DOCTOR BROUGHT INTO EXECUTION CHAMBER
0027 DOCTOR PRONOUNCES DEATH AND DEATH WARRANT SIGNED
0028 CURTAINS CLOSED
0029
0030
0031
0034 TIE DOWN TEAM/MEDICAL EXAMINER INTO DEATH CHAMBER TO REMOVE BODY
0036
0037

0038 CLEAN UP CREW INTO DEATH CHAMBER
0039
0040

0040 WARDEN GIVES DIRECTIVE FOR MEDIA TO RETURN TO EXECUTION CHAMBER
0100 MEDIA RETURNED TO STAGING AREA

(Sample for Firing Squad)

Execution Time Line

_____
Date

0005 DIRECTOR/DESIGNEE GIVES WARDEN OK TO BEGIN EXECUTION
0005 TO 0006 CURTAINS PULLED
0006 TO 0008 LAST STATEMENT BY CONDEMNED
0008 SIGNAL BY DIRECTOR/DESIGNESS TO BEGIN EXECUTION
0011 DOCTOR BROUGHT INTO EXECUTION CHAMBER
0014 DOCTOR PRONOUNCES DEATH AND DEATH WARRANT SIGNED
0015 CURTAINS CLOSED
0017
0018
0019
0021 TIE DOWN TEAM/MEDICAL EXAMINER INTO DEATH CHAMBER TO REMOVE BODY
0023
0025

0026 CLEAN UP CREW INTO DEATH CHAMBER
0031 WARDEN GIVES DIRECTIVE FOR MEDIA TO RETURN TO EXECUTION CHAMBER
0050 MEDIA RETURNED TO STAGING AREA

TMF 01/05.00 EXECUTION PROCEDURES

TMF 01/05.00 EXECUTION PROCEDURES

TMF 01/05.01 General Provisions

A. Purpose of Chapter

1. This chapter provides the procedures which are used when the Department exercises its statutory responsibility to carry out an execution.

2. The topics include those procedures which are employed:

a. immediately prior to receiving the death warrant;

b. from receiving the death warrant to and during the execution;

c. immediately following the execution; and

d. during the debriefing and audit phases of the execution.

B. Policies

1. It is the policy of the Department that the procedures employed in preparing for and carrying out an execution be comprehensive and clearly defined.

2. The procedures shall be developed consistent with state and federal law.

TMF 01/05.02 Death Warrant

A. Judgement of Death

1. When judgment of death is rendered, a warrant signed by the judge and attested by the clerk under the seal of the court, shall be drawn and delivered to the sheriff of the county where the conviction is made. 77-19-6 UCA

2. The Sheriff shall deliver the warrant and a certified copy of the judgment to the UDC Executive Director/designee at

the time of delivering the defendant to the custody of the Department. 77-19-6 UCA

3. The warrant states the conviction and judgment, the method of execution, and the appointed day the judgement is to be executed. The Department of Corrections shall determine the hour, within the appointed day, at which the judgement is to be executed.

B. Return Upon Death Warrant

1. After the execution, the UDC Executive Director/designee shall make a return upon the death warrant showing the time, place and manner in which it was executed. 77-19-12 UCA

   a. The "Certificate of Execution":

      (1) shall be signed by the Warden and the physician; and

      (2) shall include the full names and official titles of the official witnesses.

   b. The "Certificate of Execution" shall be submitted for review to the Executive Director/designee.

   c. Following review by the Executive Director/designee, the "Certificate of Execution" shall be returned to the Warden.

2. The "Certificate of Execution" shall be directed by registered mail to the clerk of the court of the county from which the individual executed was sentenced.

3. A return receipt shall be requested from the recipient.

4. A copy of the certificate shall be placed in the deceased inmate's file.

A. Statutory Requirements

1. The Executive Director/designee shall ensure that the method of judgment of death specified in the warrant is carried out at a secure correctional facility operated by the department at an hour determined by the department on the date specified in the warrant. 77-19-10 (1) UCA

2. When the judgment of death is to be carried out by lethal intravenous injection, the executive director of the department or his designee shall select two or more persons trained in accordance with accepted medical practices to administer intravenous injections, who shall each administer a continuous intravenous injection, one of which shall be a lethal quantity of sodium thiopental or other equally or more effective substance sufficient to cause death. 77-19-10 (2) UCA

B. Selection of Execution Team

1. If the judgment of death is to be carried out by intravenous lethal injection, a minimum of two persons, each trained to administer intravenous injections shall be selected for the IV team.

2. Method of Selection

a. The DIO Director/designee and the Warden of the Utah State Prison, Draper site, shall be members of the execution team by virtue of their official position.

b. The Executive Director/designee, DIO Director/designee and the

Warden shall select a minimum of four (4) additional members, other than the DIO Director/designee and Warden, for the execution team.

1. Of the four (4) additional members, a minimum of two (2) execution team members will be on the IV team.

2. No member of the execution team, other than the DIO Director/designee and Warden, shall be required to serve as a member of the execution team without consent.

3. The Executive Director/designee, DIO Director/designee, and Warden will designate one execution team member as the execution team leader.

   a. The execution team leader shall not be the DIO Director/designee or the Warden; and

   b. The execution team leader shall not be a member of the IV team.

4. The Executive Director/designee, DIO Director/designee, and Warden shall review the qualifications of the IV team members according to requirements outlined in subsection (3)(a through d) and other relevant information as to appropriate training and skills in administering intravenous injections. One IV team member will be designated as the IV team leader.

c. Following the examination and evaluation of candidates, the Executive Director/designee, DIO Director/designee and Warden, shall

select the execution team members.

d. All execution team members shall read and understand the execution procedures. The Warden shall conduct a review of the execution procedures annually.

3. IV Team Qualifications

a. At least two (2) members of the execution team shall be designated as the IV team for an execution by lethal injection.

b. Each member of the IV team shall be a:

1. Phlebotomist;

2. Emergency Medical Technician;

3. Paramedic; or

4. Military Corpsman.

c. Each member of the IV team shall:

1. Have at least one (1) year of professional experience in his specialty;

2. Remain certified in his specialty or profession; and

3. Fulfill all continuing education requirements in his specialty or profession.

d. Prior to participating in an execution, the members of the IV team shall have participated in at least three (3) complete execution practices.

4. Securing Services

a. The Warden/designee shall contact those chosen for the execution team to notify them of their selection and verify their willingness and availability to perform the duties of execution by lethal injection.

1. If any person declines participation, the Executive Director/designee, DIO Director/designee and Warden will select a replacement according to the processes outlined in this section.

2. If all of the execution team members agree to participate, their individual roles as execution team members shall be explained to them.

b.

TMF 01/05.04 Selection of Executioners by Firing Squad

A. Statutory Requirements

1. "The Executive Director of Corrections/ designee shall ensure that the method of judgment of death specified in the warrant is carried out at a secure correctional facility operated by the Department of Corrections." 77-19-10(1) UCA

2. "If the judgment of death is to be carried out by firing squad, the Executive Director of Corrections or his designee shall select a five-person firing squad of peace officers."77-19-10 (3) UCA

B. Selection of Executioners

1. A five-person execution team, plus twoalternates and a team leader shall be chosen for the firing squad.

2. The alternate(s) shall be selected to replace any member(s) of the firing squad who are unable to discharge their required functions.

3. Persons selected for the firing squad shall be POST certified peace officers.

4. Selected peace officers will be required to demonstrate proficiency with weapons designated to carry out the execution.

   a. Under conditions substantially similar to those of the execution chamber, proficiency shall be exhibited by:

      1. Firing each weapon.

      2. At a minimum of 21 feet, accurately hitting the target of the same dimension as that which will be attached to the condemned.

   b. During the proficiency test, failure to accurately hit the specified target with one round from each weapon fired shall disqualify the officer.

5.

C. Method of Selection

1. The Executive Director/designee, DIO Director and Warden shall be responsible for the selection process.

2.

3. The final choice of firing squad members shall be the responsibility of the Executive Director/designee, DIO Director and Warden.

4. The Executive Director/designee, DIO Director/designee and Warden shall review the qualifications of the firing squad, including required proficiency as outlined in section (B4) and other relevant information.

D. Securing Services

1. The Executive Director and/orWarden shall contact those chosen for the firing squad, alternates and team leader to notify them of their selection and to verify their willingness and availability to perform the execution duties.

   a. If any person rescinds his original offer to participate, the selection team shall meet to select a replacement.

   b. If all of the selectees agree, their individual roles shall be explained to them.

2.

TMF 01/05.05 Designation of Persons Required, Permitted or Prohibited from Witnessing the Execution

A. The Utah Code limits and identifies those persons who may attend and witness the execution. (See TMF 01/07.03.)

B. The Warden shall designate the required personnel to carry out the statutory requirements of an execution. Staff should include:

1. Deputy Warden;

2. Observation Officers

3. Tie-down Officers,

4. one Team Foreman for the escort/Tie-Down Team;

5. executioners (reference TMF 01/05.03 & .04);

6. Clean-up Officers (number to be determined by the Warden/designee), assigned to clean up the execution chamber immediately following the execution;

7. Guide Officers (number to be determined by the Warden/designee);

8.

9.

C. The Warden/designee shall designate the appropriate resources necessary to carry out the requirements of an execution. The designated individuals shall be responsible for:

1. advising the Warden concerning any medical supplies, etc.;

2. the preparation and supervision of meals prepared during the observation period, and for the condemned inmate's last meal;

3. ordering, verifying, picking-up the drugs, equipment, etc., necessary to carry out an execution by lethal injection; and

4. pronouncing the death of the condemned inmate.

TMF 01/05.06 Disposition of Condemned Inmate's Property

A. Contact with Condemned Inmate

1. At least 30 days prior to the scheduled execution the condemned inmate should be contacted to discuss arrangements for disposing of his property.

2. At least 14 days prior to the execution property-disposition arrangements should be finalized.

3. At least seven days prior to the execution all paperwork required for final disposition should be completed.

4. If the condemned is uncooperative, doesn't wish to make specific property-disposition arrangements, or for any other reason has not made arrangements for disposition, he shall be notified the property will be disposed of as required under 64-13-15 (1) UCA.

B. Options for Disposing of Property

1. Property may be released to an authorized visitor (family, friend or attorney). The release would follow the normal property release procedures.

2. Property may be mailed through the U.S. Postal Service. The prison's Mail Unit shall process the mailing consistent with standard mail procedures. Indigent status does not cover property-release postage.

3. Property may be donated to a charitable organization.

4. If the condemned fails to designate a property-disposition option:

"if property is not claimed within one year of death...it becomes property of the state and may be used for correctional purposes or donated to a charity within the state." 64-13-15 (1) UCA

C. Release Procedure

1. Following a decision to release the condemned's property, the property shall be:

a. inventoried by staff; and

b. transferred to the property room.

2. The release will then follow according to the appropriate release procedures. Refer to FDr14, "Inmate Property" and FDr03, "Inmate Mail."

TMF 01/05.07 Disposition of Money in Inmate Account

A. Contact with Condemned Inmate

Follow the time-table for contact with the condemned outlined for property under TMF 01/05.06.

B. Options for Disposing of Inmate Accounts

1. The condemned shall be required to complete a money transfer form releasing the money in his account to his next of kin or other person or organization of his choice.

2. If the condemned refuses or otherwise fails to complete the necessary forms, the funds shall be disposed of consistent with state law.

TMF 01/05.08 Disposition of the Body of the Condemned

A. Release to Medical Examiner

1. After the executed inmate is pronounced dead, the body shall be released from the restraints and removed from the execution chamber.

2. The body shall be immediately surrendered to the State Medical Examiner/designee.

TMF 01/05.09 Equipment Check/Inventory: Lethal Injection

A. Responsibility

1. The IV team shall conduct a check of equipment and materials necessary to conduct the execution.

2.

B. Inventory

1.

2.

3.

a.

b.

4.

C. Bloodborne Pathogen Precaution

1. As a precaution, all persons who may come in contact with the condemned's body fluids shall be issued rubber

gloves and bloodborne pathogen protection supplies and equipment.

TMF 01/05.10 Equipment Check/Inventory: Firing Squad

A. The Warden shall ensurean equipment check of appliances necessary to carry out an execution.

B.

1.

2.

3.

4.

5.

6.

7.

C. The execution team leader shall be responsible to arrange for:

1. .30-caliber rifles;

2. live rounds of ammunition;

3. blank rounds of ammunition;

4. practice sessions and dry fire;

5. ensuring equipment is clean and operable; and

6. back-up equipment for items 1, 2, 3, above.

D. prior to the execution:

1. the executioners shall be escorted into the execution chamber by the DIO Director/designee; and

2.

E. Bloodborne Pathogens Precaution

As a precaution, all persons who may come in contact with the condemned's body fluids shall be issued rubber gloves and bloodborne pathogen protection supplies and equipment.

TMF 01/05.11 Procurement, Storage and Accountability of Chemicals for Lethal Injection

A. Purchase

1. the Warden shall provide to the pharmacist for his official records a memorandum specifying:

a. The drugs which must be obtained;

b. A copy of the judgment of death; and

c. A copy of the state statute. 77-19-10(2) UCA

2. the pharmacist shall order the drugs from the vendor. Upon receiving the drugs, the pharmacist shall:

a.

b. Immediately notify the Warden that the drugs have been received;

c.

d.

e.

1.

2.

3.

4.

f.

3. Storage and Handling of Drugs

a.

b. See the next two pages for the Equipment and Materials Checklist.

Quantity	Item	Code
	Sodium Thiopental (Pentathal), 500 mgm., w/diluent	A
	Pancuronium Bromide (Paravulon), 50 mgm. Ampules	A
	Potassium Chloride, 240 miliequiv. Ampules	A
	Valium injection, 10 mgm	A
	Syringe, 60 cc Lur Lock	
	Syringe, 10 cc Lur Lock	
	Syringe, 5 cc Lur Lock	
	Needle, 18 Ga., 1 ½	
	Needle, 25 Ga., 1 ¼	
	Angiocath, 14 Ga., 2 ¼"	
	Angiocath, 18 Ga., 1 ¼"	
	Angiocath, 16 Ga., 1 ¼"	
	Normal saline, IV bad, 1000C	
	Lidocaine HCL, 2% w/Epinephrine	
	Lidocaine HCL, 2% w/o Epinephrine 2	
	Solution injection set, 70" long with	
	Y-injection site: Travenol Code: #2C0005S	
	Extension set, 35" long; Travenol Code #2C0066	
	Stethoscopes	
	Boxes of alcohol preps	
	Rolls of Kling	
	Adhesive tape, 1"	
	Adhesive tape, 2"	
	Scissors, bandage, Pr.	
	Tourniquet	
	Hemostat, sterile	
	Flashlight, w/batteries	A
	Batteries, flashlight, (spares)	A
	Ace wraps 3"	
	Needle holders	
	10 packs sterile gauze	
	Sharp containers	

	BIO-Hazardous trash bags	
	Extra large impervious gowns	
	IV hangars	
	Mayo stand	
	Terry cloth towels	
	Goose neck light	
	Blood spill kits	
	Trash containers	
	Electronic Heart Monitor (EKG)	

TMF 01/05.12 Observation Period and Related Activities

A. Access

1.

2.

3.

B. Preparation of the Observation Cell

1.

a.

b.

c.

2. Stocking the Cell

a. The observation cell shall be outfitted with the following items:

(1) mattress (1);

(2) pillow (1);

(3) pillow case (1);

(4) sheets (2);

(5) blankets (2);

(6) towel (1);

(7) soap, small (1);

(8) toilet paper, roll (1);

(9) jump suit (color to be determined by the Warden) (1);

(10) socks (1 pr.);

(11) shower thongs (1 pr.); and

(12) pocket comb, no metal (1).

b. If requested, the cell will also have the following items purchased new

(1) Bible (1);

(2) magazine

(3) newspaper
; and

(4) photographs
.

c. The following items may be given on request, as needed,

(1) toothbrush (1);

(2) toothpaste

(3)

d. If the condemned inmate receives mail the officer shall allow the condemned inmate adequate time to read the mail

f.

g. Additional property shall be approved by the warden.

3. Test Equipment

a.

b.

C.

1.

2.

3.

4.

5.

6.

a

b.

D. Securing Condemned Inmate's Property/Cell

1.

2.

3.

b.

(1)

(2)

(3)

(4)

c.

(1)

(2)

(3)

(4)

4. Personal property shall be separated from prison property, and the personal property put into a suitable container and sealed. Each search team member shall initial the seal.

5. The designated property officer shall sign for and assume responsibility for the inventoried property.

6.

a.

b.

7.

8. The personal property shall be taken to the DIO property room for storage.

E. Observation Function

1.

a.

b.

c.

d.

e.

f.

g.

2.

a.

b.

3.

4.

5.

F. Activities During the Observation Period

1.

2. Unless previously served, meal service, including the last meal, shall be served during the observation period.

3.

4.

a.

b.

c.

TMF 01/05.13 Tie-Down Procedures: Lethal Injection

A. Transfer of Condemned Inmate to Execution Site

1. The condemned inmate shall be escorted from the observation cell to the execution chamber by the Tie-Down Team.

2.

a.

b.

c.

d.

B. Positioning of Tie-down Team

1.

2.

3.

4.

5.

C. Securing Inmate to Gurney

1.

2.

a.

b.

c.

d.

e.

f.

g.

3.

4.

5. Upon completion of the execution and as directed by the Warden, the Tie-Down Team shall enter the execution chamber and remove the straps in the reverse order as outlined above.

TMF 01/05.14 Tie-Down Procedures: Firing Squad

A. Bringing Condemned Inmate to Execution Chamber

The condemned inmate should be escorted from the observation cell to the execution chamber by the Tie-Down Team

B. Positioning the Tie-Down Team

1.

2.

3.

4.

C. Securing the Inmate to the Chair

1.

2.

a.

b.

3.

4.

5. Upon completion of the execution and as directed by the Warden, the Tie-Down Team shall re-enter the execution chamber and remove the straps in reverse order as outlined above.

TMF 01/05.15 Lethal Injection Protocol

A.

1.

2.

B. Preparation of Syringes

1.

a.

b.

c.

2. The execution team leader shall providethe drug box to the IV team leader.

a. The IV team leader shall prepare each chemical in accordance with the manufacturer's instructions and draw them into the two (2) sets of syringes.

b. The second member of the IV team and the execution team leader shall observe preparation of the chemicals and verify that the instructions and procedures have been carried out correctly.

c.

3. The syringes containing the chemicals shall be prepared and loaded in the following order:

a. Two 60-cc syringes, each containing 240 milliequivalents of Potassium Chloride in 50-cc and label syringes "Syringe #3.

b. Two 60-cc syringes, each containing fifty (50) milligrams of Pancuronium Bromide in 50-cc and

label syringes "Syringe #2".

c. Two 60-cc syringes, each containing three (3) gm of Sodium Thiopental in 50-cc and label syringes "Syringe #1".

d. The secondary syringes containing each of the three chemicals are to serve the following purposes.

1. Secondary syringe of Sodium Thiopental is prepared in the event the condemned has not lost consciousness sixty (60) seconds after the first administration of the chemical.

2. Secondary syringes containing Potassium Chloride and Pancuronium Bromide are prepared in the event the condemned has not been pronounced dead after the first administration of the chemicals.

4. Any syringes that are loaded with lethal injection chemicals that are not used during the execution shall:

a. Be returned to the Warden by the execution team leader;

b. Be destroyed by the Warden,

5. Any unused chemicals that were not mixed in preparation of the lethal injection shall:

a. Be returned to the Warden by the IV team leader;

b. Be destroyed by the Warden,

C.

D.

E. The IV team leader:

1. Shall, along with the second IV team member, verify two (2) labeled sets of each of the three (3) chemicals are present, filled, and clearly labeled;

2. Provide the two (2) labeled sets of each of the three (3) chemicals contained in the drug box to the execution team leader who will verify, along with another execution team member, selected by the execution team leader, the appropriate number of syringes have been surrendered and are clearly labeled; and

3. Prepare the IV set-up.

F. IV Set-up Procedure by IV Team

1. The connector of Administration Set (McGaw V1417 or equivalent) shall be inserted into the bag of Normal Saline IV solution.

2. The Flo Trol clamp located above the "Y" site shall control the flow of solution.

3. A 35-inch Extension Set (Travenol 2C0066 or equivalent) shall be connected to the needle adapter of the Administration Set.

4. The set-up for administration into the back-up IV site may require additional Extension Sets due to the potential of additional distance.

5. All connections should then be taped to ensure they do not come apart during the procedure.

6. The tubing shall be cleared of air by removing the protector from the needle adapter and opening the Flo Trol clamp letting the tube fill with solution.

7. The Flo Trol clamp shall then be closed and the protective cap over the needle adapter replaced.

8. Steps 1 through 7 shall be repeated for the second set-up.

G. Injection Procedure by IV Team

1. The Warden shall order the condemned person escorted to the execution chamber and strapped to the gurney.

2. The IV team shall run the IV lines to the condemned person by the following:

   a. Site and insert one (1) primary IV line; and

   b. Site and insert one (1) back-up IV line.

3. The IV team members shall determine the location of the IV sites on the body of the condemned person.

4.

   a.

   b.

   c.

   d.

H. IV Placement Process by IV Team

1. The angiocath shall be inserted into the vein of the primary IV site.

2. To best ensure that a needle is inserted properly into a vein, the IV team members shall look for the presence of blood in the valve of the sited needle.

3. The inner needle is then withdrawn and the needle adapter is placed on the angiocath.

a.

b.

4. The flow of normal saline shall be started and administered at a slow rate to keep open.

5. Step 1 through 3 shall be repeated for the back-up IV site.

6. The Administration Sets shall be running at a slow rate of flow, to keep open and ready for the insertion of syringes containing the injection chemicals.

7. Both set-ups shall be observed by the IV team members to ensure they are both patent and functioning properly.

8. No further action is necessary at this time.

I. Lethal Injection Procedure

1. The execution team shall:

a. Securely connect the electrodes of the cardiac monitor to the condemned person; and

b. Ensure the equipment is functioning properly.

2. At the designated hour mandated for the execution, when everything is ready:

a. The DIO Director/designee and Warden shall pull open the curtains covering the witness room windows.

b. The Warden shall ask the condemned inmate if he has any last words or wishes to make a statement.

1. The statement should not exceed two minutes.

2. If the inmate uses foul language, the Warden should immediately proceed with the next step in the execution.

3. If the statement exceeds two minutes, the execution shall proceed without waiting for the conclusion of his remarks.

4. The Department, for the purpose of recording the condemned inmate's last words, may use audio recording equipment.

a. The Department shall permanently destroy the recording made under this subsection not later than 24 hours after the completion of the execution.

b. No form of duplication of the audio shall be permitted.

c. The Warden, witnessed by the DIO Director/designee, shall

destroy any audio recording.

c. At the conclusion of the remarks, or when the Warden determines it is time to proceed, a prearranged signal shall then be given by the Warden to the Executive Director/designee.

d. The Executive Director/designee shall order the execution team leader to begin the administration of the chemicals providing:

1. The earliest legal execution time has been verified and has passed; and

2. No instruction to halt has been received from the Attorney General's Office.

e. Following the instruction from the Executive Director/designee to execute the condemned inmate, the execution team leader shall immediately proceed with the execution.

f.

1.

2.

3.

3. Upon the Executive Director/designee's order to proceed, the execution team leader shall begin the following

sequence:

a. The flow of the normal saline into the arm shall be cut off using the Flo Trol clamp.

b. The clamp should be moved as close to the "Y" site as possible.

c. The 18 ga needle of Syringe #1 (three (3) gm of Sodium Thiopental) shall be inserted into the "Y" site and the injection shall commence.

1. A steady, even flow of the injection shall be maintained with only a minimum amount of force applied to the syringe plunger.

2. When the entire contents of the syringe have been injected, syringe #1 shall be removed from the "Y" site.

d. The Flo Trol clamp should then be opened fully and allowed to run for 15 seconds.

e. The Flo Trol clamps shall then be closed.

f. A period of sixty (60) seconds shall pass after the administration of the Sodium Thiopental and closure of the Flo Trol clamp.

1. After the passage of sixty (60) seconds:

a. If it appears to the Warden based on his visual inspection that the condemned person is not unconscious:

i. The Warden shall notify the Executive Director/designee;

ii. The Executive Director/designee

will order the execution team to switch to the back-up IV site;

iii. The Executive Director/designee shall order that the back-up IV site be used with a new flow of Sodium Thiopental (secondary syringe labeled Syringe #1); and

iv. The Executive Director/designee shall order the remaining sequence of chemicals to be injected through the back-up IV site.

2. If it appears to the Warden based on his visual inspection that the condemned person is unconscious after the first injection of Sodium Thiopental, the Warden shall notify the Executive Director/designee who will then order the execution team to continue to the next step in the sequence.

g. The 18 ga needle of Syringe #2 (fifty (50) milligrams of Pancuronium Bromide) shall be inserted into the "Y" site and the injection shall commence;

1. A steady, even flow of the injection shall be maintained with only the minimum amount of force applied to the syringe plunger.

2. When the entire contents of the syringe have been injected, Syringe #2 shall be

removed from the "Y" site.

h. After syringe #2 has been given, the Flo Trol clamp should be opened fully for 15 seconds.

i. The Flo Trol clamp shall then be closed.

j. The 18 ga needle of Syringe #3 (240 milliequivalents of Potassium Chloride) shall be inserted into the "Y" site and the injection shall commence;

1. A steady, even flow of the injection shall be maintained with only the minimum amount of force applied to the syringe plunger.

2. When the entire contents of the syringe have been injected, Syringe #3 shall be removed from the "Y" site.

k. The Flo Trol clamp shall then be opened fully and allowed to run for 15 seconds.

l. The Flo Trol clamp shall then be closed.

m. An execution team member designated by the execution team leader shall start a stopwatch once the lethal injections are complete.

n. The execution team leader shall:

1. Observe the heart monitor; and

2. Advise the attending physician electrical activity of the heart has ceased as indicated by a flat line on the heart monitor.

o. The Warden shall notify the Executive Director/designee if it appears an additional set of lethal chemicals needs to be administered

due to the following conditions:

1. Heart monitor does not indicate a flat line after ten (10) minutes; or

2. The attending physician is not able to declare the time of death after ten (10) minutes.

p. In the event death has not occurred;

1. The Executive Director/designee will order the process established in subsection (2)(f) of this section and subsequent sections to continue with the secondary set of syringes until death has occurred.

q. During the execution by lethal injection, the DIO Director/designee and Warden shall:

1. Watch the primary IV site for failure, leakage, the catheter coming out of a vein, or any other problem.

2. In the event that an IV fails, leaks, if the catheter comes out of the vein, or any other problem arises, the execution team shall be ordered to switch to the back-up IV.

3. In the event the execution team is ordered to switch to the back-up IV, the DIO Director/Warden shall watch the back-up IV site for failure, leakage, the catheter coming out of a vein, or any other problem.

J. Post Lethal Injection Steps

1. When the physician declares death, the Executive Director/designee, DIO

Director/designee and Warden shall be informed.

2. The DIO Director and Warden shall close the viewing room curtains.

3. The Executive Director/designee shall make appropriate contact with the Governor and Attorney General informing them of the completion of the execution.

K. Disposal of BIO-Hazardous Contaminated Items

1. The execution team leader shall place items that have been contaminated with blood or other potentially infectious materials (OPIM) that have the potential to puncture into a puncture proof container (sharps container).

2. The execution team leader shall place other types of blood or other potentially infectious materials in trash containers lined with a red BIO-Hazardous waste bag.

3. The Correctional Medical Administrator shall ensure that the contaminated waste is disposed of in the proper Dumpster.

TMF 01/05.16 Execution by Firing Squad

A.

B.

1. Refer to TMF 01/05.10.

2. The team leader shall load the weapons and prepare to issue them to the members of the firing squad.

3. Two rounds shall be loaded in each weapon.

4. Care shall be taken to preclude any knowledge by the members of the firing

squad of who is issued the weapon with two blank cartridges.

C. The Warden shall direct that an aiming point or target be placed over the condemned inmate's heart.

D. Upon completion of "C", above, the Warden shall direct the person who placed the target to exit the execution chamber.

E. After the target is in place and all witnesses are secured, the Warden shall direct that the viewing room curtains be opened.

F. After all preliminaries are completed, the Warden, at the conclusion of the condemned inmate's last words (which shall not exceed two minutes and cease at any point should the condemned use foul language), shall place the hood over the condemned's head.

(1) Audio recording equipment may be used by the Department for the purpose of recording the defendant's last words.

(2) The Department shall permanently destroy the recording made under this subsection not later than 24 hours after the completion of the execution.

(3) No form of duplication of the audio shall be permitted.

(4) The Warden, witnessed by the DIO Director/designee, shall destroy any audio recording.

G. The DIO Director/designee, Warden, and any other observers shall exit the execution chamber.

H. When the Warden enters the executioners' room and secures the door, if no stay or delay in the execution has been ordered, the Executive Director/designee shall immediately order the firing squad team leader to begin the cadence for the executioners to fire.

I. A designated execution team member shall start a stopwatch once the first volley has been fired.

J. If the condemned inmate appears to be unconscious, upon the order of the Executive Director, the Warden and DIO Director shall re-enter the execution chamber after the first volley.

1. The Warden shall wait a maximum of three minutes after the first volley and then call for the physician to check the vital signs of the condemned.

   a. If there are signs of life, the physician shall wait beside the condemned and check the vital signs every 60 seconds.

   b. When no vital signs are detected, the physician shall certify death in keeping with standard medical practices.

   c. After death is certified, the Warden shall direct that the viewing room curtains be closed.

2. If, after a maximum of ten minutes from the first volley, the inmate is unconscious but alive, the Warden shall direct the physician to make a final check of the condemned's vital signs.

   a. If on final check, vital signs are detected, the Warden shall order the physician to exit the execution chamber.

   b. The Warden and DIO Director shall re-enter the executioner's room.

   d. The Executive Director/designee shall order the firing squad team leader to make the weapons ready to fire.

   e. The Executive Director/designee shall immediately order the firing squad team leader to begin the

cadence for the firing squad to fire a second volley.

f. After the firing of the second volley, the Warden and DIO Director shall re-enter the execution chamber and proceed with paragraph "J,1", above.

K. If, after the first volley is fired, the condemned is obviously conscious, the Executive Director/designee shall instruct the firing squad team leader to immediately prepare the weapons to fire again.

1. The firing squad team leader shall ready the weapons in a controlled and safe manner.

2. The firing squad team leader shall ensure the executioners do not see which weapon contains the blank cartridges.

3. When the weapons are ready, if the condemned is still obviously conscious, the Warden shall ensure no staff members are in the execution chamber.

4. Upon notice from the Warden that the execution chamber is clear, the Executive Director shall immediately order the firing squad team leader to begin the cadence for the executioners to fire a second volley.

5. After the second volley, continue with "J", above.

L. The Executive Director shall make notification of the condemned's death to the Governor and the Attorney General.

TMF 01/05.17 Pre-Execution Rehearsals and Practices

A. A minimum of three rehearsals and practices shall be conducted to carry out an execution in a timely fashion maintaining the necessary

security. Practice/rehearsal shall be provided for but will not be limited to:

1. briefing;

2. removing the condemned inmate from the observation cell;

3.

4. escort to execution chamber;

5. tie-down procedures completed;

6. approximate time for IV injection procedure (execution time approximate);

7. clearing and escorting witnesses to/from execution site;

8. security curtains opened and closed;

9. condemned inmate's body removed from execution table/chair;

10.

11. clean-up;

12. debriefing outlined;

13. firing of weapons; and

14. ensure sufficient precautions are taken to minimize the risk of bio-hazardous exposure.

B. Planning backward from the execution shall be used to develop realistic time lines for each function involved in the execution.

C.

1. Discrepancies, concerns or proposed modifications due to system problems

shall be immediately reported to the Warden.

2.

TMF 01/05.18 Support Services Functions

A. Food Services

1. Observation Period Meal Service

a.

b. The Food Services Director/designee shall confirm the condemned's choice of a last meal. The confirmation should be made 48-24 hours prior to the execution.

c.

d.

e. Alcoholic beverages shall not be served nor used for cooking.

2. Beverage and Food Service for Staff

a. Because of the length of time many persons will be required to remain on site without being able to leave, it may be necessary to serve food and beverages to those assigned to the execution.

b.

c. Food and beverage services may be provided to:

(1) the command post;

(2) the Information Center;

(3) the food preparation area of the building in which the execution will occur;

(4) to the Draper site Security Deputy Warden for delivery to perimeter posts; and

(5) other sites as needed.

d.

B. Medical Staff

1. Receipt of Death Warrant

Upon receipt of the death warrant the Correctional Medical Administrator shall:

a. review the medical procedures, post orders and equipment checklist and make recommendations in writing to the Warden concerning any back-up or duplication of any medical

paraphernalia that may be necessary to carry out an execution; and

b. shall confer with the Chief Physician and assign all execution-related tasks to be completed.

2. Thirteen to Seven Days

a. At least thirteen days prior to the execution the Warden shall provide to the pharmacist, for his official record, authorization to purchase drugs. Authorization shall be in the form of a memorandum including:

(1) the names of the drugs which shall be obtained;

(2) a copy of the judgement of death; and

(3) a copy of the state statute (77-19-10 (2) UCA).

b. At least seven days prior to the execution the pharmacist shall order the drugs from the vendor (refer to chapter TMF 01/05.11).

(1) If the state's prime vendor cannot deliver the drugs, the pharmacists shall make arrangements with other vendors or hospitals to obtain the drugs.

(2) If the drugs cannot be delivered to the prison by the primary vendor or their delivery service to the prison, the pharmacist shall notify the Correctional Medical Administrator.

(2) The Correctional Medical Administrator shall make arrangements with the Draper site Security Deputy Warden to have an officer accompany them

to the location where the other drugs may be obtained.

c.

3.

4.

5.

a.

b.

c.

6.

a.

(1) the sodium pentothal syringes shall be prepared by the pharmacist at the direction of the Warden when it appears the execution shall be carried out;

(2) a medical-response team shall be on standby to provide any medical attention which may be needed during the time of the scheduled execution;

(3) a USP emergency equipment kit and a back-up kit shall be made available at the execution site; and

(4) the Correctional Medical Administrator (CMA)/designee and a USP Medical staff with skills in intravenous injections, I.V. set-up, cut-down, etc., shall be available at the execution site to provide medical assistance in the execution chamber, if necessary.

b. Equipment and lethal drugs shall be gathered up by the CMA/designee following the execution.

(1) The CMA/designee shall be responsible for the disposal of the medical equipment used for lethal injection in accordance with TMF 01/05.15.

(2)

C. Maintenance Staff

1. Receipt of Death Warrant

a. Upon receipt of the death warrant the Deputy Warden Support Services shall:

(1) review the maintenance procedures and the equipment checklist and make recommendations in writing for changes, additional equipment, etc. as is viewed essential

and provide such recommendations to the Warden prior to the scheduled execution date; and

(2) confer with the Maintenance Director and assign all execution related tasks to be completed.

b. The Maintenance Director shall then prepare a task completion calendar which shall be presented to the Deputy Warden Support Services for approval, including:

(1) a review of the maintenance procedure and the equipment checklist;

(2) recommendations to the Warden in writing of changes, additional equipment, etc. as is viewed essential prior to the scheduled execution date;

(3) identification of strategies to ensure that all systems, equipment, and mechanisms associated with the execution facility are functional and are readily repairable given an unexpected malfunction;

(4) identification of emergency equipment, materials, and substances necessary to ensure that system, equipment, and/or mechanism malfunctions are expeditiously remedied;

(5) establishment of inspection checklist and time frames for:

(a) the facility designated for the execution;

(b) the observation cell; and

(c) emergency backup systems;

(6) ensuring that all maintenance service/repair trucks are in good operational condition and supplied with equipment, tools, and supplies necessary to correct all execution related emergencies; and

(7) identification of maintenance personnel necessary to address all execution day maintenance emergencies.

2.

The Maintenance Director shall:

a. complete a pre-inventory check of the necessary equipment; and

b. complete a written report to the Deputy Warden Support Services of equipment, etc. requiring repair, replacement or duplications, including recommendations to correct problems and time frame necessary to make necessary corrections.

3.

The Deputy Warden Support Services shall direct the Maintenance Director to:

a.

c. conduct an inspection of the following equipment:

(1) execution chamber;

(2) observation cell; and

(3) emergency back-up systems and equipment.

4.

a.

(1)

(2)

(3)

b. A pre-inventory check shall be completed to ensure equipment is operational and in proper working order.

5.

a.

(1)

(2)

(a)

(b)

(c)

(3) emergency back-up systems and equipment.

b. Emergency equipment shall be checked to ensure readiness for the execution.

6.

a. Complete the procedures as outlined in 5, above.

b.

c.

d.

(1)

(2)

(3)

(4)

(5)

(6)

TMF 01/07.00 WITNESSES

TMF 01/07.01 General Provisions
TMF 01/07.02 News Media Witnesses
TMF 01/07.03 Designation of Persons Required, Permitted or Prohibited from Witnessing
TMF 01/07.04 Witness Agreement

TMF 01/07.00 WITNESSES

TMF 01/07.01 General Provisions

A. Purpose of Chapter

The purpose of this chapter is to:

1. identify the types and number of witnesses permitted to attend the execution; and

2. to provide legal requirements concerning the witnessing of the execution.

B. Policy

It is the policy of the Department that:

1. procedures for selecting witnesses to the execution shall conform with 77-19-11 UCA;

2. witnesses shall enter into written agreements before being approved for attendance; and

3. witnesses shall be subject to search prior to being admitted.

TMF 01/07.02 News Media Witnesses

A. Members of the news media shall be permitted to witness the execution.

B. Selection shall be at the discretion of the Executive Director/designee.

C. Refer to TMF 01/08 for news media selection procedures.

TMF 01/07.03 Designation of Persons Required, Permitted or Prohibited from Witnessing

A. The Utah Code limits and identifies those persons who may attend and witness the execution.

1. The Executive Director of Corrections or his designee shall:

   a. cause a physician to attend the execution, 77-19-10 (5) UCA; and

   b. permit the attendance at the execution of members of the press and broadcast news media named by the Executive Director of the Department/or his designee, 77-19-11 (4) UCA.

2. At the discretion of the Executive Director of the Department of Corrections/designee, the following may attend the execution:

   a. the prosecuting attorney, or his designated deputy, of the county in which the defendant committed the offense for which he is being executed, 77-19-11 (2)(a) UCA;

   b. no more than two law enforcement officials from the county in which the defendant committed the offense for which he is being executed, 77-19-11 (2)(b) UCA;

   c. the Attorney General or his designee, 77-19-11 (2)(c) UCA;

   d. religious representatives, friends, or relatives designated by the defendant, not exceeding a total of five persons, 77-19-11 (2)(d) UCA; and

   e. unless approved by the Executive Director, no more than five close relatives of the deceased victim, as selected by the Executive Director, but giving priority in the order listed in TMF 01/01.04.

3. The persons enumerated in Subsection (2) may not be required to attend, nor may any of them attend as a matter of right, 77-19-11 (3) UCA.

4. The following persons may also attend the execution:

   a. staff as determined necessary for the execution by the Executive Director of the Department of Corrections/designee; and

   b. no more than three correctional officials from other states that are preparing for executions, but no more than two correctional officials may be from any one state, as designated by the Executive Director of the Department of Corrections or his designee, 77-19-11 (7)(a) UCA.

5. Other necessary staff designated by the Executive Director of the Department of Corrections/designee shall be permitted to the execution.

   a. The "necessary staff" shall include those persons identified in the post orders and procedures in TMF 01.

   b. "Necessary staff" shall not be limited to members of the Utah Department of Corrections but may include members of allied agencies assisting with the execution.

6. The Department is empowered and directed by 77-19-11 (8) UCA to adopt rules governing the attendance of persons at the execution.

7. No person under the age of 18 may attend the execution.

B. For those persons who shall carry out the execution or serve in support roles in the execution area, refer to TMF 01/05.05 B, C.

TMF 01/07.04 Witness Agreement

(See following page for Witness Agreement.)

Rules of Conduct for Witnesses Observing an Execution at the Utah State Prison

1. That you will not bring onto prison property anything constituting legal or illegal contraband under any applicable statute, rule, or policy including any firearm, dangerous weapon, implement of escape, explosive, spirituous of fermented liquor, medicine, poison, or any other item creating a threat to the safety, security, or management of the prison;

2. That you agree to submit to a reasonable search for contraband and other searches as considered necessary by the Department for entry to Department prison and staging area property;

3. That you conduct yourself in a lawful and orderly manner;

4. That you comply with all lawful directives of correctional personnel while on Department property;

5. That you will not bring to the execution site any photographic or recording equipment; and

6. That you understand that the Department of Corrections will not provide mental health services to witnesses.

7. That you understand the Department of Corrections is required to record/report the names of all witnesses in attendance as well as provide the information to media representatives.

I have read the above rules and agree to abide by them. I understand that my failure to comply with the rules will result in my immediate removal from Department of Corrections property and that I may be subject to criminal prosecution.

_____ _____

Signature of Witness Date

_____ _____

UDC Representative Date

TMF 01/08.00 NEWS MEDIA PROCEDURES

TMF 01/08.01 General Provisions
TMF 01/08.02 News Media Selection
TMF 01/08.03 Alternate Coverage/Accommodations
TMF 01/08.04 News Media Attendance at the Execution
TMF 01/08.05 Limitations on Coverage
TMF 01/08.06 News Media Briefing
TMF 01/08.07 News Media Support and Equipment
TMF 01/08.08 Media Representative Agreement

TMF 01/08.00 NEWS MEDIA PROCEDURES

TMF 01/08.01 General Provisions

A. Purpose of Chapter

The purpose of this chapter is:

1. to provide the policies, procedures and requirements for providing access to the execution and information relating to the execution to the news media;

2. to provide the procedure for:

   a. releasing background information;

   b. releasing information during the execution;

   c. coverage of the execution; and

3. to provide requirements for safeguarding the institution and protected information.

B. Policy

1. It shall be the policy of the Department to permit press access to the execution and information concerning the execution consistent with the requirements of the constitutions and laws of the United States and state of Utah.

2. The Department is generally required to provide no more access to the news media, to the inmates and facilities it supervises and controls than that available to the general public.

3. The Department and the Utah Code recognize the need for the public to be informed concerning executions conducted by the Department of Corrections.

   a. The Department will participate and cooperate with the news media to inform the public concerning the execution.

   b. Information should be provided in a timely manner.

4. If the condemned is willing, the Department may allow an opportunity forthe condemned to speak with the news media. If allowed, the interview may:

   a. include those members of the news media selected to witness the execution;

   b. include additional members of the news media authorized by the Department, but not including more than one reporter from the same agency; and

   c. be held at a time and location determined by the Department.

5. During exigent circumstances, communication may be temporarily suspended until the situation has been stabilized. Exigent circumstances shall include, but not be limited to:

   a. riots;

   b. hostage situations;

   c. fires or other disasters; or

   d. other inmate disorders.

6. Refer to Chapter AGr05,"Media Relations" for general news media access to information, inmates and facilities.

TMF 01/08.02 News Media Selection

A. Number in Attendance

The Department shall permit members of the press and broadcast news media to witness the execution.

B. Authority to Select

The Executive Director/designee shall be responsible for selecting the members of the

news media who will be permitted to witness the execution. 77-19-11(4) UCA

C. Selection Process

1. After the court sets a date for the execution of the death penalty, news directors or editors may submit a written list of news media witnesses (one per organization) and other news personnel needed at the execution, to the attention of the Executive Director at least 30 days prior to the execution. When administrative convenience or fairness to the news media dictates, the Department in its discretion may extend the request deadline.

2. Requests for consideration may be granted by the Executive Director/designee provided they contain the following:

   a. a statement setting forth facts showing that the requesting individual falls within the definition of "member of the press and broadcast news media" set forth in these regulations;

   b. an agreement to act as a pool representative as described in these regulations;

   c. an agreement that the media member will abide by all of the conditions, rules and regulations while in attendance at the execution; and

   d. agreement that they will conduct themselves consistent with existing press standards.

3. Upon receipt of a news director's or editor's request for permission for news media witnesses to attend the execution, the Executive Director/designee may take such steps as he deems necessary to verify the statements made in the request. After verifying the information in the requests, selection

of witnesses shall be made by the Executive Director/designee.

4. The Executive Director/designee shall identify the media members who have been selected to witness the execution. Media members shall be selected on a rotating basis from the following organizations:

   a. Salt Lake daily newspapers;

   b. television stations licensed and broadcasting daily in the State of Utah;

   c. one newspaper of general circulation in the county in which the crime occurred;

   d. one radio station licensed and broadcasting in the State of Utah; and

   e. the remainder from a pool of broadcast, print and wire services news media organizations operating in Utah.

5. In the event that the Executive Director is unable to name a news media witness from each of the above-described organizations, he shall name other qualifying media members to attend.

6. No news media witnesses other than those named to attend the execution as described in this chapter shall be permitted to witness the execution.

D. Pool Photographers

1. Two photographers shall be appointed as pool photographers to photograph/film the execution chamber following clean up.

2. The pool photographers may be selected from agencies other than those

represented among those witnessing the execution.

TMF 01/08.03 Alternate Coverage/Accommodations

A. Additional Media Selected

1. The Executive Director may designate additional members of the press and broadcast news media who request and receive permission to be allowed at a location designated by the Executive Director on prison property during the execution.

2. The additional media selected shall be from both the print and broadcast media.

B. Alternate Location

1. The alternate location shall be a press briefing area.

2. Media members must contact the Department's Public Affairs Director at least 14 days prior to the execution date to make any special arrangements for hook ups or other necessary arrangements. Any expense incurred shall be borne by the specific news media requiring special equipment or hook ups.

3. No special access nor briefings will be provided to members of the press who are not selected as witnesses nor selected for the alternate site.

4. The alternate site shall be made available to the selected members of the news media at 1700 hours the day prior to the scheduled execution date.

C. Briefing Media at the Alternate Site

1. The Public Affairs Director shall arrange for:

a. pre-execution briefings;

b. distribution of media briefing packages;

c. briefings throughout the execution event; and

d. post-execution briefings by the news media who witnessed the execution.

2. The news media witnesses to the execution shall be returned to the media briefing area to answer questions from media members at the alternate site.

TMF 01/08.04 News Media Attendance at the Execution

A. The Warden/designee shall permit the members of the press and broadcast news media, selected by the Executive Director/designee in accordance with these regulations, to witness the execution.

B. Each news media witness attending the execution shall be carefully searched prior to admittance to the execution chamber.

1.

a. Electronic or mechanical recording devices include, but are not limited to, still, moving picture or video cameras, tape recorders or similar devices, broadcasting devices, or artistic paraphernalia, such as notebooks, and drawing pencils or pens, etc.

b. Violation of this prohibition is a class B misdemeanor. 77-19-11(5)

c. Only a small notebook (no larger than 4" x 6") and a pen or pencil issued by the Department shall be permitted.

2. Only the selected members of the news media (witnesses and two pool photographers) shall be allowed to

attend the pre-execution briefing. The group will be escorted into a briefing room.

a.

b.

c.

3.

a.

b.

4. Persons requesting to witness the execution shall be required to sign a statement or release absolving the institution or any of its staff from any

legal recourse resulting from the exercise of search requirements or other provisions of the witness agreement.

C. The Warden/designee shall not exclude any news media witness duly selected in accordance with these regulations from attendance at the execution except as described in these regulations, nor may the Warden/designee cause a selected news media witness to be removed from the execution chamber unless the media member:

1. refuses to submit to a reasonable search as permitted in these regulations;

2. faints, becomes ill or requests to be allowed to leave during the execution;

3. causes a disturbance within the execution chamber; or

4. refuses or fails to abide by the conditions and regulations set forth by the Department.

D. The execution chamber shall be arranged so as to provide space for the attending news media witnesses and the space arranged shall have a view of the execution site, with the exception of:

1. a view of the members of the firing squad, if employed; or

2. if lethal injection is chosen, those directly administering the method of execution, who shall be concealed from the view of the media members so that their identities will remain unknown.

E. The selected news media witnesses shall be transported as a group to the execution location prior to the execution and shall be allowed to remain there throughout the proceeding.

F. The Department shall designate a representative or representatives to remain with the media members throughout the execution proceedings for the purpose of supervising and escorting.

G. News media witnesses shall be admitted to the execution area on the date set for the execution only after:

1. proof of identification have been presented to the Public Affairs Director/designee at the staging area;

2. receiving an orientation by the Public Affairs Director/designee; and

3. signing an agreement to abide by conditions required of news media witnesses to the execution.

H. After the execution has been completed and the site has been restored to an orderly condition, news media witnesses may be permitted to return to the execution chamber for purposes of filming, photographing and recording the site.

1. Re-entry to the site shall be permitted only after the site has been restored to an orderly condition, including:

   a. removal of the body of the condemned;

   b. evacuation of those involved in administering the execution; and

   c. clean up of the execution chamber.

2. Restoring the site to an "orderly condition" prior to the filming opportunity shall not unnecessarily disturb the physical arrangements for the execution.

3. Media members permitted to return to the execution chamber for the filming and recording of the site shall include:

   a. the news media witnesses who were selected to witness the execution;

   b. one pool television camera man; and

   c. one pool newsprint photographer.

4. The film/videotape shall not be used in any news or other broadcast until made available to all agencies participating in the pool. All agencies receiving the film/videotape will be permitted to usethem in news coverage and to retain the film/videotape for file footage.

I. News media representatives shall, after being returned from the execution to the staging area, act as pool representatives for other media representatives covering the event.

1. The pool representatives shall meet at the designated media center and provide an account of the execution and shall freely answer all questions put to them by other media members and shall not be permitted to report their coverage of the execution back to their respective news organizations until after the non-attending media members have had the benefit of the pool representatives' account of the execution.

a. News media members attending the post-execution briefing shall agree to remain in the briefing room and not leave nor communicate with persons outside the briefing room until the briefing is over.

b. The briefing shall end when the attending news media members are through asking questions or after 90 minutes, whichever comes first.

2.

TMF 01/08.05 Limitations on Coverage

A. The Warden, with the concurrence of the Executive Director, may alter these regulations to impose additional conditions, restrictions and limitations on media coverage of the execution when such requirements become necessary for the

preservation of prison security, personal safety or other legitimate interests which may be in jeopardy.

B. If extraordinary circumstances develop, the additional conditions and restrictions shallbe no more restrictive than required to meet the exigent circumstances.

TMF 01/08.06 News Media Briefing

A. Pre-Execution Briefing Packets

1. The Public Affairs Director shall prepare a press briefing packet for reporters approved to witness the execution, or to cover the execution from the news media staging area.

2. The briefing press packet should be provided to news media representatives as they arrive at the staging area.

3. The contents of the press briefing packet shall include, but not be limited to, biographical information on the condemned, the list of official witnesses, pool reporters, family witnesses, execution procedures, sequence of events, and the history of executions in Utah.

4. Updates will generally be communicated and/or distributed to the press on an hourly basis beginning about 1700 hours the day preceding the execution. Briefing updates should include:

a. a summary of activities related to the execution procedures and sequence of events; and

b. a summary of the condemned inmate's activities during his final 24 hours.

B. Death Announcement

1. The Public Affairs Representative/designee shall read a prepared statement to the press, prior to the post-execution press conference, announcing that the execution has been completed.

2. The announcement shall include, but not be limited to:

a. the time of the execution;

b. the time the condemned was pronounced dead; and

c. the condemned's final words.

C. Post-Execution Conference

1. The post-execution conference shall begin immediately following the arrival of the pool reporters from the execution site.

2. The Public Affairs Director shall introduce the members of the press who witnessed the execution and facilitate the post-execution conference.

3. The Executive Director, Deputy Director, Institutional Operations Division Director and/or Warden may appear and answer questions at the press conference.

4. The post-execution conference shall continue for ninety minutes or until the questioning of the reporters who witnessed the execution has been completed; whichever comes first.

D. Travel Routes

1.

2.

E. Media Center

1. The Media Center shall be located in the designated staging area.

2. The Public Affairs Director shall assume responsibility for routine press briefings at the Media Center.

3. Press briefings and the post-execution conference will be held at the Media Center.

4. News media personnel may not access nor occupy any other part of the staging area. The media shall have access only to the designated media center.

5. Members of the news media may not seek, speak to or interview any official visitor while at the staging area.

6.

TMF 01/08.07 News Media Support and Equipment

A. Telephones

1. The Public Affairs Director shall coordinate all telephone needs with the Deputy Warden Support Services at the Utah State Prison.

2. Each news agency requiring dedicated telephone lines, shall submit in writing its telephone needs to the Public Affairs Director 14 days prior to the scheduled execution. Agencies requesting dedicated phone lines will be responsible for the cost of those lines.

3. The Department shall install a reasonable number of telephones, for local use and collect calls only, for news media use at the Media Center. If the Department is unable to install collect-call only telephones, personal cellular phones may be used.

B. Electrical Outlets

Each news agency must communicate its needs for electrical power to the Public Affairs Director 14 days prior to the scheduled execution.

C. Refreshments

The Public Affairs Director may inquire about having a private caterer at the staging area for the media to purchase items.

D. News Media Support Vehicles

1.

2.

TMF 01/08.08 Media Representative Agreement

(See following page for Media Representative agreement.)

Rules of Conduct for Media Representatives Observing an Execution at the Utah State Prison

1. That you will not bring onto prison property anything constituting legal or illegal contraband under any applicable statute, rule, or policy including any firearm, dangerous weapon, implement of escape, explosive, spirituous of fermented liquor, medicine, poison, or any other item creating a threat to the safety, security, or management of the prison;

2. That you agree to submit to a reasonable search for contraband and other searches as considered necessary by the Department for entry to Department prison and staging area property;

3. That you conduct yourself in a lawful and orderly manner;

4. That you comply with all lawful directives of correctional personnel while on Department property;

5. That you will not bring to the execution site any photographic or recording equipment;

6. That you understand that the Department of Corrections will not provide mental health services to witnesses; and

7. That you understand the Department of Corrections is required torecord/report the names of all witnesses in attendance as well as provide the information to media representatives.

I have read the above rules and agree to abide by them. I understand that my failure to comply with the rules will result in my immediate removal from Department of Corrections property and that I may be subject to criminal prosecution.

News Organization_____

_____ _____
Signature of News Media Witness Date

_____ _____
News Agency Editor/Producer Date

TMF 01/20.00 REVIEWAND DOCUMENTATION

TMF 01/20.01 General Provisions
TMF 01/20.02 Review Assignment
TMF 01/20.03 Documentation of Execution
TMF 01/20.04 Retention and Safeguarding Documentation
TMF 01/20.05 UDC Employee Questionnaire

TMF 01/20.00 REVIEW AND DOCUMENTATION

TMF 01/20.01 General Provisions

A. Purpose of Chapter

The purpose of this chapter is to provide the policies, procedures and requirements for reviewingthe execution process.

B. Policy

1. It shall be the policy of the Department that of the execution process shall be performed as ordered by the Executive Director.

2. Auditors assigned to perform thesereviewsshall beallowed access to designated aspects of the executionpreparation.

3. Auditors participating in the reviewof the execution are not to be involved in the execution preparationprocess, but shall act as observers only and, at all times, act in such a way that they create the least disruption possible in that process.

5. Appropriate documentation of the execution shall be created, collected, safeguarded, and retained to provide an adequate review trail and a proper historical record.

6. Documentation shall be protected in accordance with 64-13-25(2) UCA.

TMF 01/20.02 ReviewAssignment

Authority to Conduct a Review

1. The Executive Director shall be responsible for determining if a reviewis to take place in each execution.

2. The Auditor(s) selected for the execution review shall, upon direction

from the Executive Director, prepare a questionnaire to be completed by staff involved in the execution process. The survey shall be approved by the Executive Director and all responses shall be confidential. Only the Executive Director may grant release of the survey responses.

TMF 01/20.03 Documentation of Execution

Documentation to be Retained

Documentation which shall be retained shall include:

1. the warrant and all other legal papers;

2. correspondence, both official and unofficial, which is received by the Department of Corrections;

3. minutes of meetings held for purposes of planning or disseminating information;

4. inter-agency written communication;

5. intra-departmental written communication;

6. logs, journals, chronological notes, etc., of key locations; and

7. a newspaper file.

TMF 01/20.04 Retention and Safeguarding Documentation

A. Execution File

1. An execution file shall be established for each condemned person. The file shall be organized into sections which should include:

a. legal documents;

b. official correspondence;

c. unofficial correspondence;

d. intra-departmental written communication;

e. chronological notes, logs, etc.; and

f. meeting minutes.

2. Each section of the execution file shall have material filed in chronological order.

3. All working documents which cannot be filed during the execution process or immediately after, shall be copied and a copy shall be placed in the execution file.

4. All intra-departmental communication shall have a courtesy copy to the execution file.

B. Execution File Maintenance

1.

2.

C. Access to Execution File

Only those individuals authorized by the Executive Director of Corrections, DIO Director, or Warden, shall have access to the execution file.

D. Long-Term Storage

To ensure that all documents concerning an execution shall be retained to provide a reviewtrail and an adequate historical record, the execution file shall be stored in accordance with the archive's plan of the Department.

TMF 01/20.05 UDC EMPLOYEE QUESTIONNAIRE

_____
Name of the Condemned

INSTRUCTIONS:

Please complete this questionnaire as soon after the execution as possible. Answer each question completely and accurately. Add as many pages as necessary if answers need more space.

Complete and return this questionnaire to the AuditBureau at Utah Department of Corrections, 14717 S. Minuteman Drive, Draper, 84020, by _____.

Thank you.

FULL NAME: _____

TITLE: _____

LOCATION: _____

FUNCTION DURING THE EXECUTION: _____

1. Were you provided adequate direction for your area of responsibility?

   If you answered "No," please explain what direction would havebeen beneficial to you.

   _____
   _____
   _____

2. Were you adequately trained or briefed in your area of responsibility?

   Yes___No___

   If you answered "No," please explain what training or briefing would have been beneficial to you.

   _____
   _____
   _____
   _____

3. Did you observe anything that you thought was not adequately addressed?

   Yes___No__

   If you answered "Yes," please explain.

   _____
   _____
   _____
   _____
   _____

4. Please make any additional comments or suggestions.

THANK YOU!

TMF 01/21.00 TRAINING AND BRIEFING

TMF 01/21.01 General Provisions
TMF 01/21.02 Training and Briefing Components

TMF 01/21.00 TRAINING AND BRIEFING

TMF 01/21.01 General Provisions

A. Purpose of Chapter

The purpose of this chapter is to provide the policy and procedure concerning briefing and training of staff, members of allied agencies and others involved in an execution.

B. Policy

It is the policy of the Department that staff and others involved in carrying out an execution:

1. receive comprehensive briefings covering:

   a. their duties and responsibilities;

   b. the specifics of post orders covering assigned positions;

   c. communication and chain of command;

   d. overview of functions and activities during the execution;

2. are provided copies of post orders outlining the duties and responsibilities of assigned positions;

3. receive the level of briefing and training necessary based on the requirements of assigned duties;

4. rehearse and practice functions which involve:

   a. difficult timing;

   b. a high degree of skill;

   c. procedures of a highly critical nature; and/or

   d. moderately difficult or complex interaction with others; and

5. receive instructions concerning back-up systems to provide:

   a. problem-resolution assistance;

   b. policy decisions;

   c. crisis management assistance; and

   d. information requests.

TMF 01/21.02 Training and Briefing Components

A. General

Training and briefing shall include, but not be limited to:

1. issuing all members or other participants a post order for their assigned positions;

2. providing an orientation or briefing covering assigned duties and general operational information;

3. if necessary, detailed training covering legal, operational or technical aspects of assigned position;

4. if necessary, rehearsal of job functions; and

5. key positions in Manual TMF 01.

B. Post Orders

1. Each member or other participant shall be issued the post order or instructions for his assigned position.

2. The post order shall include, but not be limited to:

   a. the position title;

   b. location(s) of assignment;

   c. title of supervisor;

d. supervisory role, if any;

e. duties and responsibilities--general and specific; and

f. emergency role.

3. When appropriate, one or more chapters of TMF 01 may be issued with a post order.

4. All post orders (and any accompanying manual material) shall be returned at the completion of the execution event.

C. Briefing/Orientation

1. Most assignments will be very specialized, involving a narrow range of duties. For such positions, briefing/orientation sessions will be all the training required in addition to the general training skills and experience of the persons assigned.

2. Orientation sessions shall include but not be limited to:

a. an overview of the execution process and operational components;

b. location of assigned post;

c. chain of command and organizational information;

d. an overview of the countdown of activities and procedures leading to the execution;

e. an explanation of support and crisis intervention systems;

f. interaction with the news media;

g. a review of the specific post order requirements, duties and other elements; and

h. a question-and-answer period.

D. Training/Rehearsal

1. For assignments requiring more technical or complex functions, critical timing or interaction elements, or duties of a particularly difficult nature, more comprehensive training shall be required.

2. Team leaders shall be responsible for training and scheduling rehearsals as needed for team members.

AFFIDAVIT OF JOSEPH CUMMINGS, III

I, Joseph Cummings, III, do declare as follows:

1. I am currently employed as an Investigator with the Eastern District Federal Public Defender Office of Arkansas. I was assigned to complete a work request pertaining to the Lethal Injection Litigation that is currently being litigated by our office. One of the work requests I received requested that I contact various pharmaceutical companies to obtain information about the products sevoflurane and isoflurane. First, was to verify if sevoflurane and/or isoflurane are available for purchase to Department of Correction Agencies. Second, to establish whether the company has any objections to the use of their products by Department of Correction Agencies for use in executions; and if the company has any provisions set forth in their distribution contracts to prevent their products from being obtained by Department of Correction Agencies for use in executions.

2. On July 18, 2016, I contacted Piramal Healthcare. Piramal Healthcare is located at 3950 Schelden Circle in Bethlehem, Pennsylvania. I spoke to Ester Kessler by telephone to discuss the issues stated above. Ms. Kessler is a Sales Representative for Piramal Healthcare. Ms. Kessler stated if the Arkansas Department of Correction was a member of the Federal Supply Schedule or Managed Healthcare Associates, the Arkansas Department of Correction would have access to their products, isoflurane and sevoflurane, through multiple wholesale companies at a discounted price for purchase. Ms. Kessler stated the products, isoflurane and sevoflurane, would be available for direct purchase from the manufacturer if the Arkansas

Department of Correction was not a member of the Federal Supply Schedule or Managed Healthcare Associates.

3. I declare under penalty of perjury under the laws of the United States of America that the above information is true and correct to the best of my knowledge.

FURTHER AFFIANT SAYETH NOT.

Joseph I. Cummings, III
Capital Habeas Unit Investigator
Federal Public Defender Office-Eastern District

ACKNOWLEDGMENT

STATE OF ARKANSAS)
)
COUNTY OF PULASKI)

Subscribed and sworn to before me, a Notary Public, on this 20th day of July, 2016.

Notary Public

My Commission Expires:

CYNTHIA L. WESTLAKE
PULASKI COUNTY
NOTARY PUBLIC - ARKANSAS
My Commission Expires May 31, 2017
Commission No. 12361103

Nitrogen Induced Hypoxia as a Form of Capital Punishment

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Thom Parr, M.S.

Christine Papas, J.D., Ph.D.

East Central University

Executive Summary

At the request of Oklahoma State Representative Mike Christian, the authors of this study researched the question of whether hypoxia induced by nitrogen gas inhalation could serve as a viable alternative to the current methods of capital punishment authorized under Oklahoma law. As per the above, this study does not express an opinion on the wider question of whether Oklahoma should continue to administer capital punishment in general. The scope of this study is limited to the assumption that capital punishment will continue to be administered in Oklahoma, and given that assumption, analyzing whether hypoxia via nitrogen gas inhalation would be an effective and humane alternative to the current methods of capital punishment practiced in Oklahoma law.

This study was conducted by reviewing the scientific, technical, and safety literature related to nitrogen inhalation.

The study found that:

1. An execution protocol that induced hypoxia via nitrogen inhalation would be a humane method to carry out a death sentence.
2. Death sentence protocols carried out using nitrogen inhalation would not require the assistance of licensed medical professionals.
3. Death sentences carried out by nitrogen inhalation would be simple to administer.
4. Nitrogen is readily available for purchase and sourcing would not pose a difficulty.
5. Death sentences carried out by nitrogen inhalation would not depend upon the cooperation of the offender being executed.

Accordingly, it is the recommendation of this study that hypoxia induced by the inhalation of nitrogen be offered as an alternative method of administering capital punishment in the State of Oklahoma.

The views expressed in this study are solely those of its authors and do not necessarily reflect those of the university at which we are affiliated.

Introduction

Nitrogen is an inert gas that at room temperature is colorless, odorless, and tasteless. It is the most common gas in the earth's atmosphere, comprising 78.09% of the air that humans breathe on a regular basis.

When combined with the normal 20.95% oxygen found in the atmosphere, nitrogen is completely safe for humans to inhale. However, an environment overly enriched in nitrogen will lack the appropriate level of oxygen necessary for human survival and will thus lead to hypoxia and rapid death. (U.S. Chemical Safety and Hazard Investigation Board, 2003, p.1).

Nitrogen hypoxia has been suggested as a means of administering capital punishment in the popular media on previous occasions. For example, in1995 the National Review featured an article by Stuart Creque titled *Killing With Kindness: Capital Punishment by Nitrogen Asphyxiation (1995).* Creque's article was written in response to a 9th Circuit U.S. District Court decision that California's gas chamber was an unconstitutionally cruel and unusual punishment. The article suggested nitrogen could provide a simple and painless alternative to the gas chamber that would require no elaborate medical procedures to administer.

The idea of administering capital punishment via nitrogen hypoxia resurfaced more recently in a Tom McNichol Slate magazine article titled *Death by Nitrogen (2014).* The article was inspired by the stay of execution issued by the U.S. Supreme Court for a Missouri man facing execution via lethal injection. Again, the author suggested nitrogen induced hypoxia as a painless alternative to traditional methods of execution, adding that it offered the additional benefits of requiring no medical training to administer and lacked any of the supply issues that exist with lethal injection.

The capital punishment protocols cited that utilize nitrogen to administer a death sentence do not actually rely on the nitrogen itself to bring about death. Nitrogen simply displaces the oxygen normally found in air and it is the resulting lack of oxygen which causes death. Without oxygen present, inhalation of only 1-2 breaths of pure nitrogen will cause a sudden loss of consciousness and, if no oxygen is provided, eventually death. (European Industrial Gases Association, 2009, p. 3).

Since nitrogen has not previously been used for capital punishment there is a lack scientific literature that specifically addresses its performance for that purpose. However, there have been medical experiments which involved human subjects breathing pure nitrogen until they became unconscious. Beyond those experiments, most of the data related to nitrogen induced hypoxia comes from documented suicides in humans and research in high altitude pilot training.

> *Author's Note: in some cases the lay press will inadvertently refer to hypoxia as asphyxiation. This is technically inaccurate in this context, as asphyxia is the inability to breathe in oxygen* ***and*** *the inability to exhale carbon dioxide. Hypoxia is the pathology related to the inability to intake oxygen even though one may still be able to exhale carbon dioxide. As will be seen later, the ability to exhale carbon dioxide is critical to the proposed method of execution, as it prevents the acidosis normally associated with asphyxiation.*

Medical Literature

The adult brain uses about 15 per cent of the heart's output of oxygenated blood (Graham, 1977, p.170). Hypoxia is the condition of having a lower-than-normal amount of oxygen in the blood. Anoxia is an extreme form of hypoxia in which there is a complete absence of oxygen in the blood (Brierley, 1977 p.181). If the supply of oxygen in the blood is reduced

below a critical level it will result in a rapid loss of consciousness and eventually irreversible brain damage will occur (Graham, 1977, p.170).

A complete immediate global loss of oxygen to the brain, (a scenario in which no residual oxygen in the lungs or blood is delivered to the brain), will result in a loss of consciousness in eight to ten seconds, and a loss of any electrical output by the brain will occur a few seconds later. The heart may continue to beat for a few minutes even after the brain no longer functions (Brierley, 1977 p.182).

Ernsting (1961) performed a study on human volunteers that hyperventilated on pure nitrogen gas. The subjects performed the test multiple times, varying the length of time they inhaled the nitrogen. When the subjects inhaled nitrogen for eight-to-ten seconds they reported a dimming of vision. When the period was expanded to fifteen-to-sixteen seconds, the subjects reported some clouding of consciousness and impairment of vision. When the tests were expanded to seventeen-to-twenty seconds, the subjects lost consciousness. There was no reported physical discomfort associated with inhaling the pure nitrogen. (p. 295)

Unlike asphyxiation, hypoxia via the inhalation of nitrogen allows the body to expel the carbon dioxide buildup that is normally associated with the respiratory cycle. This helps prevent a condition known as hypercapnia - an accumulation of carbon dioxide in the blood. The result of this buildup of carbon dioxide is respiratory acidosis - a shifting of the ph levels in the blood to become more acidic. This is the pathology many people associate with suffocating. Some of the symptoms of respiratory acidosis are expected to be present in cases of asphyxiation, but not expected to be present under pure hypoxia are anxiety and headaches, (Merrick Manuel, 2013).

Suicide Data

Perhaps one of the greatest testaments to both the humanity of nitrogen induced hypoxia as well as the ease of administration is its rapidly gaining popularity as a self-selected means of suicide. Suicide by hypoxia using an inert gas is the most widely promoted method of human euthanasia by right-to-die advocates (Howard, M.O. et. al., 2011, P. 61).

The trend toward using an "exit bag" filled with an inert gas such as nitrogen or helium likely started with a publication of *Final Exit: The Practicalities of Self Deliverance and Assisted Suicide for the Dying*. The authors of the publication sought to identify methods of death that were swift, simple, painless, failure-proof, inexpensive, non-disfiguring and did not require a physician`s assistance or prescription (Howard, M.O. et. al., 2011. p 61).

This method of suicide is indeed simple. It involves a clear plastic bag fitted over the head, two tanks filling the bag with helium via vinyl tubing, and an elastic band at the bottom of the bag to prevent the bag from slipping off the head. The parts needed to create the bag are inexpensive and available locally without prescription (Howard, M.O. et. al., 2011. p 61-62).

Reports of deaths observed via this method suggest that it is painless. Jim Chastain, Ph.D. President of the Final Exit Network of Florida described the process this way:

> In the several events I have observed the person breathes the odorless, tasteless helium deeply about three or four times and then is unconscious. no gagging or gasping. Death follows in 4-5 minutes. A peaceful process.

Derek Humphrey, current chair of the Final Exit advisory board is quoted as saying:

> In the approximate 300 cases which have been reported to me there has never been mention of choking or gagging. When I witnessed the helium death of a friend of mine it could not have been more peaceful (Final Exit, 2010).

However, it should be noted that deviations from the above protocols have not always been as successful. When masks were placed over the face (instead of using bags of helium over

the head) it has been reported some problems have occurred. This is typically a result of the mask not sealing tightly to the face, resulting in a small amount of oxygen being inhaled by the individual. This extends the time to become unconscious and extends the time to death. This may result in purposeless movements by the decedent (Ogden et al, 2010. p 174-179).

Research on High Altitude Pilot Training

A great deal of research on the effects of hypoxia on human beings comes from aerospace medicine. Pilots that fly at high altitudes are subject to becoming hypoxic if their cabins lose air pressure. Altitude hypoxia has similar effects as the hypoxia one gets from breathing inert gases although it is caused by the inability of the lungs to absorb the oxygen in the air rather than a lack of oxygen in the air.

The Federal Aviation Administration (2003, p. 11) states:

> Hypoxia is a lack of sufficient oxygen in the body cells or tissues caused by an inadequate supply of oxygen, inadequate transportation of oxygen, or inability of the body tissues to use oxygen. A common misconception among many pilots who are inexperienced in high-altitude flight operations and who have not be exposed to physiological training is that it is possible to recognize the symptoms of hypoxia and to take corrective actions before becoming seriously impaired. While this concept may be appealing in theory, it is both misleading and dangerous for an untrained crew member. Symptoms of hypoxia vary from pilot to pilot, but one of the earliest effects of hypoxia is impairment of judgment. Other symptoms can include one or more of the following:
> (1) Behavioral Changes (e.g. a sense of euphoria).
> (2) Poor coordination.
> (3) Discoloration in the fingernails (cyanosis).
> (4) Sweating.
> (5) Increased breathing rate, headache, sleepiness, or fatigue
> (6) Loss or deterioration of vision
> (7) Light-headedness or dizzy sensations and listlessness.
> (8) Tingling or warm sensations.

Indeed, hypoxia has caused several airline accidents which are often fatal. The onset of hypoxia is typically so subtle that it is unnoticeable to the subject. The effects of hypoxia are often difficult to recognize. (Federal Aviation Administration, 2014, Ch. 8-1-2 (A) 5)

Attempts to train pilots to notice hypoxia are conducted using a hyperbaric chamber to simulate high altitudes. Often a trainee will be asked to remove his or her mask and perform simple tasks. At low levels of hypoxia, trainees typically feel little more than euphoria and a sense of confidence. At higher levels of hypoxia, trainees will quickly become unconscious. Time of useful consciousness at altitudes above 43,000 is 5 seconds (Federal Aviation Administration, 2003, p. 13).

Findings

Based on the review of the literature related to hypoxia induced by inert gases, this study makes the following findings:

1. An execution protocol that induced hypoxia via nitrogen inhalation would be a humane method to carry out a death sentence.
2. Death sentence protocols carried out using nitrogen inhalation would not require the assistance of licensed medical professionals.
3. Death sentences carried out by nitrogen inhalation would be simple to administer.
4. Nitrogen is readily available for purchase and sourcing would not pose a difficulty.
5. Death sentences carried out by nitrogen inhalation would not depend upon the cooperation of the offender being executed.
6. Use of nitrogen as a method of execution can assure a quick and painless death of the offender

Finding 1. An execution protocol that induced hypoxia via nitrogen inhalation would be a humane method to carry out a death sentence.

Rationale:

As an inert gas, nitrogen is odorless, colorless, tasteless and undetectable to human beings. It is 78% of the air we breathe on a daily basis, and thus there is little chance that any subject would have an unusual or allergic reaction to the gas itself.

Because the subject is able to expel carbon dioxide, the anxiety normally associated with acidosis in asphyxiation would not be present.

The literature indicates after breathing pure nitrogen, subjects will experience the following: within eight-to-ten seconds the subjects will experience a dimming of vision, at fifteen-to-sixteen seconds they will experience a clouding of consciousness, and at seventeen-to-twenty seconds they will lose consciousness. There is no evidence to indicate any substantial physical discomfort during this process.

There is a possibility that subjects will feel euphoria prior to losing consciousness and a slight possibility they will feel a tingling or warm sensation. After the subjects are unconscious, it should be expected some of the subjects will convulse. Most electrochemical brain activity should cease shortly after loss of consciousness, and the heart rate will begin to increase to varying degrees until it stops beating 3 to 4 minutes later. Observed suicides involving inert gas hypoxia are described as peaceful, so long as caution is taken to eliminate the possibility of the subject inadvertently receiving supplemental oxygen during the process. Inert gas hypoxia is considered such a humane and dignified process to achieve death that it is recommended as a preferred method by right-to-die groups.

Finding 2. Death sentence protocols carried out using nitrogen inhalation would not require the assistance of licensed medical professionals.

Rationale:

The administration of a death sentence via nitrogen hypoxia does not require the use of a complex medical procedure or pharmaceutical products. The process itself, as demonstrated by those who seek euthanasia, requires little more than a hood sufficiently attached to the subject's head and a tank of inert gas to create a hypoxic atmosphere.

While a state execution would likely have a more elaborate mechanism to create hypoxia, nothing in the process would require specialized medical knowledge or the use of regulated pharmaceutical products. Accordingly, except for the pronouncement of death, the assistance of licensed medical professionals would not be required to execute this protocol.

Finding 3. Death sentences carried out by nitrogen inhalation would be simple to administer.

Rationale:

When considering a substitute method of capital punishment it is important to consider more than just what happens if everything goes according to protocol. The likelihood of mishaps must also be considered, as well as the consequences that would flow if those mishaps should occur.

Because the protocol involved in nitrogen induced hypoxia is so simple, mistakes are unlikely to occur. Oxygen and nitrogen monitors may be placed inside the contained environment to insure the proper mixes of gas are being expelled into the bag and inhaled by the subject.

However, the protocol should be careful to prevent the possibility of oxygen entering into the hood, as that can prolong time to unconsciousness and death, as well as increase the possibility of involuntary movements by the subject.

The risks to witnesses are minimal, as any potential leak of the nitrogen would not be harmful in a normally ventilated environment.

Finding 4. Nitrogen is readily available for purchase and sourcing would not pose a difficulty.

Rationale:

Nitrogen is utilized harmlessly in many fields within United States industries. Nitrogen is used in welding, hospital and medical facilities, cooking, and used in the preparation of liquid nitrogen cocktails. Nitrogen is used as a process to extend the life of food products such as potato chips. Nitrogen is used in doctor's offices to remove skin tags as well as other procedures. Accordingly, sources of nitrogen to be used for administering a death sentence should be easy to find and readily available for purchase for such purpose.

Finding 5. Death sentences carried out by nitrogen inhalation would not depend upon the cooperation of the offender being executed.

Rationale:

Some forms of capital punishment require the offender to submit or comply to some degree in order to assure an efficient and humane method of execution. With proper protocol and utilizing such devices as a restraint chair, nitrogen inhalation can be administered despite the presence of a non-compliant offender. The use of nitrogen can be used by non-medical personnel and a delivery system can be designed to ensure the execution is carried out without issue.

Conclusion

As per the above, it is the recommendation of this study that hypoxia induced by the inhalation of nitrogen be offered as an alternative method of administering capital punishment in the State of Oklahoma.

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Appendix D

Death by Nitrogen: Will This New Method of Execution Save the Death Penalty?

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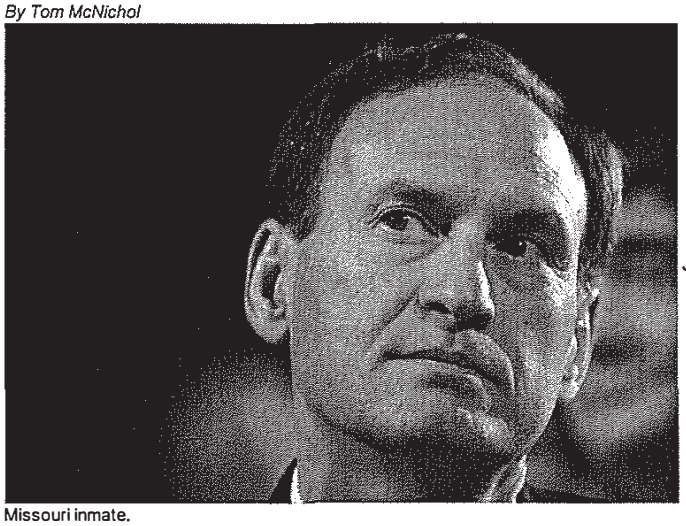
Death by Nitrogen

If lethal injection falls out of favor, death penalty states could turn to a new method: nitrogen gas.

By Tom McNichol



Justice Samuel Alito issued an order halting the execution of a Missouri inmate.

Photo by Saul Loeb/AFP/Getty Images

On Wednesday night, the Supreme Court stopped an execution by lethal injection. The condemned Missouri man, Russell Bucklew, says he has a medical condition, affecting his veins, that would make the injection cause hemorrhaging—and make him feel like he's choking on his own blood. The court took the unusual step of intervening at the last minutes, when every other court had turned Bucklew down, and also of sending the case back to the lower courts to decide whether to hold a hearing about Bucklew's claim.

The Supreme Court ruled in 2008 that Kentucky's three-drug protocol for carrying out lethal injections was constitutional, but there's no question that the method looks grimly suspect in the wake of Clayton Lockett's apparently painful, botched execution in Oklahoma last month. Not so long ago, though, this was the method that represented progress. Hanging. Firing squad. The guillotine. The electric chair. The gas chamber. Lethal injection. Every age seems to feature a new and improved method of capital punishment, billed as more efficient and humane. The spectacle of Lockett's death, and the Supreme Court's hesitation, shines a spotlight on the latest idea—death by nitrogen.

As long as there's a will to kill criminals, someone will come up with an improved form of capital punishment.

This new proposed method, known as nitrogen asphyxiation, seals the condemned in an airtight chamber pumped full of nitrogen gas, causing death by a lack of oxygen. Nitrogen gas has yet to be put to the test as a method of capital punishment—no country currently uses it for state-sanctioned executions. But people do die accidentally of nitrogen asphyxiation, and usually never know what hit them. (It's even possible that death by nitrogen gas is mildly euphoric. Deep-sea divers exposed to an excess of nitrogen develop a narcosis, colorfully known as "raptures of the deep," similar to drunkenness or nitrous oxide inhalation.)

You can oppose the death penalty and still see the merit in making executions more humane. As Boer Deng and Dahlia Lithwick argued in ***Slate***, opponents of the death penalty inadvertently have made lethal injection *less* safe, by forcing prison officials into using inferior methods and substandard drug providers. As the states struggle to obtain drugs, such as pentobarbital, for lethal injections because of an export ban by the European Union, lethal injection has been turned from a method of execution into a medical experiment.

Proponents say that death by nitrogen, by contrast, adheres to the constitutional prohibition against cruel and unusual punishment. The condemned prisoner would detect no abnormal sensation breathing the odorless, tasteless gas, and would not undergo the painful experience of suffocation, which is caused by a buildup of carbon dioxide in the bloodstream, not by lack of oxygen.

In late April, Louisiana Department of Corrections Secretary James LeBlanc suggested to a state legislative committee that Louisiana should look into using nitrogen gas as a new method of execution, since lethal injection has become so contentious. "It's become almost impossible to execute someone," LeBlanc complained to the Louisiana House Administration of Criminal Justice Committee.

"Nitrogen is the big thing," LeBlanc told the committee. "It's a painless way to go. But more time needs to be spent [studying] that." The committee instructed LeBlanc to do some research on the subject and report back. In the meantime, Louisiana has delayed a pending execution. "I'm not taking anything off the table," says state Rep. Joseph P. Lopinto III, chairman of the state's Administration of Criminal Justice Committee. "If someone says nitrogen gas is the way to go, then we can debate that and do it if need be."

As long as 32 states have capital punishment on the books, there should be a less reliably cruel method of execution than lethal injection. "If we're going to take a life, then we should do it in the most humane, civilized manner as is possible," says Lawrence Gist II, an attorney and professor of business and law at Mount St. Mary's College. "Right now, nitrogen is the best of the available options."

Gist, a death penalty opponent, runs a website dedicated to promoting nitrogen asphyxiation for state-sanctioned executions. Polling suggests the public could get behind the idea. In a recent NBC News poll, 1 in 3 people said that if lethal injections are no longer viable, executions should be stopped altogether. But many others were open to alternative methods of putting prisoners to death. About 20 percent opted for the old version of the gas chamber (which traditionally used hydrogen cyanide to kill), 18 percent for the electric chair, 12 percent for death by firing squad, and 8 percent for hanging.

Nitrogen gas, unlike the lethal drugs that states have relied on, is widely available. The gas is used extensively in industrial settings, from aerospace to oil and gas production "Lethal injection is just fine if you can get the pentobarbital," says Kent Scheidegger, legal director of the Criminal Justice Legal Foundation, a group that favors capital punishment. "But if that's not available, an alternative like nitrogen gas would work."

Top Comment

I always thought that people who voluntarily went to witness a cyanide gas chamber execution were morons. You have to have a special kind of faith in window caulking. More...

-Pete R

Join In

In contrast to lethal injection, no medical expertise would be needed to introduce nitrogen gas into a sealed chamber. The gas chamber itself is technology that has been around since the 1920s. In fact, three states—Arizona, Missouri, and Wyoming—still authorize lethal gas as a method of execution (depending on the choice of the inmate, the date of the execution or sentence or the possibility that lethal injection is held unconstitutional).

The last gas chamber execution in the U.S. was in 1999—the method fell out of favor because hydrogen cyanide is a poison causing suffering that lasts 10 minutes or longer. Lethal injection, of course, was supposed to be painless and better. What if it's not? That's the question the Supreme Court now finally seems to be returning to. The history of capital punishment suggests that as long as there's a will to kill criminals, someone will come up with an improved way. The new tool in the executioner's bag may turn out to be nitrogen, a better way to carry out a gruesome task.

Tom McNichol is a writer in San Francisco.

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alt.suicide.methods

Killing with kindness - capital punishment by nitrogen asphyxiation (too old to reply)

Philbert 9 years ago

http://www.findarticles.com/p/articles/mi_m1282/is_n17_v47/ai_17374449

Capital punishment needn't be cruel or unusual -- especially if you use nitrogen asphyxiation to put people to sleep.

LAST October, Judge Marilyn Hall Patel of the 9th U.S. District Court ruled that execution in California's gas chamber is a form of cruel and unusual punishment, the first ruling ever by a state or federal judge to invalidate a method of execution on Eighth Amendment grounds. She noted that the evidence showed that the condemned man might remain conscious for several minutes, experiencing the emotions of `anxiety, panic, terror,' as well as `exquisitely painful muscle spasms' and `intense visceral pain.'

On its face, Judge Patel's ruling applies only to the gas chamber, but every method of execution in current use involves toxic chemicals or physical trauma to induce death -- and every method can go awry. An ideal hanging snaps the condemned man's neck cleanly; a botched one either strangles him slowly or severs the head entirely from the body. A firing squad that misses its mark leaves the condemned man conscious as he bleeds to death. In the electric chair, according to eyewitness accounts, some condemned men have literally been cooked until their flesh was charred and loosened from the bone; some had sparks and flame emanating from their cranial-cap electrodes.

Besides society's concern for the condemned man's physical suffering, all of these methods implicitly require an executioner to inflict some degree of trauma upon the condemned. Concern for the executioner's conscience drives such customs as loading one of the guns for a firing squad with a blank cartridge, so that each member of the squad can imagine that his will be the non-lethal shot. And with lethal injection, the executioner's use of skills and procedures normally devoted to life-saving poses ethical questions for medical caregivers.

Given these defects, abolitionists will presumably press to have each of these methods declared `cruel and unusual.' The intended result of these efforts is to make the death penalty unconstitutional in practice, even if it remains constitutional in theory.

It is in fact possible to conceive of a method of execution that would cause neither pain nor physical trauma, require no medical procedure (other than pronouncing death), and use no hazardous chemicals. A case of accidental

death suggests such a method.

Early in the Space Shuttle program, a worker at Kennedy Space Center walked into an external fuel tank (a vessel nearly as big inside as a Boeing 737) to inspect it. He was not aware that it had been purged with pure nitrogen gas to prevent oxygen in the air from corroding its interior. Since nitrogen is the major component of ordinary air, pure nitrogen has no distinctive feel, smell, or taste; the worker had no indication that anything was out of the ordinary. After walking a short distance into the tank, he lost consciousness and collapsed. A co-worker, not realizing that his collapse had an external cause, ran in to aid him and succumbed also. By the time other workers realized what was happening, the two men were dead.

More recently, a bizarre accident involving nitrogen killed two people in the Bay Area. They had stolen from a hospital a gas cylinder containing what they thought was laughing gas. However, the cylinder contained not the anaesthetic nitrous oxide but pure nitrogen. When the two men stopped their car to partake of their booty, the nitrogen gas displaced the air in the car, leaving them without oxygen. Had they had any indication of the problem, they could have saved their lives simply by opening the car doors.

These deaths were similar in cause to a relatively common drowning accident known as shallow-water blackout, mentioned specifically in certification classes for recreational scuba diving. When a person is skin diving (that is, without scuba gear), his bottom time is limited by how long he can hold his breath. Occasionally, a skin diver will attempt to lengthen the time he can stay under by hyperventilating before a dive. Unfortunately, this can lead to his losing consciousness underwater, sometimes only a few feet before reaching the surface.

THE connection between nitrogen asphyxiation and shallow-water blackout lies in human respiratory physiology. When you hold your breath, you begin to develop a powerful urge to breathe. This is caused not by the depletion of oxygen from your body, but by the buildup of carbon dioxide in your bloodstream, which changes the pH of the blood. The ambitious skin diver ``blows off' most of the carbon dioxide in his bloodstream when he hyperventilates; as a result, he notices the urge to breathe much later than he normally would, at a point when his blood oxygen is dangerously low. If his blood oxygen falls too low before he reaches the surface, he blacks out and drowns. Because the Kennedy Space Center workers continued to exhale carbon dioxide with each breath, neither of them noticed an unusual urge to breathe, even though they were completely deprived of oxygen.

Nitrogen asphyxiation is a unique way to die. The victim is not racked by a choking sensation or a burning urge to breathe, because as far as his body

knows, he is breathing normally. Carbon dioxide is not building up in his bloodstream, so he never realizes that anything is wrong, nor does he experience any discomfort; he simply passes out when his blood oxygen falls too low.

Nitrogen asphyxiation is therefore a perfect method of execution. It uses a cheap and universally available working medium that requires no special environmental precautions for its storage and disposal. Its first symptom is loss of conscious sensation, a primary goal in a humane execution. It involves no physical trauma, no toxic drugs; the executed man's organs will even be suitable for donation, a factor cited in a recent stay of execution for a Georgia killer.

Assuming that the prisoner's guilt has been sufficiently proved, nitrogen asphyxiation is perhaps the most gentle way to deal with him. A condemned man awaiting death by nitrogen asphyxiation would experience no more pain or suffering than he created in his own mind.

nubbins 9 years ago

x-no-archive:yes

Maybe even go out laughing.

- nubbins -

Philbert 9 years ago

> *Post by nubbins*
> x-no-archive:yes
> Maybe even go out laughing.
> - nubbins -

You're thinking of nitrous oxide aka laughing gas. The article is about nitrogen.

nubbins 9 years ago

x-no-archive:yes

> *Post by Philbert*
> > *Post by nubbins*
> > Maybe even go out laughing.

> You're thinking of nitrous oxide aka laughing gas. The article is about nitrogen.

You are absolutely correct, sir. I was not paying due attention. Gets me in trouble in class all the time. Who would mind if a doctor diagnosed onychomycosis as cryptorchidism, really? Details, details.

- nubbins -

d*@hotmail.com** 9 years ago

Awesome article. I think you just solved the puzzle for me. Thank you.

Philbert 9 years ago

Google nitrogen suicide for a lot of stuff. Basically people find that euthanising animals works pretty well using nitrogen, plus it's safe to use
unless it's in a very high concentration.

Rabbits don't like nitrogen because they have adaptive traits for living in
holes where nitrogen can build up, unlike other animals and humans.

On 4/6/06 3:25 PM, in article

> *Post by d***@hotmail.com*
> Awesome article. I think you just solved the puzzle for me. Thank you.

slunky 9 years ago

Thanks for finding an article on it. I've been saying it for weeks, and was starting to wonder if I had just imagined it or what.

--
-slunky

Cesar 9 years ago

Thanks for the great post and it was interesting and informative. I have concern that when the death penalty is ruled out as cruel and inhumane, it leaves the potential that the prisoners on death row could at some point get release and re-enter society. When prisons become too full, it can be ruled that a certain amount of prisoners be released early. In the years to come, laws could change and see a prisoner sentenced to death instead getting a life sentence of 20 years then getting out. Of course, it would help those that were wrongly convicted in the first place.

Jimmy 9 years ago

HAZARDS OF INERT GASES AND OXYGEN DEPLETION

IGC Document 44/09/E

Revision of IGC Doc 44/00/E

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IGC Doc 44/09/E

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Table of Contents

1 Introduction

EIGA is very concerned about the accidents that industrial gas companies and users of inert gases continue to report each year, where the direct cause has been lack of oxygen resulting in asphyxiation. EIGA identified that existing information on the hazards of inert gases was not sufficiently directed at the users who were most at risk. This document sets out the essential information that is necessary to prevent asphyxiation accidents involving inert gases.

2 Scope and purpose

It is intended that this document is used as a training package suitable for supervisors, line managers, direct workers and users wherever inert gases are produced, stored, used, or where oxygen depletion could otherwise occur.

This document has 4 parts:

The main document is intended for line managers and supervisors and gives the background of the subject, the typical description of oxygen deficiency accidents and the recommended rescue preparations to be in place in case of accident.

Appendix A is a simplified summary of the main document, designed to be reproduced as a pamphlet for sharing with workers and end users.

Appendix B gives an introduction to rescue considerations from normally accessible rooms, confined spaces or pits and trenches.

Appendix C lists some actual accidents that have taken place in recent years, which can be used as examples to underline the potentially fatal hazards of inert gases.

Appendix D gives an example of a warning sign or poster to highlight the hazards of inert gases and asphyxiating atmospheres.

3 Definitions

Asphyxiation: the effect on the body of inadequate oxygen, usually resulting in loss of consciousness and/or death. This is also known as suffocation or **anoxia**.

Asphyxiant: any material which reduces the amount of available oxygen either by simple dilution or by reaction.

Inert gas: A gas that is not toxic, which does not support human breathing and which reacts little or not at all with other substances. The common inert gases are nitrogen and the rare gases like helium, argon, neon, xenon and krypton.

Flammable gas: a gas whose major hazard is flammability. Note that all flammable gases also act as asphyxiants.

User: for the purpose of this document this term covers any individuals, companies or other organisations that make use of the products sold by industrial gas companies. Users may be, but are not necessarily, customers.

4 General Information about Inert Gases and Oxygen Depletion

In spite of the wealth of information available, such as booklets, films and audio-visual aids, there are still serious accidents resulting in asphyxiation caused by the improper use of inert gases or by oxygen depletion. It is therefore absolutely essential to draw attention to the hazards of inert gases and oxygen depletion. Accidents due to oxygen depleted atmospheres are usually very serious and in many cases fatal.

Although carbon dioxide is not an inert gas, most of the information in this document is applicable as it too will cause oxygen depletion. However, the specific hazards and physiological effects of carbon dioxide are more complex than those of inert gases. This document does not cover these aspects. (See IGC Doc. 67 "CO2 cylinders at user's premises" for more details about the additional hazards of carbon dioxide).

4.1 Oxygen is essential for life

Oxygen is the only gas that supports life. The normal concentration of oxygen in the air we breathe is approximately 21 %. Concentration, thinking and decision-making are impaired when the oxygen concentration falls only slightly below this norm. These effects are not noticeable to the affected individual.

If the oxygen concentration in air decreases or, if the concentration of any other gases increase, a situation is rapidly reached where the risks of asphyxiation are significant. For this reason any depletion of oxygen below 21 % must be treated with concern:

Asphyxia – Effect of O_2 Concentration (from NLI77 Campaign against Asphyxiation)

O_2 (Vol %)	Effects and Symptoms
18-21	**No discernible symptoms** can be detected by the individual. A risk assessment must be undertaken to understand the causes and determine whether it is safe to continue working.
11-18	Reduction of physical and intellectual performance **without the sufferer being aware**.
8-11	Possibility of fainting within a few minutes without prior warning. **Risk of death below 11%.**
6-8	Fainting occurs after a short time. **Resuscitation possible** if carried out immediately.
0-6	Fainting almost immediate. **Brain damage**, even if rescued.

***WARNING**: The situation is hazardous as soon as the oxygen concentration inhaled is less than 18 %.*
With no oxygen present, inhalation of only 1-2 breaths of nitrogen or other inert gas will cause sudden loss of consciousness and can cause death.

4.2 Inert gases give no warning

It is absolutely essential to understand that with inert gases such as nitrogen, argon, helium, etc., asphyxia is insidious - there are no warning signs!

- Inert gases are odourless, colourless and tasteless. They are undetectable and can therefore be a great deal more dangerous than toxic gases such as chlorine, ammonia, or hydrogen sulphide, which can be detected by their odour at very low concentrations.
- The asphyxiating effect of inert gases occurs without any preliminary physiological sign that could alert the victim. Lack of oxygen may cause vertigo, headache or speech difficulties, but the victim is not capable of recognising these symptoms as asphyxiation. Asphyxiation leads rapidly to loss of consciousness – for very low oxygen concentrations this can occur within seconds.

4.3 Inert gases act quickly

In any accident where the supply of oxygen to the brain is affected, prompt emergency treatment is critical. Proper medical treatment (resuscitation) if given quickly enough can prevent irreversible brain damage or even death in some instances.

Furthermore, and this is often poorly understood, the emergency rescue procedure to save the victim must be carefully thought out in advance to avoid a second accident, where members of the rescue

team can become victims. Unplanned interventions resulting in the fatalities of would-be rescuers are sadly not unusual.

4.4 The ambiguity of inert gases

Everyone, particularly customers, must be aware of the ambiguity of the expression "inert gas" (sometimes called "safety gas", when it is used to prevent fire or explosion), whereby an "inert gas" is often perceived, understood and wrongly taken to be a harmless gas!

4.5 Watchfulness with regard to inert gases and oxygen depletion

Considering the hazards mentioned above, it is essential to provide all those who handle or use inert gases (gas company personnel as well as customers) with all the information and training necessary regarding safety instructions. This includes the means of prevention and procedures to be respected to avoid accidents, as well as planned rescue procedures to be implemented in the event of an accident.

5 Some typical situations with inert gas and/or oxygen depletion hazards

5.1 Confined or potentially confined spaces and enclosures

Confined, restricted or enclosed spaces are particularly dangerous situations where an inert gas may be **normally present** (inside a process vessel), may have **accumulated** (from leaks or vents) and/or because the space has not been **adequately vented or purged**, and/or the renewal of air is poor or **ventilation is inadequate**.

Examples of such spaces include:

- Confined spaces: tanks, vessels, reservoirs, the inside of "cold boxes" of liquefaction equipment, cold storage rooms, warehouses with fire suppressant atmospheres, etc.
- Enclosures: analyzer or instrument cabinets, small storage sheds, temporary/tented enclosures, or spaces where welding protective gas is used, etc

The precautions required for safe access by personnel will be different in each of these cases as explained in Appendix B.

5.2 The use of inert cryogenic liquids

It is to be noted, that the use of inert cryogenic liquids such as nitrogen or helium is accompanied by two primary hazards:

- The fluids are very cold (-196°C for nitrogen and -269°C for helium) and can cause serious cold burns on contact with the skin.
- Once vaporised both products will generate a large volume of cold inert gas (e.g. 1 litre of liquid nitrogen will yield 680 litres gaseous product) that will displace ambient air, causing oxygen deficiency and may accumulate in low points.

In processes where cryogenic liquids are handled and vaporisation takes place, special care must be taken to avoid situations where personnel are exposed to oxygen deficiency. These may be in rooms which people regularly enter or work in.

Examples of such spaces include:

- The internal rooms of a building where cryogenic liquid cylinders/dewars are filled and/or stored,
- Laboratory rooms,
- Elevators (lifts) used for transport of dewars,
- Rooms where liquid nitrogen food freezers are operated. (Tunnel, cabinet)
- Rooms where Magnetic Resonance Imaging (MRI) scanner or other liquid helium cooled equipment is used
- Rooms in which cryogenic de-flashing equipment is operated.

Notes: Due to the extremely low temperature of liquid helium a secondary hazard may exist where the product is flowing through hoses or pipes. In this case it is possible for the components of air to liquefy on the outside of the hose/pipe, possibly leading to pooling of liquid containing levels of enriched oxygen. [See Ref. 7].

5.3 Areas near where inert gases are vented or may collect

The risk of asphyxiation can arise, even outdoors, in the vicinity of:

- Gas leaks
- Vent exhausts
- Outlet of safety valves and rupture disks
- Openings of machines in which liquid nitrogen is used for freezing
- Blind flanges
- Near manways/access to vessels or purged enclosures (e.g. ASU cold boxes, electrical enclosures)

Any cold gas or heavier-than-air gas will travel or "flow" – often unseen - and collect even outdoors, in low spaces such as:

- Culverts
- Trenches
- Machine pits
- Basements
- Elevator (lift) shafts

Similarly and just as dangerously lighter-than-air gases (e.g. helium) will rise and collect in unventilated high points such as:

- Behind false ceilings
- Under a roof

5.4 Use of inert gas instead of air

Planned Use

In many workplaces, there are often compressed inert gas distribution networks that are used for process applications, safety or instrumentation purposes, e.g. inerting/purging of reactors or using nitrogen as a pressure source to operate pneumatic equipment (such as jackhammers) or as instrument fluids.

Additionally, nitrogen is often used as either a backup to, or substitute for, an instrument air system. Where it is used as a backup supply in case of instrument air compressor failures it is quite common to find a nitrogen supply connected to an air supply by means of isolation valves, It must be appreciated that most pneumatically operated instruments vent continuously and that the vented nitrogen may accumulate in poorly ventilated control panels/cubicles or plant rooms. This can present a serious asphyxiation risk. Where nitrogen is used temporarily to substitute for compressed air in this way, it must be done under strictly controlled conditions such as a permit to work, and all relevant personnel shall be informed.

Improper Use

In situations where piped breathing systems exist there is always the potential for employees, who are insufficiently trained or not familiar with the systems, to connect the breathing apparatus to a nitrogen system with fatal results. Such systems must be clearly marked and ideally the breathing air system should have a dedicated connection type not used elsewhere in the premises.

5.5 Dangers of improper inhalation (abuse) of inert gases

There has been increased of reporting and presentations in TV-programmes on the careless approach and dangerous misuse of breathing in gases such as helium and other inert rare gases. The media reports in particular trivialise the effects of inhaling helium to achieve a very high-pitched voice. Inhalation of helium can lead to unconsciousness, cessation of breathing and sudden death.
[See Ref. 6 for more information]

6 Hazard mitigation and preventive measures

6.1 Information, training

All persons who handle or who use inert gases shall be informed of:
- Safety measures that should be adopted when using gases.
- The hazard represented by the release of inert gases in to the working space and the potential for oxygen depletion.
- Procedures to be observed should an accident occur.

This information and training should be systematically and periodically reviewed in order to ensure that it remains up to date and appropriate for the hazards identified.

6.2 Proper installation and operation

Equipment for the manufacture, distribution or use of inert gas must be installed, maintained and used in accordance with:
- All applicable regulations.
- The recommendations of the supplier
- Industrial gas industry standards and codes of practice

Newly assembled equipment for inert gas service must undergo a proof test and be leak-checked using suitable procedures.

Each inert gas pipeline entering a building should be provided with an easily accessible isolation valve outside the building. Ideally such valves should be remote activated by push buttons or other safety monitoring equipment.

Discontinued inert gas lines shall be physically disconnected from the supply system when not in use.

At the end of each work period, all valves that isolate the inert gas should be securely closed to avoid possible leakage between work periods.

6.3 Identification and safeguarding of potentially hazardous areas

Measures should be taken to identify potentially hazardous areas, or restrict access to them, e.g.
- Warning signs should be displayed to inform of an actual or potential asphyxiation hazard (An example is shown in Appendix D). The warning sign should be associated with measures to prevent unauthorised entry to the areas.
- Temporary or permanent barricades, for example physical lock on vessel manway or barricades around temporary excavations.
- Communication to site personnel to ensure awareness and understanding.

6.4 Ventilation and atmospheric monitoring for inert gases and oxygen deficiency

Typically there are three situations where the need for ventilation or atmospheric monitoring must be assessed in order to avoid asphyxiation accidents from inert gases and/or oxygen depletion:

6.4.1 Ventilation/ monitoring of rooms which people regularly enter or work in

Examples in this category would include:
- Rooms containing **inert gas pipelines** with possible leaks such as compressor houses, control rooms (with control/analyser panels).
- Rooms where **inert cryogenic liquid** is used or stored (see 5.2 above)

Building/room size, ventilation capacity, system pressures, etc. must be determined for each specific case. The following guidelines can be applied to ventilation system design:
- Ventilation must be continuous while the hazard exists. This can be achieved by interlocking the ventilation system with the process power supply.

- Ventilation system design should ensure adequate air flow around the normal operating areas.
- Good engineering practice indicates a minimum ventilation capacity of 6-10 air changes per hour.
- The use of devices to indicate correct system operation, such as:
  - Warning lights
  - "Streamers" in the fan outlet,
  - Flow switches in the suction channels (monitoring should not rely only upon secondary controls such as "power on" to the fan motor).
- Exhaust lines containing inert gases shall be clearly identified, and should be piped to a safe, well ventilated area outside the building, away from fresh air intakes.
- Consideration should be given to the use of workplace atmospheric monitoring, e.g. personal oxygen analyser or an analyser in the work area, location to be based on assessment of the areas described in 5.3.
- People working in or entering the area shall be aware of action required in event of alarms from atmospheric monitors or loss of ventilation.

6.4.2 Ventilation/ monitoring prior to entry into confined spaces or enclosures

As described in 5.1 above, these spaces would include enclosures or vessels which:
- Are not routinely entered and
- Are known to have contained inert gas or
- May contain inert gas or low concentration of oxygen
- Any vessel not known and verified to contain atmospheric air.

In these cases the following guidelines apply to prepare a safe atmosphere prior to entry:
- Sources of inert gas must be isolated from the space or enclosure by positive blinds or by disconnection of lines. Never rely only on a closed valve.
- The vessel or enclosure must be adequately purged with air (i.e. remove the inert gas and substitute with air).
  - It is necessary to have at least 3 complete air changes within the enclosure involved.
  - Purging shall continue until analysis confirms that the quality of the vessel atmosphere is safe for personnel entry. If there is any doubt that effective purging has taken place, the analysis should be made in the interior of the vessel by taking a sample at several locations by probe, or if this is not possible, by a competent person using a self contained breathing apparatus.
  - The purge system must ensure turbulence for adequate mixing of air and inert gas to take place (to avoid "pockets" of dense or light inert gases remaining or to avoid "channelling" of gases due to inadequate purging).
  - Removal of argon or cold nitrogen from large vessels and deep pits can be difficult due to the relatively high density of the gas compared with air. In that case the gas should be exhausted from the bottom of the space.
  - Ventilation should never be carried out with pure oxygen, but exclusively with air.
- Another method of removing inert gases is to fill the vessel with water and allow air to enter when the water is drained off.
- Oxygen content of the atmosphere in the enclosure/vessel shall be monitored continuously or repeated at regular intervals.
- Consideration should also be given to the use of personal oxygen monitors.

Where a safe atmosphere cannot be created and confirmed, then the task must only be performed by competent personnel provided with a positive breathing air supply.

6.4.3 Ventilation/monitoring for entry into other spaces where inert gases may be present

This type of confined space is one that has any of the following characteristics:
- Limited opening for entry and exit
- Unfavourable natural ventilation

Examples are listed in sections 5.1 and 5.3 and include;
- Underground works
- Trench/pit deeper than 1 metre
- Small rooms where gases are stored but not designed for continuous worker occupancy.

In the majority of these cases the presence of inert gases is not anticipated when entering such spaces. However, the one essential safeguard in all cases is to sample the atmosphere in the room, enclosure, trench, pit, etc. for oxygen prior to any entry. Where appropriate a continuous fixed point monitoring device should be used.

The fact that an oxygen deficient atmosphere is not normally expected is the greatest danger.

6.4.4 Notes on purging requirements

The guidance for air changes, mentioned in section 6.4.2, is valid where nitrogen is the inert gas involved because its density is very near to that of air and oxygen.

If the gas to be purged has a density very different from the density of air, such as helium, argon or carbon dioxide, etc. the ventilating air may not adequately mix and the purge may be inadequate.

For inert gases of this type the volume of gas to be displaced (air changes) must be at least 10 times that of the volume involved. The preferred method of removal of very dense gases (e.g. argon or cold nitrogen vapour) is to suck out the gas from the bottom of the space.

In the presence of toxic or flammable gases, it is mandatory to perform an additional analysis of the gases present in the confined space, before entry of personnel. For obvious reasons, the measurement of only the oxygen content is not sufficient in this case. All other dangerous toxic or flammable gases must also be analysed.

In the specific case of flammable gases, a nitrogen purge must be used first to prevent any explosion risk and then subsequently purge with ventilating air.

6.5 Testing of oxygen content

Historically, the need to check that an atmosphere is respirable has been considered to be of the greatest importance. In the past, simple means were employed, such as, for example, the lighted candle or the canary bird.

Currently, various types of oxygen analysers are available, which are often reliable and simple and to operate. The selection of the type of apparatus depends on the nature of the work in the place to be monitored (presence of dust, temperature and humidity, multiple detectors, portable equipment, etc.).

- Oxygen analysers are critical equipment and must be properly maintained and calibrated in order to sufficiently reliable. It is also important to ensure that fixed and portable detectors are properly positioned to measure a representative sample of the atmosphere.
- A simple way check to confirm that an oxygen analyser is operating properly before use is to measure the oxygen content of the open air (21 %). This check should be part of the work permit requirements.
- All oxygen analysers should be fitted with an alarm device to indicate possible defects (e.g. low battery).
- The minimum safe oxygen concentration for entry into a space that is being controlled or measured because of the risk is 19.5 % oxygen. There are applications with oxygen concentrations below 19.5 % where entry is permitted provided that further precautions are taken in accordance with proper risk assessment and national regulations (e.g. fire suppression). [See Ref 4]

6.6 Work permit

For certain types of work, safety instructions and a special work procedure must be set up in the form of a work permit, this particularly relates to any form of confined space entry. [See Ref 8]
This procedure is necessary during work carried out by subcontractors in air separation cold boxes, or where vessel entry is required.

It is important that a work permit procedure deals with the detailed information that must be given to involved personnel before the start of work. This information should include contractual conditions together with documented risk assessments, procedures and the training of site workers.

6.7 Lock-out Tag-out procedure

To ensure any sources of inert gas have been properly isolated, the implementation of a stringent, formal lock-out and tag-out procedure is necessary before safe entry into a confined space.

6.8 Protection of personnel

The type of work to be performed, the layout of the premises and the assessment of potential rescue scenarios will determine the provision of additional protective measures. This additional protection should include organisational measures and/or safety equipment such as:

- Fixed or personal oxygen monitoring equipment
- The wearing of a harness so that the worker can be easily and rapidly taken out of an enclosed space in the case of an emergency. Preferably, this harness is to be connected to a hoist to facilitate removing the victim. (In practice, it is extremely difficult for one person to lift up another person in the absence of a mechanical aid of some kind.)
- The provision of an alarm system in case of an emergency.
- The wearing of a self contained breathing apparatus (not cartridge masks, which are ineffective in a case of lack of oxygen).
- In the case of work inside a confined space, a standby person should be placed on watch outside the space/vessel.
- Having a self contained breathing apparatus on stand by.
- The wearing of other personal protective equipment such as safety boots, hard hat, goggles or gloves, depending on the hazards of the location and task.

7 Confined space entry

The employer has an overriding duty to ensure that tasks in confined spaces with potentially hazardous atmospheres are performed **without entry** whenever this is practical. Only if it there is no practical alternative shall people be required to enter confined spaces.

Any entry into a confined space or enclosure with a potentially hazardous atmosphere shall be carefully controlled and have:

- A written method statement for the work to be undertaken with the space.
- A documented risk assessment for performing this task in this particular vessel.
- Formal, stringent lock-out and tag-out procedures.
- An assessment of potential scenarios where rescue may be required.
- An emergency (rescue) plan to deal with any possible accident scenario related to entry in to the enclosure or vessel.
- Rescue personnel and equipment should be available as required by the rescue plan.
- Trained and competent personnel in roles of; entrant, stand-by watch, rescue team (where required) and supervisor/permit issuer.
- A safe work permit issued and signed before entry is allowed.

This document is not a detailed procedure for confined space entry, but focuses on the considerations which are important where there is an actual or potential hazard from inert gases or oxygen deficiency.

8 Rescue and first-aid

Awareness training in the hazards of inert gases and oxygen deficient atmosphere is of vital importance for everyone who might enter a space or who might discover and affected person in a space with potentially asphyxiant atmosphere, in order to prevent subsequent fatalities as result of "unplanned rescue" attempts.

Training in rescue work is fundamental since quickly improvised rescue without the formality of a procedure, often proves to be ineffective, if not catastrophic, i.e. the rescue worker lacking foresight becomes a second or even a third victim. This is one of the most common causes of multiple fatalities in cases involving asphyxiation.

8.1 Basic rules

If a person suddenly collapses and no longer gives any sign of life when working in a vessel, a partially enclosed space, a trench, a pit, a small sized room, etc., it MUST be assumed that the person may lack oxygen due to the presence of an inert gas (which is, as mentioned, odourless, colourless and tasteless):

WARNING: *the discoverer must assume that* ***his life is at risk*** *entering the same area!*

The risk is that the rescuer will become the second victim, which obviously must be avoided at all costs. Ideally he should raise an alarm and call for assistance so that a prepared rescue can be carried out.

Rescuers intent on saving a possible asphyxiation victim should only do so if they have the necessary equipment, have been suitably trained, have proper assistance and support.

8.2 Rescue plan elements

The method of rescue will be determined by the access to particular space. If practical a non-entry rescue is preferred. Appendix B lists the considerations which should be given to rescue plans from three different situations:

- Rescue from normally accessible rooms
- Rescue from Confined Spaces
- Rescue from pits, trenches or excavations

In each case the Rescue plan must have elements which address:

- How the alarm is raised
- Identification of possible rescue scenarios (not only for low oxygen effects)
- Any scenarios in the surrounding work place which may or may not require immediate exit from the space (e.g. site evacuation in event of fire elsewhere)
- Stand-by watch trained to keep visual and verbal contact with the entrant and to ensure the entrant exits the space if symptoms of oxygen deficiency are suspected or observed
- Any assistance which may be needed/given from outside the space to help entrant escape from the space, without further entry.
- Re-checking/confirmation of atmosphere prior to rescue
- Manpower and equipment required to move unconscious person from that space
- Provision of first aid/medical treatment (e.g. resuscitation and/or oxygen treatment) inside the space if necessary
- Safe access by rescue and/or medical personnel if necessary
- How to make the space safe/prevent further injury after the rescue.

8.3 Equipment

A successful rescue action may need some of the following equipment. The actual needs must be assessed as part of the rescue plan and made available and accessible during the confined space work:

- A portable audible alarm devices, e.g.; personal horn, whistle, klaxon etc. to alert nearby people that assistance is required.
- Telephone or radio at the work site so that an alarm can be raised in event of problems
- A safety belt or harness connected to a line
- Mechanical aid such as pulley, hoist, to extract the victim.
- Possibly a source of air or oxygen to ventilate the confined space, such as:
  - A compressed air hose connected to the plant compressed air network,
  - A ventilation device.

- Additional oxygen monitors for rescue team for re-checking conditions inside the space
- Positive pressure breathing air supply. This may be an externally fed breathing air system or self-contained breathing apparatus (SCBA).
  ***WARNING**: Cartridge masks for toxic gases are not suitable as they do not replenish missing oxygen.*
- A resuscitation kit supplied with oxygen for the victim. In general, such a kit includes a small oxygen cylinder, a pressure regulator, an inflatable bag, and a mask to cover both the nose and mouth of the victim.
- Stretcher to carry injured person out of the space, away from work place and/or to ambulance.

It should be noted that any equipment identified as necessary to carry out an emergency rescue from a confined space should be defined on the basis of a full risk assessment and the emergency plan developed from it. Where this equipment is not available, a rescue should not be undertaken.

8.4 Rescue training

Where an emergency plan considers that a rescue is to be performed, it is recommended that there is an annual programme of training including **practical rescue drills**. It is also a good practice to consider a rescue exercise before start of confined space work.

8.5 First Aid

Where there is a potential hazard from inert gases/oxygen deficiency it is advisable to have personnel available who are formally qualified to give first aid and/or perform **resuscitation** in the event of an accident. The simplest first aid treatment for someone suffering from effects of oxygen deficiency is to bring the affected person **into fresh air** – as long as it safe to do so!

In most countries additional training is required so that first aiders are qualified to **provide Oxygen** as medical treatment for anoxia and other conditions.

9 Conclusions

There are two essential points to remember related to oxygen deficiency accidents involving inert gases:

- Accidents resulting from oxygen deficiency due to inert gases happen unexpectedly and the reactions of personnel may be incorrect. To avoid this, all personnel who may work with, or may be exposed to, inert gases must have routine awareness training in respect of the hazards of these gases.
- Accidents involving asphyxiant atmospheres are always serious, if not fatal. It is absolutely necessary to carry out both regular and periodic awareness training sessions for all personnel, as well as rescue drills.

10 References

[1] CGA document SB-2 2007 Oxygen-Deficient Atmospheres

[2] EIGA Asphyxiation campaign documents 2003 – including Dangers of Asphyxiation leaflet; Oxygen Deficiency training presentation and Newsletter 77/xx

[3] Oxygen deficiency hazards. Video tape EIGA, 1997

[4] EIGA Position Paper PP-14: Definitions of Oxygen Enrichment/Deficiency Safety Criteria – August 2006.

[5] US Chemical Safety and Hazard Investigation Board website Video Room www.csb.gov

[6] EIGA position Paper PP-24: Abuse of Gases

[7] IGC Doc 004 Fire Hazards of Oxygen and Oxygen Enriched Atmospheres

[8] IGC Doc 040 Work Permit Systems

Appendix A: Summary for operators

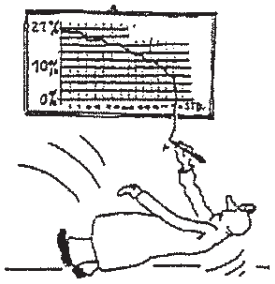
1 Why do we need oxygen?

OXYGEN IS ESSENTIAL FOR LIFE

WITHOUT ENOUGH OXYGEN WE CANNOT LIVE

When the natural composition of air is changed, the human organism can be affected or even severely impaired.

If gases other than oxygen are added or mixed with breathing air, the oxygen concentration is reduced (diluted) and oxygen deficiency occurs.



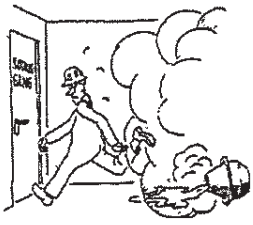
If oxygen deficiency occurs due to the presence of inert gases (e.g. nitrogen, helium, argon, etc.) a drop in physical/mental efficiency occurs without the person's knowledge; at about 11 % oxygen concentration in air (instead of the normal 21 % concentration) fainting occurs without any prior warning.

Below this 11 % concentration there is a very high risk that death due to asphyxiation will occur within a few minutes, unless resuscitation is carried out immediately!

See also EIGA Safety Newsletter **NL/77 Campaign against Asphyxiation**

2 Causes of oxygen deficiency

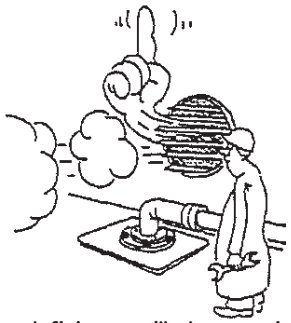
a) When liquefied gases (such as liquid nitrogen, liquid argon, or liquid helium) evaporate, one litre of liquid produces approximately 600 to 850 litres of gas. This enormous gas volume can very quickly lead to oxygen deficiency unless there is adequate ventilation.



b) In the event of gases other than oxygen leaking out of pipe work, cylinders, vessels, etc., oxygen deficiency must always be expected. Checks should be made periodically for possible leaks.

Spaces with limited or inadequate ventilation (e.g. vessels) must not be entered unless air analysis has been made, safe conditions are confirmed and a work permit has been issued.

c) If work has to be carried out in the vicinity of ventilation openings, vent pipes or vessel man ways for example, personnel must be prepared to encounter gases with low oxygen concentration or without oxygen at all, being discharged from these openings.



d) Oxygen deficiency will always arise when plant and vessels are purged with nitrogen or any other inert gases.

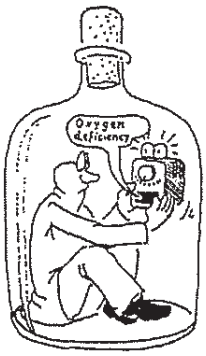
3 Detection of oxygen deficiency

HUMAN SENSES CANNOT DETECT OXYGEN DEFICIENCY

Measuring instruments give an audible or visual alarm of oxygen concentration and can indicate the oxygen content.

These instruments should always be tested in the open air before use.

If the presence of toxic or flammable gases is possible, specific instruments should be used.



4 Breathing equipment

Breathing equipment must be used in situations where oxygen deficiency has to be expected and which cannot be remedied by adequate ventilation.

Cartridge gas masks necessary for use in the presence of toxic gases (such as ammonia, chlorine, etc.) are useless for this purpose.

Recommended types of breathing equipment are:
- Self contained breathing apparatus using compressed air cylinders;
- Full-face masks with respirator connected through a hose to a fresh air supply.

NOTE:

- It should be born in mind that when wearing these apparatus, particularly with air filled cylinders, it might sometimes be difficult to enter manholes.
- Periodic inspection of the correct functioning of the equipment shall be carried out in accordance with local regulations.
- Users shall be trained and shall practice handling of the equipment regularly.

5 Confined spaces, vessels, etc.

Any vessel or confined space where oxygen deficiency is expected and which is connected to a gas source shall be disconnected from such a source:

By the removal of a section of pipe; or
by inserting a blanking plate before and during the entry period.

Reliance on the closure of valves alone might be fatal.

A space or vessel should be thoroughly ventilated, and the oxygen content shall be measured periodically before and during entry period.

If the atmosphere in such a vessel or space is not breathable, a qualified person shall use breathing equipment.

Permission to enter such a space shall be given **only after** the issue of an **entry permit** signed by a **responsible** person.

As long as a person is in a vessel or confined space, a watcher shall be present and stationed immediately outside of the confined entrance.

He shall have a self-contained breathing apparatus readily available.

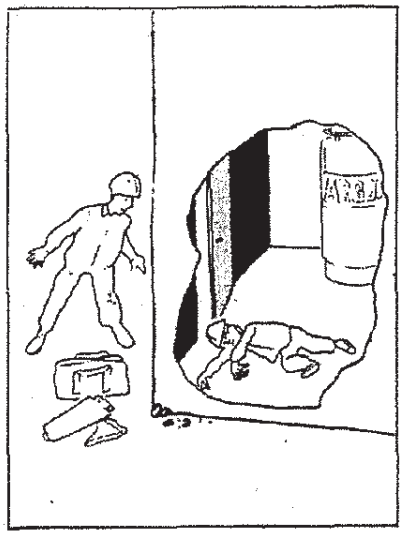
The person inside the confined space to facilitate rescue shall wear a harness and rope. The duty of the watcher should be clearly defined. A hoist may be necessary to lift an incapacitated person.

6 Emergency Measures

In the event of a person having fainted due to oxygen deficiency, he can only be rescued if the rescue personnel are equipped with breathing apparatus enabling them to enter the oxygen deficient space without risk.

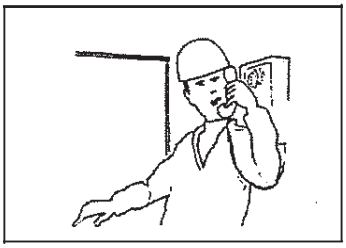
Remove the patient to the open air and administer oxygen without delay from an automatic resuscitator if available or supply artificial respiration. Guidelines and instructions for resuscitation can be obtained from the European Resuscitation Council (Internet Homepage: www.erc.edu).
Continue until patient revives or advised to stop by qualified medical personnel.

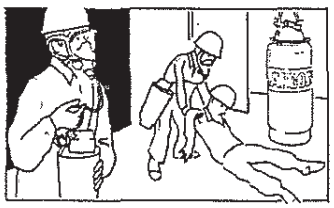
Appendix B1: Rescue considerations from normally accessible rooms

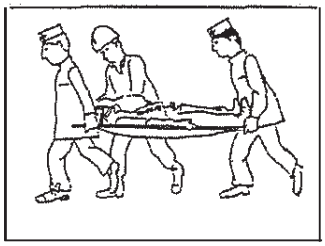


Planned Rescue Scenario:
If work is undertaken **on inert gas or cryogenic liquid systems within an enclosed room** it is suggested that:

- The entrant carries a personal oxygen monitor in addition to any fixed systems as the oxygen concentration may vary within the room if ventilation is absent or inadequate for the leak rate.
- The atmosphere within the space is checked before entry
- A stand-by watch is posted outside the space, to keep visual and verbal contact with the entrant and to ensure the entrant leaves the room unaided in case of early symptoms of oxygen deficiency
- The stand-by watch can raise an alarm by telephone or radio on event of problems
- The stand-by watch has Self Contained Breathing Apparatus (SCBA) ready so that he can safely enter the enclosed room to go to the assistance of, or to extract the victim if necessary.
- Unless a plan is in place so that the entrant can be safely removed by the standby-watch alone, then the rescue team should have been warned of the confined space entry work in progress, and be ready with Self Contained Breathing Apparatus (SCBA) and other equipment so that they can safely enter the Confined space to go to the assistance of, or to extract the victim if necessary.
- Plans have been made to obtain treatment/assessment from qualified medical personnel for the victim as soon as possible after he is retrieved from the room.





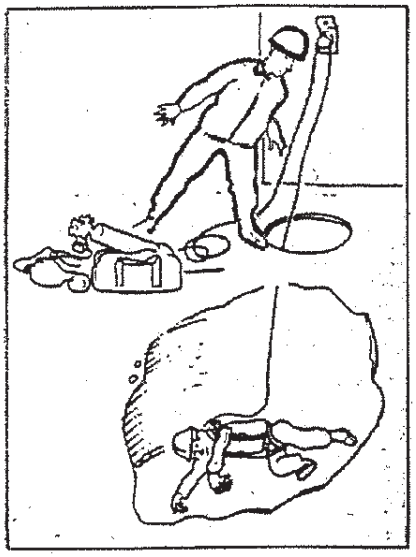


Unplanned Rescue Scenario:
If a person is found collapsed in a room where there is a potential inert gas leak / oxygen deficient atmosphere, then the discoverer must assume that **his life is at risk** entering the same area.
He should raise an alarm and call for assistance so that a prepared rescue can be carried out.

ONLY if the collapsed person can be reached, from outside the room should any consideration be given to extracting the victim from the space and bringing him out to fresh air and medical attention.

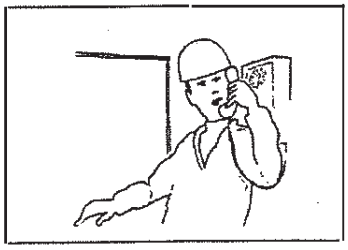
IF the victim has collapsed as a result of an oxygen deficient atmosphere and been there for any length of time it is very likely that he is dead and the discoverer's life is risked in vain.

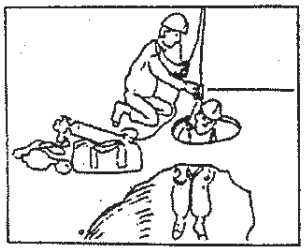
Appendix B2: Rescue considerations from Confined Spaces

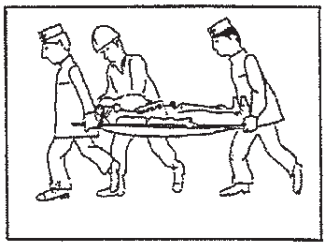


Planned Rescue Scenario:
If work is undertaken within a **Confined Space** such as a vessel or a difficult access space, with potential inert gas/ oxygen deficient atmosphere, it is essential that:

- The atmosphere within the space is made safe, ventilated and checked before entry
- The entrant carries a personal oxygen monitor.
- If practical the entrant wears a body harness with life line, so that he can be removed from the space by persons outside. A hoist or other mechanical aid may be needed
- A stand-by watch is posted outside the space, to keep visual and verbal contact with the entrant and to ensure the entrant exits the Confined Space if symptoms of oxygen deficiency are suspected or observed
- The stand-by watch can raise an alarm to call a trained rescue team by telephone or radio on event of problems
- The rescue team should have been warned of the confined space entry work in progress, and be ready with Self Contained Breathing Apparatus (SCBA) and other equipment so that they can safely enter the Confined space to go to the assistance of, or to extract the victim if necessary.
- The stand-by watch should never enter the Confined Space.
- Plans have been made to obtain treatment/assessment from qualified medical personnel for the victim as soon as possible after he is retrieved from the room.





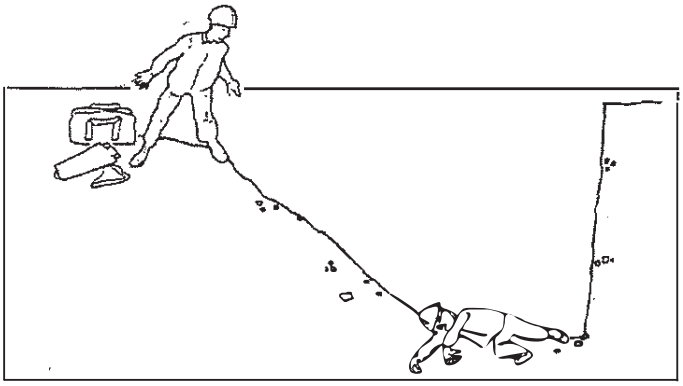


Unplanned Rescue Scenario:
All Confined Spaces shall be closed or barricaded to prevent unauthorised access. There should be no possibility for uncontrolled entry into the Confined Space, so the "unplanned rescue" situation should not occur!

If however a person is found collapsed in a Confined Space where there is a potential inert gas / oxygen deficient atmosphere, then the discoverer must assume that **his life is at risk** entering the same area. He must raise an alarm and call for assistance so that a prepared rescue can be carried out.

IF the victim has collapsed as a result of an oxygen deficient atmosphere and been there for any length of time it is very likely that he is dead and the discoverer's life is risked in vain.

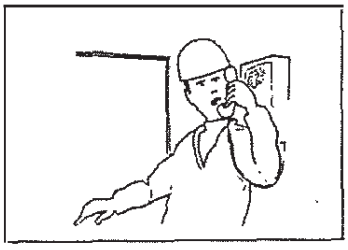
Appendix B3: Rescue considerations from pits, trenches

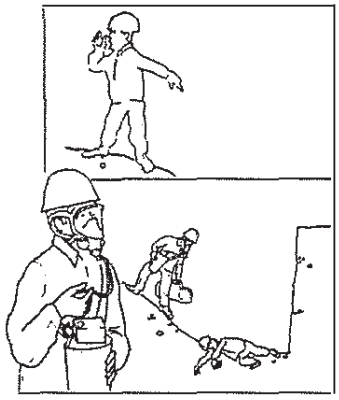


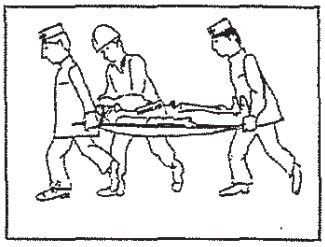
Planned Rescue Scenario:

If work is undertaken in an **excavation, trench, pit**, or other open spaces with potential inert gas / oxygen deficient atmosphere, it is strongly recommended that:

- The atmosphere within the space is checked before entry
- The entrant carries a personal oxygen monitor, as the oxygen concentration may vary within the space if there is limited fresh air circulation.
- A stand-by watch is posted outside the space, to keep visual and verbal contact with the entrant and to ensure the entrant exits the area unaided if symptoms of oxygen deficiency are suspected or observed.
- The stand-by watch can raise an alarm to call a trained rescue team by telephone or radio on event of problems.
- The stand-by watch has Self Contained Breathing Apparatus (SCBA) ready IF it is practical for him enter the enclosed room to go to the assistance of, or to extract the victim alone. OR
- The rescue team should have been warned of the confined space entry work in progress, and be ready with Self Contained Breathing Apparatus (SCBA) and other equipment so that they can safely enter the space to extract the victim if necessary
- Plans have been made to obtain treatment/assessment from qualified medical personnel for the victim as soon as possible after he is retrieved from the room.







Unplanned Rescue Scenario:
If a person is found collapsed in a trench, pit or other space where there is a potential inert gas leak / oxygen deficient atmosphere, then the discoverer must assume that **his life is at risk** entering the same area. He should raise an alarm and call for assistance so that a prepared rescue can be carried out.

IF the victim has collapsed as a result of an oxygen deficient atmosphere and been there for any length of time it is very likely that he is dead and the discoverer's life is risked in vain.
In addition it will often require several people to remove a victim from these kinds of spaces.

Appendix C: Accidents involving oxygen deficiency

The following list highlights real accidents recorded by EIGA, some of them very recent. The list illustrates how essential it is to regularly draw the attention of our personnel, as well as that of our customers, to the hazards of inert gases and oxygen deficiency.

1. A new pipeline in a trench was being proof tested with nitrogen. A charge hand entered the trench to investigate the cause of an audible leak. He was overcome by nitrogen and died.

2. A workman was overcome by lack of oxygen after entering a large storage tank, which had been inerted with nitrogen. Two of his workmates, who went to his aid, without wearing breathing equipment, were also overcome and all three died.

3. A man was overcome on entering a steel tank which had been shut up for several years. The atmosphere inside the tank was no longer capable of supporting life due to removal of oxygen from the air by the rusting of steel.

4. A worker from a contractor company had to carry out welds inside a vessel. The vessel had been under a nitrogen blanket, but was ventilated with air before work started. In order to be on the safe side, the welder was asked to wear a fresh air breathing mask. Unfortunately a fellow worker connected the hose to a nitrogen line and the welder died from asphyxiation.

   This accident happened because the nitrogen outlet point was not labelled and had a normal air hose connection.

5. Welding work with an argon mixture was performed inside a road tanker. During lunchtime the welding torch was left inside the tank, and as the valve was not properly closed, argon escaped. When the welder re-entered the tank, he lost consciousness, but was rescued in time.

   Equipment that is connected to a gas source, except air, must never be left inside confined spaces during lunch breaks, etc. Merely closing the valves is not a guarantee against an escape of gas. If any work with inert gas is carried out in vessels, etc. take care with adequate ventilation or the use of proper breathing equipment.

6. A driver of a small-scale liquid nitrogen delivery service vehicle was making a delivery. He connected his transfer hose to the customer-installed tank, which was situated in a semi-basement. After he had started to fill, one of the customer's employees told him that a cloud of vapour was forming around the tank. The driver stopped the filling operation and returned to the area of the tank to investigate. On reaching the bottom of the stairs, he collapsed, but fortunately he was seen by one of the customer's staff that managed to put on breathing apparatus, go in and drag the man to safety. The driver fully recovered.

   Unknown to the driver, the bursting disc of the storage tank had failed prior to the start of his fill and as soon as he started filling, nitrogen escaped in the vicinity of the storage tank. The oxygen deficient atmosphere overcame him when he went down to investigate without wearing his portable oxygen monitor, which would have warned him of the oxygen deficiency. The installation had been condemned and was no longer being used. Not only was the tank situated in a semi-basement, but the relief device was also not piped to a safe area.

7. During a routine overhaul of an air separation plant, a maintenance technician had the task of changing the filter element on a liquid oxygen filter. The plant was shut down and a work permit was issued each day for each element of work. In spite of these precautions, the technician collapsed when he inadvertently worked on the filter after it had been purged with nitrogen. The fitter collapsed apparently asphyxiated by nitrogen. All efforts to revive him failed.

8. At a cryogenic application, the equipment pressure relief valve located on the equipment **inside** the building opened because the pressure in the storage tank **outside** increased above the setting of the equipment pressure relief valve. Personnel about to enter the room the next morning were warned by the frosted appearance and did not enter.

9. A customer was supplied with 2 low temperature-grinding machines, which were located in the same area in the factory. The customer installed a joint nitrogen extraction system between the two machines. One machine was switched off for cleaning while the other machine was left running. One of the operators who had entered the unit for cleaning fell unconscious and was asphyxiated before help arrived. The linked extraction system had allowed exhausted nitrogen from the operating machine to flow into the unit to be cleaned.

10. A driver was fatally asphyxiated during commissioning of a nitrogen customer station. The customer station tank was located in a pit that was not recognized as a confined space by the design team, distribution operation team or the driver. The driver was sent to do the commissioning by himself.
    During the commissioning the driver made a mistake in opening the liquid supply line valve, instead of the gas vent valve, for purging and cool down of the tank. It is believed he did not immediately notice the valving error partially due to a modified manifold that allowed gas to vent from an uncapped drain in the liquid supply line. When the driver opened the valve gas started venting as would normally occur except from the wrong location. Once he noticed that liquid rather than gas venting, he went into the pit to correct the valving error. At this point he walked into a nitrogen rich/oxygen deficient atmosphere.

11. A group of workers were routinely working at the in-feed end of a tunnel freezer. As the temperature of the tunnel was approaching the desired set point, a new operator noticed that there was a cloud of N_2 gas coming out at exit end of the freezer. He suddenly increased the speed of the scroll fan in order to remove the gas from exit to product entrance. The exhaust and scroll fans were running on manual mode. As a result, the N_2 cloud moved to product entrance and five workers who were working around the loading table passed out. Fortunately, there were no serious injuries and all of them returned to work after taking a rest.

12. On an ASU still in commissioning phase three painters from a sub-subcontractor were working on a ladder to complete external painting works on nitrogen/water tower. To complete the painting of top tower section a wooden plank was put across the exhaust section to atmosphere. One painter climbed on the plank, surrounded by the nitrogen stream, and fell off inside the tower. The two other painters rushed from the ladder to the plank to rescue their team mate. Both collapsed into the tower as well. The three painters died before they could be rescued.

13. An experienced contractor was used to purge a natural gas pipeline, 0.5m diameter 10 km long, with nitrogen before start-up. When one contractor employee and two customer employees entered the remotely located chamber, they were asphyxiated and later found dead in the chamber. Two blind flanges were leaking and the oxygen monitor was not used.

14. A customer nitrogen tank, volume 10 m^3, on a PSA plant was to be inspected by the competent body. The inspector entered the tank and lost consciousness immediately. Two persons from the gas company participating in the inspection managed to bring the inspector out without entering the tank. The inspector recovered.

15. A liquid CO_2 tank was installed. The tank should be purged with air but mistakenly the hose was connected to nitrogen. The tank manhole was situated 4 m above ground. For reasons unknown, a contract employee brought a ladder, entered the tank and was asphyxiated. Previously that morning employees had been told not to enter the tank before the atmosphere was officially checked.

16. Employee stepped into a control cubicle where the instrument air was temporarily replaced with N2 during shutdown. The green light outside the door was on indicating safe atmosphere. As soon as he stepped into the cubicle his personal O_2 monitor alarmed indicating 18% O_2 or less. After exiting safely he opened the door and when O_2 level was OK, checked the fan. The ventilation fan was not running. The light was wrongly wired.

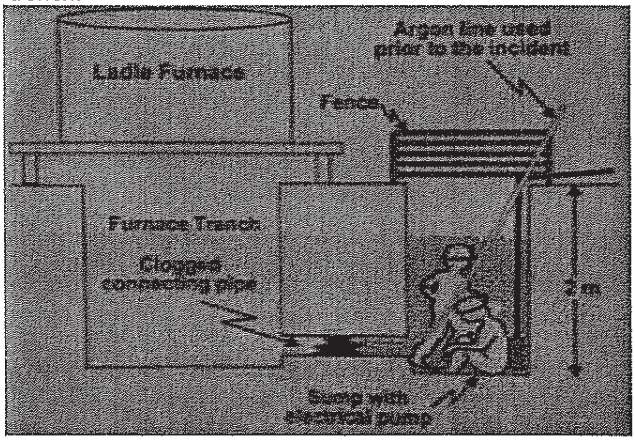
17. The perlite in a storage tank under erection had to be emptied by a contractor company, familiar with this job. During this work one of the workers fell down in the perlite, depth approximately 3m, and was asphyxiated.

18. During the cleaning and painting maintenance of the internal and external surfaces of a water tank, one operator suffered anoxia due to nitrogen being used to purge the vessel instead of air. Two employees tried to rescue the victim and fainted. These two operators were rescued and transported to hospital for intensive care however the original operator died.

19. During the installation of a new LIN phase separator on LIN pipe work at a customer site, a technician went into the roof space. His personal oxygen-monitoring device began to alarm immediately, indicating low oxygen levels. The technician left the roof space immediately and informed the customer. Later in the same week, the customer owned food-freezing machinery was operating, and a project engineer measured concentrations far below 19% in the production room. He left the room, asked all subcontractors to stop work and leave the room, and informed the customer. Investigation showed that the customer had not connected the exhaust ducting to the food-freezing machine that they owned and installed. The exhaust pipes ended in the attic space, not being extended to the atmosphere. Customer had "bridged" the alarm/trip output so LIN supply would not be shut off by low O_2 concentrations.

20. An experienced site employee wanted to take some photographs to add to a report concerning production problems relating to problems with leaks in the argon condenser. In the control room he asked a Contractor to accompany him to take photographs of equipment in the cold box. One hour later the two men were found unconscious in a manhole access to the cold box. Emergency authorities were called and declared the two men dead.

21. Two people on a customer's site were asphyxiated and died whilst attempting to unblock a pipe, using Argon gas in a confined space. The use of Argon gas in this application is not authorised. The incident took place in a sump 2 metres below ground level, which is used to drain water from a nearby trench.



22. An air compressor that provided instrument air to an acetylene plant and for breathing air failed. A back-up nitrogen supply from a liquid cylinder was connected to the piping system to replace the function of the air compressor. An operator put on a full respiratory face mask to load Calcium Carbide into the hopper and inhaled nitrogen. He died.

Appendix D: Hazard of inert gases sign

DANGER OF DEATH

Potential Asphyxiating Atmosphere

Safety Bulletin

U.S. Chemical Safety and Hazard Investigation Board

HAZARDS OF NITROGEN ASPHYXIATION

No. 2003-10-B | June 2003

Introduction

Every year people are killed by breathing "air" that contains too little oxygen. Because 78 percent of the air we breathe is nitrogen gas, many people assume that nitrogen is not harmful. However, *nitrogen is safe to breathe only when mixed with the appropriate amount of oxygen.*

These two gases cannot be detected by the sense of smell. A nitrogen-enriched environment, which depletes oxygen, can be detected only with special instruments. If the concentration of nitrogen is too high (and oxygen too low), the body becomes oxygen deprived and asphyxiation occurs.

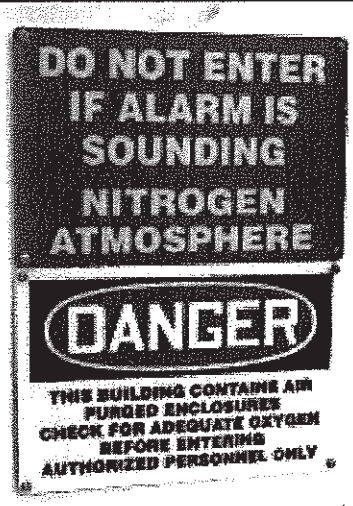
This Safety Bulletin is published to bring additional attention to the continuing hazards of nitrogen asphyxiation.[1]

- Nitrogen is widely used commercially. It is often used to keep material free of contaminants (such as oxygen) that may corrode equipment, present a fire hazard, or be toxic.
- Nitrogen asphyxiation hazards in industry resulted in 80 deaths from 1992 to 2002. These incidents occurred in a variety of facilities, including industrial plants, laboratories, and medical facilities; almost half involved contractors.
- Good practices and awareness of hazards minimize the risk of nitrogen asphyxiation (Figure 1).

Many incidents reviewed by CSB were caused by inadequate knowledge of the hazard or inadvertent use of nitrogen rather than breathing-air delivery systems.

This bulletin focuses only on the hazard of asphyxiation, though nitrogen also presents cryogenic and high-pressure hazards.

* Figure 1. Sign warning of nitrogen hazard.



Commercial Uses of Nitrogen

One of the most important commercial uses of nitrogen is as an inerting agent to improve safety. Nitrogen is inert under most conditions (i.e., it does not react with or affect other material).

It is often used to keep material free of contaminants, including oxygen— which can corrode equipment or present a fire and explosion hazard when in contact with flammable liquids or combustible solids. In such cases, a flow of nitrogen is maintained in a vessel to keep oxygen out. Nitrogen is also used to purge air from equipment prior to introducing material, or to purge flammable or toxic material prior to opening equipment for maintenance.

In industrial and commercial settings where a nitrogen-enriched environment may present a hazard, such as when using supplied air or working in or around spaces that are confined,

[1] In 1998, the U.S. Chemical Safety Board (CSB) investigated a nitrogen asphyxiation incident that occurred in Hahnville, Louisiana. As part of that investigation, CSB reviewed the prevalence of asphyxiation incidents.

precautions must be taken to ensure that sufficient oxygen is provided to personnel.

* Nitrogen is safe to breathe only when mixed with the appropriate amount of oxygen.

Effects of Oxygen-Deficient Atmosphere

Nitrogen is not a "poison" in the traditional sense. It presents a hazard when it displaces oxygen, making the atmosphere hazardous to humans. Breathing an oxygen-deficient atmosphere can have serious and immediate effects, including unconsciousness after only one or two breaths. The exposed person has no warning and cannot sense that the oxygen level is too low.

The Occupational Safety and Health Administration (OSHA) requires employers to maintain workplace oxygen at levels between 19.5 and 23.5 percent. As shown in the table on page 3, the human body is adversely affected by lower concentrations.

As the oxygen concentration falls below 16 percent, the brain sends commands to the breathing control center, causing the victim to breathe faster and deeper. As the oxygen level continues to decrease, full recovery is less certain. An atmosphere of only 4 to 6 percent oxygen causes the victim to fall into a coma in less than 40 seconds. Oxygen must be administered within minutes to offer a chance of survival. Even when a victim is rescued and resuscitated, he or she risks cardiac arrest.

* In industrial and commercial settings where a nitrogen-enriched environment may present a hazard, . . . precautions must be taken to ensure that there is sufficient oxygen in the atmosphere.

* Nitrogen . . . presents a hazard when it displaces oxygen.

Statistics on Nitrogen Asphyxiation

From reported data for the United States, CSB identified 85 nitrogen asphyxiation incidents that occurred in the workplace between 1992 and 2002. In these incidents, 80 people were killed and 50 were injured.[2]

Profile of Affected Industries and Activities

Of the 85 incidents reported, 62 percent occurred in chemical plants and refineries, food processing and storage facilities, metal and manufacturing operations, and other industrial, maritime, and manufacturing sites, including nuclear plants.

Approximately 13 percent of the incidents involved maintenance

CSB Safety Bulletins offer advisory information on good practices for managing chemical process hazards. Case studies provide supporting information. Safety Bulletins differ from CSB Investigation Reports in that they do not comprehensively review all the causes of an incident.

U.S. Chemical Safety and Hazard Investigation Board
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202-261-7600
www.chemsafety.gov

[2] Data sources for the CSB review include regulatory agencies, media reports, technical publications, and contacts with safety personnel; however, only those incidents that were reported and accessible are represented. Although the summary data reported above are not all-inclusive, the numbers clearly indicate that nitrogen asphyxiation presents a serious hazard in the workplace. Statistical analysis is based on available, limited information.

Effects of Oxygen Deficiency on the Human Body

Atmospheric Oxygen Concentration (%)	Possible Results
20.9	Normal
19.0	Some unnoticeable adverse physiological effects
16.0	Increased pulse and breathing rate, impaired thinking and attention, reduced coordination
14.0	Abnormal fatigue upon exertion; emotional upset, faulty coordination, poor judgment
12.5	Very poor judgment and coordination, impaired respiration that may cause permanent heart damage, nausea, and vomiting
<10	Inability to move, loss of consciousness, convulsions, death

SOURCE: Compressed Gas Association, 2001.

* CSB identified 85 nitrogen asphyxiation incidents that occurred in the workplace between 1992 and 2002 . . . 80 people were killed and 50 were injured.

activities, such as railcar and tank truck cleaning, painting, maintenance, and repair. These incidents are categorized as "maintenance" because incident reports do not include enough information on the type of industrial setting; they could have occurred at manufacturing sites, which would increase the 62 percent estimate above.

Likewise, trenches and manholes—not specifically identified as being in manufacturing facilities—account for about 14 percent of the incidents. The remainder of the incidents occurred in laboratories and miscellaneous industries, such as medical and transportation.

The data show that employees and contractors alike are victims of asphyxiation. Of the 85 incidents reviewed, 42 involved contractors, including construction workers;

* Of the 85 incidents reviewed, 42 involved contractors, including construction workers; these 42 incidents account for over 60 percent of the fatalities.

* . . . 130 workplace fatalities and injuries occurred from breathing nitrogen-enriched air. Over 60 percent of these victims were working in or next to a confined space.

these 42 incidents account for over 60 percent of the fatalities.

Causal Information

From the CSB data, a combined total of 130 workplace fatalities and injuries occurred from breathing nitrogen-enriched air. Over 60 percent of these victims were working in or next to a confined space.[3,4]

One characteristic of a confined space is its capability to contain an atmosphere that may be totally different from outside air. Confined spaces in manufacturing sites typically include equipment such as reactors, vessels, tanks, and boilers. Other such spaces are railcars, trenches, and areas accessible by manholes.

[3] "Next to a confined space" means that a person's breathing zone is affected by the atmosphere emanating from the space. The person may be standing in the immediate area but not actually in the space.

[4] According to OSHA, a confined space can be entered to perform work, has limited means of egress, and is not designed for continuous employee occupancy. A "permit-required confined space" includes a space that contains or has the potential to contain a serious safety or health hazard, such as a hazardous atmosphere.

Failure to Detect Oxygen-Deficient Atmosphere

Failure to detect an oxygen-deficient (nitrogen-enriched) atmosphere was a significant factor in several incidents.

In the data evaluated for this study, 67 of the 85 incidents involved circumstances where personnel were in or around a confined area—such as a railcar, room, process vessel, or tank (Figure 2)—and nitrogen was initially present in high levels or later collected in the area. These incidents accounted for 62 fatalities and 33 injuries. In each of the 67 incidents, personnel failed to detect elevated levels of nitrogen and take appropriate precautions.

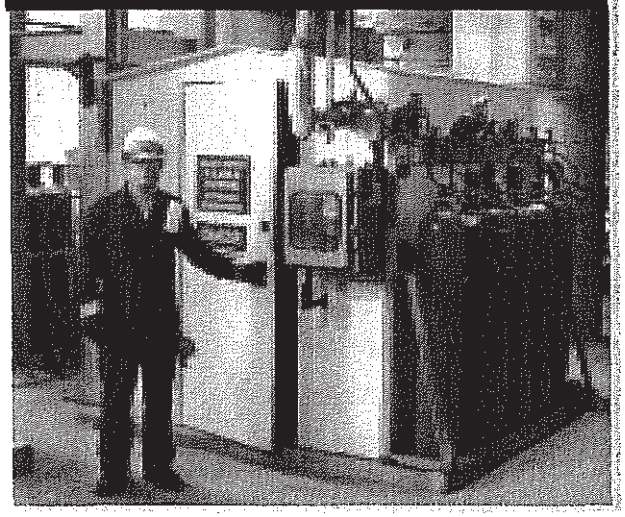
When fatalities and injuries occurred in "open areas" (including areas with ventilation, laboratories, buildings, and outside in the vicinity of equipment), the hazard of asphyxiation was not expected and personnel were typically caught off guard. In some cases, personnel unknowingly created a nitrogen-enriched atmosphere by mistakenly using nitrogen instead of air to flush equipment prior to entry. In either situation, inadequate knowledge of the hazard and failure to detect additional nitrogen resulted in a fatal concentration of gas.

* When fatalities and injuries occurred in "open areas" . . . the hazard of asphyxiation was not expected and personnel were typically caught off guard.

Mix-Up of Nitrogen and Breathing Air

Confusing nitrogen gas with air and problems with breathing-air delivery systems accounted for 12 of the 85 incidents, and approximately 20 percent of fatalities.

* Figure 2. Confined area.



The data provide examples of workers inadvertently using nitrogen instead of air because of interchangeable couplings on lines and poor or nonexistent labeling.

In one incident, a worker mistakenly used nitrogen instead of air to purge a confined space. An inert atmosphere was unexpected and undetected. One worker was killed, and a colleague also died while attempting rescue. In another case, workers inadvertently connected the hose for their breathing-air respirator to a pure nitrogen line.

* In one incident, a worker mistakenly used nitrogen instead of air to purge a confined space . . . In another case, workers inadvertently connected the hose for their breathing-air respirator to a pure nitrogen line.

Fatalities and Injuries During Attempted Rescue

One of the most difficult issues concerning hazardous atmosphere emergencies is the human instinct to aid someone in distress. Approximately 10 percent of fatalities from the CSB data were due to attempts to rescue injured persons in confined spaces.

* Approximately 10 percent of fatalities from the CSB data were due to attempts to rescue injured persons in confined spaces.

Asphyxiation Hazards Outside Industry and Effect on General Public

Asphyxiation hazards may also be present outside industry, especially among people who use breathing air, such as firefighters, divers, and medical patients. Statistics on these types of incidents are difficult to collect and are not included in this bulletin, though one such case is summarized below.

Selected Case Studies

Failure to Recognize Asphyxiation Hazards Near Confined Spaces

Employee Dies After Partially Entering a Nitrogen-Purged Tank

Two coworkers and the victim were cleaning filters in a hydrogen purifying tank. The tank was partly purged with nitrogen to remove internal dust particles. The victim used a lift to access the *external* area of the upper tank, which was fitted with a manway. As he leaned into the tank opening, his coworkers noticed that he was not responding to their communication. They found the victim unconscious, and he later died as a result of oxygen deficiency.

Employee Overcome While Testing Atmosphere

An operator was conducting a flammable gas test on a tower feedline that discharged into a low-pressure flare gas header. The test was required for a hot work permit to take flash photos.

The chief operator issued a work permit that required a supplied-air respirator. Two contractor pipefitters wore respirators and removed the safety valve. The operator, however, wore no respiratory protection. After climbing the scaffold, he was overcome by nitrogen gas from the open flare line before he could complete atmospheric sampling.

The operator backed away, turned, and slumped to his knees. He was disoriented and briefly lost consciousness. An investigation concluded that the incident was due to elevated levels of nitrogen gas that had inadvertently entered the flare system.

Inadequate Monitoring of Atmosphere

Contractor Asphyxiated Inside Tank Car

White mineral oil in a tank car at an oil refinery was offloaded by injecting nitrogen gas into the car. An employee of a railcar cleaning company was asphyxiated while cleaning the nitrogen-filled tank car.

Corrupt Breathing Air Supply

Two Laborers/Painting Contractors Asphyxiated

Two painting contractors were abrasive-blasting tubes inside a boiler at a chemical plant. They each wore supplied-air respirators connected to a 12-pack cluster of compressed air cylinders. Another subcontractor monitored the work outside the confined space.

Work proceeded normally throughout the night shift; however, at 3:00 am, the attendant got no response after repeatedly sounding the air horn. When another contractor employee was sent into the boiler to assess the situation, he found the two men lying on opposite ends of the scaffolding.

When the plant health, safety, and environmental department tested the compressed air 12-pack, they found that it contained less than 5 percent oxygen. The "air" had been manufactured with too low a

concentration of oxygen. (Note: This fatal incident prompted OSHA to issue a safety alert on the batch of breathing air.)

Mix-Ups Between Nitrogen and Air

Three Employees Asphyxiated in Coating Tank

The atmosphere inside a coating tank was tested and ventilated the day before work was to be performed. On the following day, a contractor entered the tank to clean it and collapsed. Two plant employees entered to attempt rescue, but they were also overcome.

The tank had been ventilated with what was thought to be compressed air but was actually nitrogen. The atmosphere was not tested prior to beginning work. All three men were asphyxiated.

Employee Killed by Overexposure to Pure Nitrogen

A contractor planned to use an air-powered hammer to chip residue from a furnace in an aluminum foundry. He wore an airline respirator. Of two compressed gas lines with fittings, one was labeled "natural gas" and the other had an old paper tag attached with "air" handwritten on it. However, this line actually contained pure nitrogen.

A splitter diverted one part of the gas stream to the air hammer and the other part to the airline respirator. Once the respirator was in place, the worker breathed pure nitrogen and was asphyxiated.

Four Killed and Six Injured in Nursing Home

A nursing home routinely ordered large pure oxygen compressed gas cylinders for residents with respiratory system diseases. The supplier mistakenly delivered one cylinder of pure nitrogen with three cylinders of oxygen; a nursing home maintenance employee mistakenly accepted the nitrogen tank.

Another maintenance employee took this cylinder, which had a nitrogen label partially covering an oxygen label, to connect it to the oxygen supply system. The tank was fitted with nitrogen-compatible couplings. The employee removed a fitting from an empty oxygen cylinder and used it as an adapter to connect the nitrogen tank to the oxygen system. Four deaths and six injuries occurred as a result of pure nitrogen being delivered to the patients.

Good Practices for Safe Handling of Nitrogen

Implement Warning Systems and Continuous Atmospheric Monitoring of Enclosures

The atmosphere in a confined space or small enclosed area may be unfit for breathing prior to entry, or it may change over time, depending on the type of equipment or work being performed. Recognizing this hazard, good practice calls for continuous monitoring of a confined space to detect oxygen-deficient, toxic, or explosive atmospheres. The entire confined space should be monitored—not just the entry portal.

* The atmosphere in a confined space or small enclosed area may be unfit for breathing prior to entry, or it may change over time . . .

Warning and protection systems include flashing lights, audible alarms, and auto-locking entryways to prevent access. Such devices, if properly installed and

maintained, warn workers of hazardous atmospheres. Personal monitors can measure oxygen concentration and give an audible or vibration alarm for low oxygen concentrations.

* Good practice calls for continuous monitoring of a confined space to detect oxygen-deficient, toxic, or explosive atmospheres.

Ensure Ventilation With Fresh Air

Because the atmosphere of a confined space or small/enclosed area often changes during the course of work, it is essential to maintain continuous forced draft fresh-air ventilation before the job begins through to completion. Areas with the potential to contain elevated levels of nitrogen gas should be continuously ventilated prior to and during the course of the job.

Ventilation is also required in rooms and chambers into which nitrogen may leak or vent. In a few of the study cases, people who were simply working close to the nitrogen-containing confined space, room, or enclosure were asphyxiated.

Systems must be in place to properly design, evaluate, and maintain ventilation systems. A warning system will alert workers of a dangerous atmosphere. Personnel should be trained on how to properly respond and evacuate in the event of failure of the system.

Implement System for Safe Rescue of Workers

Rescue may be necessary in the event of continuous monitoring, ventilation failure, or another emergency condition. The ability to immediately retrieve immobilized workers is a critical component of confined space entry preplanning.

* It is essential to maintain continuous forced draft fresh-air ventilation before the job begins through to completion.

One method is to attach a body harness and lifeline to personnel entering confined areas. This procedure also benefits potential rescuers because they do not have to enter the confined area to retrieve the victim. However, when a worker enters a pipeline, some furnaces, ducts, or other narrow-diameter confined spaces, pulling on a line attached to a body harness may cause the person to bunch up and become stuck inside.

Depending on the situation, wristlets or anklets attached to a lifeline and a retrieval mechanism allow the confined space attendant to pull the person out by the arms or legs. The attendant and rescue personnel should be available at all times. Rescuers must have an effective system to communicate with personnel inside enclosures. No one should enter a dangerous atmosphere without proper personal protective equipment.

The last measure of defense requires personnel to actually enter the confined area to retrieve the victim. This approach should be used only when personnel are appropriately trained, have donned rescue equipment, and have dependable breathing air.

Approximately 10 percent of fatalities from the survey data occurred to personnel attempting rescue. These deaths could have been prevented if a reliable retrieval system was in place. Such a system would also prevent many entry worker fatalities because it provides for quickly removing the worker from a dangerous atmosphere to a safe one.

Ensure Uninterrupted Flow and Integrity of Breathing Air

Breathing air must be supplied when workers enter environments where oxygen is or may become deficient. Workers may use either a self-contained breathing apparatus (SCBA) or an airline respirator, which consists of a long hose connecting a breathing air supply to the respirator or hood.

Because a worker using an airline respirator does not control the

* Breathing air must be supplied when workers enter environments where oxygen is or may become deficient.

source of supply, air may suddenly or inadvertently be interrupted. For example, a power failure may stop an air compressor, the air supply may simply run out, or the supply hose may become twisted or obstructed (e.g., by a vehicle). When supplied air is used, facility management systems must protect against interruption of airflow and provide alternate sources of power for the compressors.

A comprehensive management system includes the following:

- Continuous monitoring of air supply.
- Routine inspection and replacement of supplied-air hoses.
- Restriction of vehicular traffic in the area of supply hoses.

When using supplied air, a worker should carry a small backup cylinder (escape pack)—attached to a different supplied-air system—with enough breathing air to last 5 to 10 minutes.

Breathing air is manufactured either by purifying and compressing air or by mixing nitrogen and oxygen to the appropriate ratio. A breathing-air compressor and its hoses should be specifically manufactured for and dedicated to breathing-air systems. The compressor should have a moisture trap, an oil trap, and a carbon monoxide sensor and alarm. When breathing air is manufactured by mixing nitrogen and oxygen, the pressure of the cylinders during filling must be known to ensure that the correct amounts are mixed. The final product must be tested to ensure its integrity.

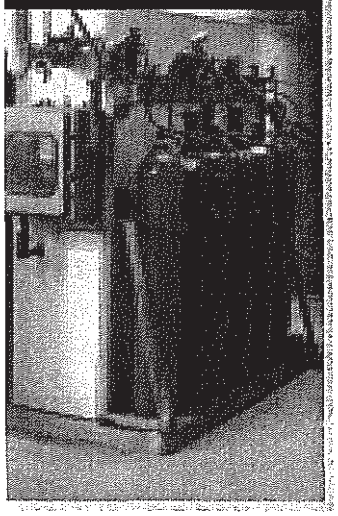
Prevent Inadvertent Mix-Up of Nitrogen and Breathing Air

To prevent interchanging compressed nitrogen with compressed industrial grade air or compressed breathing-quality air, specific fittings should be used for each cylinder. Cylinders for nitrogen, industrial grade air, and breathing-quality air have distinct, incompatible fittings that cannot be cross-connected.

* Personnel should understand that the fittings are *intended* to be incompatible to ensure safety.

Personnel should understand that the fittings are *intended* to be incompatible to ensure safety. Cylinders should be clearly labeled; typical cylinders are shown in Figure 3. Labels on piping systems, compressors, and

* Figure 3. Compressed gas cylinders.



fittings are additional reminders of which gas is contained inside. Color coding also helps to identify systems.

Develop and Implement Comprehensive Training Programs

The good practices for safe handling of nitrogen, described above, are effective only if personnel are trained on the importance of the following:

- Use of ventilation systems, retrieval systems, and atmospheric monitoring equipment—both how to use them and how to determine when they are not working properly.
- Dangers of nitrogen-enriched atmospheres and the systems to

prevent interchanging breathing air and nitrogen.

- Implementing good hazard communication, which includes safe handling of air and nitrogen delivery systems.
- Mandatory safety practices and procedures for entry into confined spaces, such as permits, providing an attendant, monitoring, ventilating, rescue, and contractor oversight.
- Precautions when working around equipment that may contain elevated levels of nitrogen.
- The reason for special fittings on compressed gas cylinders.
- Proper use of air supply equipment.

Training should cover new and revised procedures for confined space entry, and establish measurements for employee proficiency. Contractors as well as employees should be trained.

* Contractors as well as employees should be trained.

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Salus Populi Est Lex Suprema
People's Safety is the Highest Law

J. clin. Path., **30**, Suppl. (Roy. Coll. Path.), **11**, 181-187

Experimental hypoxic brain damage

J. B. BRIERLEY

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The majority of hypoxic episodes that result in histologically proven damage in the human brain cannot be adequately defined in physiological terms. They are usually accidents so that basic information such as the precise duration of a cardiac arrest or the blood pressure and heart rate during a period of severe hypotension is very rarely available. In such cases, neuropathological descriptions, however exhaustive, may well explain the final neuropsychiatric status of the patient but can at best indicate only tentatively the nature of the episode itself.

The experimental approach is justified if it can indicate whether damage of a particular type in neurones and in white matter is or is not a direct consequence of a particular hypoxic stress adequately delineated in physiological terms.

At the outset it must be recalled that the energy for the normal functioning of the central nervous system is derived from the oxidative metabolism of glucose. A deficiency of oxygen or glucose will impair function and if severe and protracted enough will lead to irreversible brain damage. Interruption of the oxygen supply produces the most rapid impairment of brain function. Thus consciousness is lost about 10 sec after circulatory arrest. Abrupt anoxia exemplified by inhalation of an inert gas or sudden decompression to an altitude above 50 000 ft leads to loss of consciousness after a slightly longer interval (17-20 sec). This rapid loss of consciousness in instances of profound hypoxia may well be responsible for the widely held view that enduring brain damage may begin soon after consciousness is lost.

Types of hypoxia

Before considering the relationships between the known neuropathological patterns in the human brain that are ascribed to hypoxia and their apparent counterparts in the brains of experimental animals, it will be useful to classify the several types of hypoxia. However, it will be shown that there is no justification for the assumption that each type of hypoxia can, *per se*, give rise to brain damage. The original classification of Barcroft (1925) must be modified in the light of subsequent information from human and experimental animals sources as follows:

1 ISCHAEMIC
Blood flow is arrested in the brain as a whole or in the territory of a single artery.

2 OLIGAEMIC
A reduction in blood flow in the brain as a whole or within the territory of a single artery may occur as a result of a greatly reduced cardiac output or major systemic hypotension from any cause.

3 ANOXIC
The arterial oxygen tension is 0 mm Hg. It occurs if inert gases are inhaled, if there is total obstruction of the upper respiratory tract or in the event of sudden exposure to an altitude greater than 50 000 ft (the combined tensions of water vapour and carbon dioxide within the pulmonary alveoli then exceed the ambient pressure and no oxygen can enter the lungs).

4 HYPOXIC
There is some reduction in a pO_2 short of anoxaemia. This occurs in chronic pulmonary disease and in congestive heart disease; when the inspired oxygen is diluted by an inert gas (as in some anaesthetic accidents) and also in exposures to altitudes less than 50 000 ft.

5 ANAEMIC
There is some reduction in the amount of circulating haemoglobin available for combination with oxygen. It can occur after severe haemorrhage, in severe hypochromic anaemia but the commonest apparent cause of anaemic brain damage is carbon monoxide intoxication.

6 HISTOTOXIC
This implies the poisoning of oxidative enzymes within neuronal mitochondria. Cyanide and azide are examples.

7 HYPOGLYCAEMIA
A deficiency of the principal substrate, glucose, *per*

se can also give rise to ischaemic cell change even if the level of arterial oxygenation is normal.

The previous contributors to this section of the Symposium have defined the nature and time course of ischaemic cell change and have pointed out that it is the principal neuronal response to all types of hypoxia in the brains of rodents as well as in those of primates including man. In this survey of the brain damage attributable to hypoxia in all its forms, only the patterns of distribution of ischaemic cell change will be considered with emphasis on the contributions from experimental studies.

1 Ischaemic

Arrest of circulation within a single brain artery results in an infarct which can range in size from the 'total territory' in an anatomical sense to a small volume of tissue close to the point of arterial occlusion. Where the cortex of cerebrum or cerebellum is concerned the extent of infarction is determined by the level of systemic blood pressure at and after the instant of occlusion and, in particular, by the functional efficiency of the leptomeningeal vessels that anastomose with the cortical branches of neighbouring arteries. If these anastomotic systems and the major arteries in the neck and the circle of Willis are normal, the cortical infarct will be small. If one or both are the site of occlusive vascular disease, the infarct will be larger.

It must be borne in mind that the basal ganglia and the internal capsule, in particular, are supplied by end-arteries (penetrating or ganglionic branches of the major cerebral arteries). Occlusion of an arterial trunk proximal to the ganglionic branches produces an infarct in these deeply placed regions of grey and white matter even in the healthy experimental primate. Evidently the retrograde flow of blood from leptomeningeal anastomoses into the arterial stem may never enter all its ganglionic branches or, if it does so, it may be too little and too late to avert irreversible tissue damage. Thus, for example, division of the middle cerebral artery close to its origin from the internal carotid artery in the baboon leaves the sensory and motor cortex intact and cortical infarction is confined to some portion of the insula. A variable hemiparesis involves only the contralateral face and upper limb and its neuropathological basis has been shown to lie entirely within white matter, ie, in the genu and supralentiform portions of the internal capsule, where after a survival of three years there is a sharply circumscribed cystic infarct (Symon and Brierley, 1976). The limited neurological deficit and the small, deeply placed infarct that follow division of the middle cerebral artery in a healthy experimental primate are sharp reminders that such 'models' cannot provide two of the most important factors in the aetiology of 'stroke' in man. These are some impairment in cardiac function (leading to some reduction in cerebral blood flow) and some degree of occlusive vascular disease. These factors, singly or together, account for the extension of the infarct into the centrum semi-ovale and even into the whole of the anatomical cortical territory. It follows, that in the human brain, ischaemic necrosis in some portion of an arterial territory can seldom be explained satisfactorily without careful examination of the myocardium, the coronary arteries and the major arteries of the neck and brain.

Overall or global arrest of the brain circulation leads to a loss of consciousness in eight to 10 sec and the EEG is isoelectric a few seconds later. Respiration fails at about the same time while the heart may continue to beat for a matter of minutes. Neuropathological descriptions of the consequences of circulatory arrest (including 35 personal cases) provide the best examples of the involvement of the 'selectively vulnerable' regions of the brain in hypoxia. Frequently, little of the cerebral cortex is normal but damage is usually greater in the posterior half of each cerebral hemisphere, in the floors of sulci rather than over the crests of gyri and in the third, fifth and sixth layers rather than in the second and fourth. Certain portions of the hippocampus (zones h.1—Sommer sector—and h.3-5,—endfolium) are vulnerable as are the Purkinje cells of the cerebellum. Many sensory nuclei in the brain stem are vulnerable in the infant and young child (Ranck and Windle, 1959; Brierley, 1965, 1976).

Where circulatory arrest has been studied in the experimental animal, it is important to recognize that earlier studies were concerned to define the maximum period of arrest of the cerebral circulation beyond which some degree of irreversible brain damage would occur. Attempts to define such a 'threshold' have been reviewed by Hoff *et al* (1945), Meyer (1963) and Brierley (1976). The general conclusion from these studies has been stated by Schneider (1963) as follows: 'A complete revival without neurological or histological damage cannot be brought about after a complete stop of brain circulation of more than four to five min duration'.

In contrast to the experiments summarized above, certain recent studies have attempted to define a much greater period of circulatory arrest after which there can be some evidence of recovery in at least a neurophysiological sense and histological examination can show that some parts of the brain are normal. Thus Hossmann and Sato (1970) claimed that '. . . unequivocal signs of neuronal recovery can be detected after complete ischaemia of more than one

hour's duration'. Hirsch *et al* (1975) failed to confirm these results and attributed 'recovery' after such protracted ischaemia in the experiments of Hossmann and Sato (1970 and subsequent studies) to the protective effects of anaesthesia and the progressive fall in temperature that must occur in the isolated head during such periods of time.

It must be emphasized that experimental studies of the effects of circulatory arrest (or any other form of hypoxia) on the brain, whether directed towards the definition of a 'threshold' for a particular hypoxic stress or to the capacity for recovery after an extended period of the same stress, have clinical relevance only if spontaneous respiration has been resumed in the unmedicated animal, and detailed neurological assessments, together with serial recordings of the EEG, have been made during an adequate period of survival. All these are essential for a meaningful appraisal of 'recovery'. Finally, after *in-vivo* perfusion-fixation of the brain, neuropathological examination of the brain must be comprehensive. Unfortunately clinico-pathological studies according to such standards have not yet been reported in support of the claim that 'recovery' of the central nervous system can occur after periods of circulatory arrest far in excess of those hitherto accepted as 'critical' where the inception of minimal brain damage is concerned.

2 Oligaemic hypoxia

A reduction of blood flow in a single artery of the human brain is usually due to a combination of systemic hypotension and occlusive disease in the vessel itself. If flow is sufficiently impaired the outcome will be an infarct involving grey and white matter. Such a local reduction in flow can only be inferred if thrombosis and embolism can be excluded. There are, as yet, no experimental models of this particular situation.

Global oligaemia implies some reduction in the overall flow of blood through the brain. Experimental studies in the Rhesus monkey have shown that, if arterial oxygenation remains normal, cerebral perfusion pressure (mean arterial blood pressure – venous sinus pressure) must be reduced to 25 mm Hg for at least 15 min before brain damage is produced (Brierley *et al*, 1969; Meldrum and Brierley, 1969). However, it was only possible to damage the brain if the profound hypotension was continued beyond the point of apnoea when mechanical ventilation was required in order to maintain a normal arterial oxygen tension. These experiments clearly demonstrated that in the healthy spontaneously breathing primate, global oligaemia *per se* is unlikely to lead to brain damage if respiration does not fail. In these monkeys, typical ischaemic neuronal alterations were not evenly distributed in the cerebral cortex but were restricted to the arterial boundary zones of the cortex of the cerebrum and also of the cerebellum. They were variable in the basal ganglia. The pysiological basis of lesions along arterial boundary zones has been discussed by Zülch and Behrend (1961) and by Meldrum and Brierley (1971). When perfusion pressure falls below 45-50 mm Hg the capacity of the vascular bed to maintain a constant cerebral blood flow (autoregulation) is lost (there is then maximum vasodilatation) and flow becomes directly dependent upon perfusion pressure. The reduction in flow is greatest in the vessels most remote from the arterial stem, ie, at the boundary of each arterial territory.

In the clinical situation, a reduction in brain perfusion pressure while arterial oxygenation remains normal is virtually confined to the technique of hypotensive anaesthesia with controlled ventilation and then only when perfusion pressure through the brain is lowered by excessive head-up tilt (Brierley and Cooper, 1962). The two additional factors that may result in brain damage after a period of relatively moderate hypotension are some degree of hypoxaemia and some element of occlusive disease in the extra- and/or intracranial arteries. The frequency of these two factors in addition to the reduction in brain blood flow due to the initial systemic hypotension is largely responsible for the fact that ischaemic damage along arterial boundary zones of the cortex of cerebrum and cerebellum is the commonest neuropathological outcome of hypoxia in all its forms. It is important to appreciate that no experimental model permitting the introduction and control of oligaemia, hypoxaemia and partial vascular occlusion is yet available.

Previous contributors to this section of the Symposium have emphasized that this 'boundary zone' pattern of brain damage can only be identified if blocks for histological examination are selected with an awareness of the anatomical distribution of the cortical arteries of cerebrum and cerebellum.

3 Anoxic

Anoxia, induced by breathing pure nitrogen, has been studied in human volunteers by Gastaut *et al* (1961) and Ernsting (1963). After a few seconds the EEG shows low voltage activity at 11 to 13 c/s and consciousness is lost at 17 to 20 sec. In experimental animals, longer periods of nitrogen breathing lead, after an initial hyperventilation, to slowing of respiration, bradycardia and a falling blood pressure. Apnoea occurs at about the third minute while blood pressure is still appreciable (5-20 mm Hg) at

the fifth minute (Swann and Brucer, 1949). In the Rhesus monkey, the responses to nitrogen breathing are similar and if mechanical ventilation is begun soon after the 'last breath', the blood pressure rises, spontaneous respiration is resumed and the EEG, previously isoelectric, returns to normal. Subsequent neuropathological examination reveals no brain damage (Brierley and Meldrum, unpublished observations). Evidently the period of anoxaemia and of secondary circulatory impairment is too brief to lead to ischaemic neuronal alterations so that it must be concluded that pure anoxic anoxia cannot produce brain damage.

4 Hypoxic

In spontaneously breathing experimental animals, including primates, the minimal level of arterial oxygen tension that does not lead to early apnoea and cardiac failure is about 20 mm Hg. At this level the cerebral vascular bed is fully dilated, the cerebral A-V oxygen difference is reduced (due to reduced oxygen consumption and increased blood flow) but the EEG is normal. This precarious state can be disturbed by a slight fall in perfusion pressure and the immediate decline in the EEG is evidence of some reduction in cerebral blood flow. This may occur as a consequence of a period of cardiac arrhythmia. A progressive fall in heart rate and blood pressure together with slowing of respiration herald the cardio-respiratory crisis that sets the limit to the period during which the organism can tolerate this level of hypoxia. Where the circulatory failure is concerned the final bradycardia and falling blood pressure may not be a direct effect of hypoxia on the myocardium but a consequence of the stimulation of chemoreceptors in the carotid bodies or brain stem (Cross *et al*, 1963). As blood pressure continues to fall respiration ceases and the EEG becomes isoelectric at about the same time. Adequate resuscitation commenced soon after the 'last breath' can, as after anoxic anoxia, allow the heart to recover, spontaneous respiration to be resumed and the EEG to return to normal. Brain damage is rarely seen and only when there has been a prolonged period of cardiac impairment and an even longer period of isoelectric EEG (Brierley, Prior, Calverley, and Brown—unpublished results). Brain damage in such animals consists of ischaemic neuronal alterations along the arterial boundary zones of the cerebrum and cerebellum and sometimes in the basal ganglia. This pattern of damage, indistinguishable from that seen after oligaemic hypoxia, underlines the fact that systemic hypoxaemia can only bring about brain damage through the medium of a secondary reduction in perfusion pressure.

In the human subject exposed to hypoxia not severe enough to bring about failure of respiration and the heart, the initial increase in cerebral blood flow may be so restricted by occlusive vascular disease in the arteries of the brain and/or neck that ischaemic brain damage may ensue.

5 Anaemic

There is no convincing evidence that a simple reduction in circulating haemoglobin due to severe hypochromic anaemia (iron-deficient or haemolytic) or to haemorrhage can result in brain damage. Carbon monoxide intoxication remains the sole example of anaemic hypoxia (due to the formation of stable carboxyhaemoglobin) that can be associated with ischaemic cell change and also with damage in white matter. The pathology in the human brain has been reviewed by Meyer (1963), Lapresle and Fardeau (1966) and Brierley (1976). Ischaemic alterations may be seen in the vulnerable regions of the cortex of cerebrum and cerebellum and of the hippocampus. Necrosis in the globus pallidus is not invariable (Meyer, 1928; Lapresle and Fardeau, 1967) and damage in white matter varies considerably.

The presence of some element of perfusion failure in the genesis of, at least, the cortical damage was suggested by the report of Poursines *et al* (1956). A woman, aged 33 years, lived 26 days after attempted suicide with illuminating gas. In her brain, laminar necrosis was distributed along arterial boundary zones but information concerning respiratory and cardiac functions early in the survival period was lacking. The case of Neubuerger and Clarke (1945), dying 13 days after carbon monoxide poisoning, exhibited patchy myocardial infarction suggesting a direct effect of carbon monoxide on the myocardium.

Among experimental studies, that of Lewey and Drabkin (1944) in the dog was important because, after intermittent exposures to carbon monoxide for up to 11 weeks the electrocardiograms were abnormal and the brain damage was considered to be similar to that seen in man but was not described in detail. Further details of electrocardiographic abnormalities were presented by Ehrich *et al* (1944). Recently Ginsberg *et al* (1974) exposed 19 Rhesus monkeys to 0·2 or 0·3 per cent carbon monoxide for 60 to 325 min with a carboxyhaemoglobin level of 72 to 77 per cent throughout. Cardiac arrhythmias and some degree of hypotension were common but the EEG was only intermittently isoelectric. Grey matter damage (globus pallidus and hippocampus) was seen in less than a fifth of the brains while white matter was abnormal in the majority. Apparently the degree of intoxication was not sufficient to produce the

more extensive grey matter damage so often seen in the human brain.

Further confirmation of a direct effect of carbon monoxide on the heart was provided by Hodjati *et al* (1976) who irrigated the cerebral circulation of one dog from one carotid artery of a donor animal. A mean carboxyhaemoglobin level of 52 per cent in the donor animal led to bradycardia, hypotension and its death in 10 to 15 min. All the recipients survived.

6 Histotoxic

Cyanide, the best known cause of histotoxic hypoxia, acts by inhibiting cytochrome oxidase in mitochondria while the oxygen tension and content of arterial blood remain normal. The few human cases with delayed death and evidence of brain damage have been reviewed by Brierley (1976). There was loss of neurones in cerebral cortex and cerebellum and a single case showed haemorrhagic necrosis in each globus pallidus. Hyperaemia and haemorrhages occurred in white matter.

Numerous experimental studies have suggested that cyanide, in any form and administered by any route, can damage neurones and myelin sheaths. In the first experimental study (Meyer, 1933) subcutaneous injections of potassium cyanide in dogs and rabbits produced typical ischaemic alterations in cerebral cortex, globus pallidus, hippocampus and cerebellum. White matter damage was most marked in the corpus callosum. Subsequent studies were more concerned with white matter damage because of its apparent similarity to the plaques of multiple sclerosis. However, the report of Levine and Stypulkowski (1959) was noteworthy because it suggested that grey matter damage in the rat brain after the administration of cyanide was largely due to concomitant ischaemia and hypoxic hypoxia. Brierley *et al* (1976) gave sodium cyanide to rats by intravenous infusion. There was full physiological monitoring in an anaesthetized group and restricted monitoring in the unanaesthetized remainder. White matter, particularly the corpus callosum, was damaged in six of 19 animals and grey matter additionally in only one. In the latter animal bradycardia, epileptic seizures and hypotension were particularly marked and it was concluded that the neuronal damage was brought about through the medium of the secondary effects of cyanide on the circulation. In a recent study in *M mulatta* (Brierley *et al*, 1977) sodium cyanide was given by intravenous infusion. The effects of the infusion on respiration, heart rate, blood pressure, blood gases and the EEG were monitored in the lightly anaesthetized animals. Brain damage was seen in four of 11 animals. It involved white matter in all four but ischaemic cell change was restricted to the striatum of a single animal. In the latter there had been a period of bradycardia, hypotension and raised central venous pressure. It was concluded that in the lightly anaesthetized and spontaneously breathing Rhesus monkey, as in the rat, there is no evidence for the entity of hypoxic neuronal damage of purely histotoxic type.

7 Hypoglycaemia

Hypoglycaemic damage in the human brain is usually associated with irreversible coma and Meyer (1963) stated that the neuropathological findings '. . . closely resemble those which occur in other types of anoxia'. Most of the selectively vulnerable regions may be involved but with a tendency to spare the globus pallidus and cerebellum. Although hypoglycaemic coma may be associated with cardiovascular disturbances and epileptic seizures the ability of hypoglycaemia *per se* to produce ischaemic damage in physiologically monitored experimental primates has been demonstrated only recently.

Kahn and Myers (1971) and Myers and Kahn (1971) studied the long-term effects of insulin-induced hypoglycaemia in Rhesus monkeys. Blood glucose fell to 20 mg/100 ml after one and a half to three h and was maintained at this level for four to 10 h with normal blood oxygenation. In seven of 11 animals there was neuronal loss with a gliomesodermal reaction in striatum, cerebral cortex and hippocampus.

In order to define the earliest neuronal alterations due to insulin-induced hypoglycaemia, lightly anaesthetized Rhesus monkeys received insulin intravenously while EEG, EKG, heart and respiratory rates were recorded and blood gas tensions, pH and glucose content were measured at intervals (Meldrum *et al*, 1971). When blood glucose was below 20 mg/100 ml for more than two h and the brains were fixed by perfusion, typical ischaemic cell change (from the stage of microvacuolation) was seen in the cortex and occasionally in striatum, hippocampus and cerebellum. Thus a major deficiency in substrate alone can produce the same type of neuronal damage as a deficiency of oxygen.

Conclusion

It will be evident from this brief review that ischaemic cell change is the cytopathological common denominator in all types of hypoxia. Nevertheless there is no pattern of its distribution specific for each category with the exception of circulatory arrest (global ischaemia) and pure hypoglycaemia after both of which ischaemic neuronal alterations may occur

uniformly within the 'selectively vulnerable' regions of the brain. In the remaining categories of hypoxia, ie, oligaemic, anoxic, hypoxic, histotoxic and probably anaemic (carbon monoxide), an initially pure hypoxic stress in the intact and spontaneously breathing animal gives rise, sooner or later, to terminal secondary impairments of respiration and particularly of circulation. In the healthy experimental animal, however, it is only rarely that the associated period of reduced cerebral blood flow is long enough to cause brain damage but not too long to preclude recovery. In such instances, brain damage consists of a concentration of ischaemic cell change along the arterial boundary zones.

Experimental studies have shown that the terminal hypoxic cardio-respiratory deterioration or crisis consists of a slowing of respiration to the point of apnoea with a fall in blood pressure and in heart rate (but the heart may continue to beat long after the 'last breath'). There is a more or less parallel decline in EEG background activity and an isoelectric state is reached at about the time of the 'last breath'. There is no evidence to suggest that systemic hypoxia of any type can lead to brain damage unless the EEG has been isoelectric for an appreciable period. In the paralyzed and mechanically ventilated animal exposed to systemic hypoxia, initial hyperventilation as well as the 'last breath' cannot occur and the duration of hypoxia may be considerably prolonged. For this reason 'thresholds' for brain damage defined in such preparations must be applied with considerable caution to the spontaneously breathing experimental animal and to man.

There is now ample evidence to show that in the intact healthy, and spontaneously breathing animal tolerance to hypoxia is limited by the respiratory and circulatory systems and not by the intrinsic energy reserves of the brain itself. If effective resuscitation is begun soon after the 'last breath' the EEG will return and the brain will be undamaged. Thus a depression of central nervous system function up to and some time after the 'last breath' and the appearance of transiently isoelectric EEG need have no structural consequences.

The relative frequency of all degrees of ischaemic damage in the human brain after hypoxic episodes does not, however, necessarily imply a greater susceptibility of the brain itself. The existence of a single type of hypoxia in human patients is rare. It should be stressed that several types of hypoxia, each constituting a relatively mild stress can, in combination, produce brain damage. The additional factors most probably responsible for the increased extent and frequency of brain damage in man are twofold. Preexisting cardiac disease will impair the capacity to maintain a high level of blood flow through a cerebral vascular bed initially fully dilated by hypoxia. It will also impair the rapid restoration of normal cerebral blood flow after any terminal cardio-respiratory crisis. Secondly, preexisting occlusive disease in the arteries of brain and neck and any impairment of the normal reactivity of the smaller cerebral vessels will further reduce cerebral blood flow during and after hypoxia.

In conclusion, experiments in physiologically monitored, spontaneously breathing animals can show that hypoxia gives rise to an integrated series of responses in the respiratory and circulatory systems and in the nervous system itself. Initially these serve to maintain brain function and respiration in particular. Ultimately these compensatory cardio-respiratory responses may fail. Experiments have also shown that where the human brain is concerned the commonest cause of damage must be sought in some failure of brain perfusion.

The author is greatly indebted to Dr Pamela F. Prior (The EEG Department, the London Hospital) for many helpful suggestions and comments in the preparation of the manuscript.

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J. Physiol. (1963), **169**, *pp.* 292–311
With 9 text-figures
Printed in Great Britain

THE EFFECT OF BRIEF PROFOUND HYPOXIA UPON THE ARTERIAL AND VENOUS OXYGEN TENSIONS IN MAN

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(*Received* 23 *January* 1963)

The partial pressure of oxygen in the alveolar gas may be reduced either by decreasing the total pressure of the environment or by replacing the oxygen normally present in the inspired air by an inert gas. The severe anoxia induced by rapid decompression from 565 to 155 mm Hg absolute, whilst breathing air, may be terminated by the delivery of 100% oxygen to the respiratory tract. The effects of such brief profound anoxia upon the alveolar and arterial gas tensions and upon the central nervous system have been studied extensively (Ernsting & McHardy, 1963; Ernsting, Gedye & McHardy, 1960; Ernsting, 1962). The effect of the resultant severe but short-lived arterial hypoxaemia upon the supply of oxygen to various organs of the body is of considerable interest. The oxygen content of the venous blood flowing from a region reflects the balance between the supply of oxygen to it and its metabolic oxygen consumption. Continuous measurements of the oxygen content of the venous blood flowing from several regions have been made in subjects exposed to brief but profound hypoxia. In the experiments described in this paper a short period of overventilation, nitrogen being used as the inspired gas, was employed in place of rapid decompression to induce hypoxia. This method allowed more extensive observations to be made than were considered practical in a decompression chamber.

METHODS

Induction of hypoxia. Three healthy men, aged from 33 to 38 years, were used. The subject lay on a couch and breathed through a valve box, to the inlet of which two taps were connected in series. The side arm of the tap next to the box was open to the atmosphere. One arm of the second tap was connected to a demand valve which was supplied with nitrogen, whilst the other arm was connected to a second demand valve supplied with oxygen. Before the experiment was started the hoses between the two demand regulators and the second tap were purged with the gas delivered by the corresponding regulator. The dead space between the two taps was purged with nitrogen to ensure that 100% nitrogen was delivered directly the first tap was operated. During each rest period the first tap was positioned so that the subject breathed air. Nitrogen was administered by instructing the subject to expire maximally at the end of a normal expiration, and at this instant the first tap was turned so that the subject breathed from the demand valve which supplied nitrogen.

During the period of breathing nitrogen the subject was instructed to breathe as deeply as possible at a rate of about 20 breaths per minute. After 7–20 sec over-ventilation with nitrogen the first tap was returned to its original position so that air was breathed again. At the same time the subject was told to cease over-breathing.

Respired gas tensions. The partial pressures of oxygen and carbon dioxide in the gas passing the subject's lips were recorded continuously in all the experiments by means of a respiratory mass spectrometer (Fowler & Hugh-Jones, 1957). Preliminary studies showed that the output of the instrument was linearly related to the partial pressure of each of these gases. The delay between a sudden change of partial pressure of either at the sampling tip and the beginning of the response of the recording pen motor was 0·2 sec and 90% of the total response occurred in a further 0·1 sec. Calibrations employing gas mixtures of known composition were performed at intervals throughout each experiment. Over a 30 min period no significant change occurred in the sensitivity of the instrument. The pulmonary ventilation was recorded in some of the experiments by collecting the expired gas in a recording Tissot spirometer.

Blood sampling. In separate experiments blood was sampled continuously from various sites in the cardiovascular system. Blood was obtained from the brachial artery and the femoral vein through a Cournand needle introduced into the vessel after local analgesia had been produced with 2% lignocaine. A catheter was introduced into the right side of the heart through a large-bore needle which had been inserted into a vein in the antecubital fossa. The position of the catheter was determined during its introduction by recording the pressure at the tip by means of a strain-gauge pressure transducer. The catheter was advanced until its tip lay in the pulmonary artery. Blood flowing through the internal jugular vein was sampled by means of a radio-opaque catheter which was introduced into a vein which had been exposed through an incision in the right antecubital fossa. This catheter was advanced under direct fluoroscopic control with the subject's head held against his left shoulder. The catheter entered the right internal jugular vein and was placed so that its end lay above the level of the tip of the right mastoid process. When in place, the patency of the Cournand needle or the intravascular catheter was maintained when sampling was not in progress by a flow of sterile physiological saline (NaCl 0·9 g/100 ml.), approximately 2 ml./min containing heparin (200 i.u./100 ml.).

Recording of blood oxygen saturation and pH. The blood from the intravascular needle or catheter flowed through a tubular cuvette oximeter (Fig. 1) and was then diluted 1:10 with neutral physiological saline to which heparin had been added (Sherwood-Jones, Robinson & Cooke, 1960). The diluted suspension of blood was then passed through a microflow-glass-electrode–calomel-reference-electrode system. The saline reservoir and microflow-electrode system were immersed in a water-bath which was maintained at 38° C. The flow of blood and the desired dilution of the blood with saline were produced by means of a two-cylinder pump with a single piston, the velocity of which could be varied. The pump was constructed so that the cross-sectional area of one cylinder, which was charged with saline, was 10/11 of that of the other cylinder into which the mixture of saline and blood was drawn after it had passed through the glass-electrode system. In all the experiments a blood sampling rate of 20 ml./min was used.

The outputs of the oximeter amplifier and of the pH meter were fed on to two of the pen motors of a recorder. Preliminary experiments showed that the output of the oximeter amplifier was linearly related to the oxygen saturation of the blood flowing through the cuvette. At the beginning and end of each period of recording the output of the oximeter was calibrated by drawing a fully saturated sample of blood and a second sample of a known degree of unsaturation through the cuvette. A linear relation was also found between the pH of the blood and the output of the pH meter. The output of the latter was calibrated at intervals by using two phosphate buffers (pH 6·84 and 7·60). The time course of the response of the entire measuring system to a sudden change in the oxygen saturation and pH of the blood entering the sampling system was determined at the end of each experiment.

When sampling was required the drip of heparinized saline was turned off and the speed of the sampling pump was increased until blood was withdrawn at 20 ml./min. Sampling was continued for 1 min before the subject breathed nitrogen and was maintained until all the disturbances produced by the procedure had subsided.

Electroencephalogram (e.e.g.) and electrocardiogram (e.c.g.) recording. In many of the experiments the e.e.g. was recorded. Two pairs of saline pad electrodes were placed on the scalp over the frontal and occipital regions of the left side of the head. The potential changes from each pair of electrodes were amplified and recorded at a high paper speed. In addition, lead II of the e.c.g. was recorded.

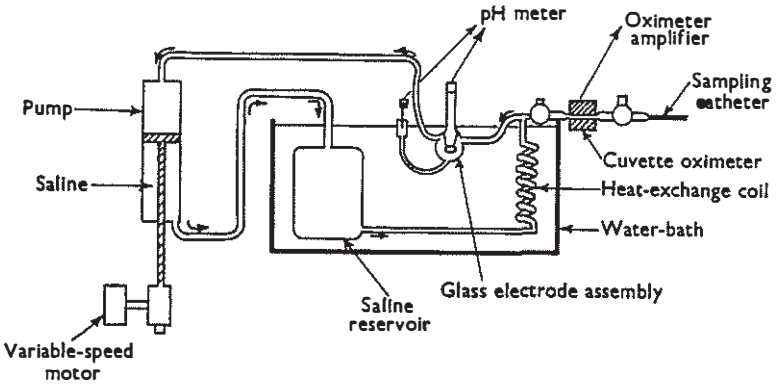

Fig. 1. Apparatus for the continuous measurement of the oxygen saturation and pH of blood. Blood is drawn into the apparatus through a catheter and then it passes through the cuvette oximeter. Saline at 38° C driven by the pump in the direction indicated by the arrows mixes with the blood and the diluted blood flows through the pH electrode assembly back to the pump.

Arterial pressure and calf blood flow. The arterial blood pressure was recorded through a Riley needle by means of an unbonded strain-gauge pressure transducer which was filled with physiological saline containing heparin. The needle was connected to the transducer by means of a 3 cm length of polyethylene tubing with an internal diameter of 1 mm. Preliminary measurements demonstrated that the complete recording system faithfully reproduced the magnitude and phase of sinusoidal pressure fluctuations at frequencies of up to 20 c/s. The Riley needle was inserted into the brachial artery and the transducer was placed on the same horizontal plane as the tip of the needle. The output of the amplifier connected to the transducer, which was fed to one channel of the recorder, was calibrated by means of a mercury manometer before and after each series of measurements. Blood flow through the calf was measured by means of venous occlusion plethysmography, with a mercury-in-rubber strain gauge (Whitney, 1953) to measure changes in the circumference of the calf. The lower limb was supported so that the lower border of the calf was just above the horizontal level of the sternal angle. The circulation to the foot was occluded by means of a cuff placed around the ankle, which was inflated to 250 mm Hg 1 min before the calf blood-flow measurements were started. The venous outflow from the calf was obstructed for 5 sec of every 10 sec period by inflating the cuff placed around the lower part of the thigh to between 30 and 40 mm Hg. The exact pressure used in the venous cuff was adjusted at the beginning of each experiment so that the circumference of the calf increased at a constant rate during each collection period. The output of the gauge was calibrated while it was in position by producing a known reduction of its length. The circumference of the calf at the level at which the gauge was fixed was measured at the end of each experiment.

In all the experiments the subject was carefully observed during and following the period of over-ventilation with nitrogen. If any severe disturbance of consciousness or respiration occurred, oxygen was administered.

RESULTS

Effect upon consciousness. The increase of pulmonary ventilation achieved by each subject during nitrogen breathing was measured from the spirometer records. The mean pulmonary ventilation of the three subjects was increased to 80 l./min at b.t.p.s. during the period of over-ventilation. When the duration of over-ventilation with nitrogen was greater than 8–10 sec the subject reported a transient dimming of vision. In the experiments in which nitrogen breathing was carried out for 15–16 sec the subject experienced some general clouding of consciousness and impairment of vision. Vision was frequently lost in these experiments for a short period. In the few experiments in which nitrogen was breathed for 17–20 sec unconsciousness supervened and was accompanied on most occasions by a generalized convulsion. The duration of the interval between the start of over-ventilation with nitrogen and the onset of symptoms was 12–14 sec.

End-tidal gas tensions. A typical record of the partial pressures of oxygen and carbon dioxide in the gases flowing through the mouth-piece is presented in Fig. 2. The end-tidal oxygen tension fell very rapidly when the subject commenced over-ventilation with nitrogen. It reached a value of less than 10 mm Hg at the end of the third expiration and remained below this level until air was inspired after 16 sec of nitrogen breathing. During the over-ventilation period the end-tidal carbon dioxide tension also fell rapidly. With the restoration of air breathing and the cessation of over-breathing the end-tidal oxygen and carbon dioxide tensions rose gradually to regain their control values. Each of the three subjects over-ventilated, whilst breathing nitrogen for a period of 15–16 sec on six separate occasions. The time course of the changes of the end-tidal tensions of oxygen and carbon dioxide has been measured for each of these 18 experiments and mean curves for each of these variables are presented in Fig. 3.

Arterial blood oxygen saturation and pH. Blood was sampled from the brachial artery of each subject on three separate occasions during which the subject over-ventilated with nitrogen for 16 sec. The records of the response of the entire system to a sudden change in the composition of blood at the tip of the Cournand needle showed a mean delay of 0·7 sec to the beginning of the response of the pen motor recording oxygen saturation and a further 0·9 sec elapsed before 90 % of the total response had occurred. The corresponding times for the response of the pH recording system were 1·4 sec and 2·0 sec respectively. Corrections for these delays in response were applied to the recorded values of oxygen saturation and pH. A

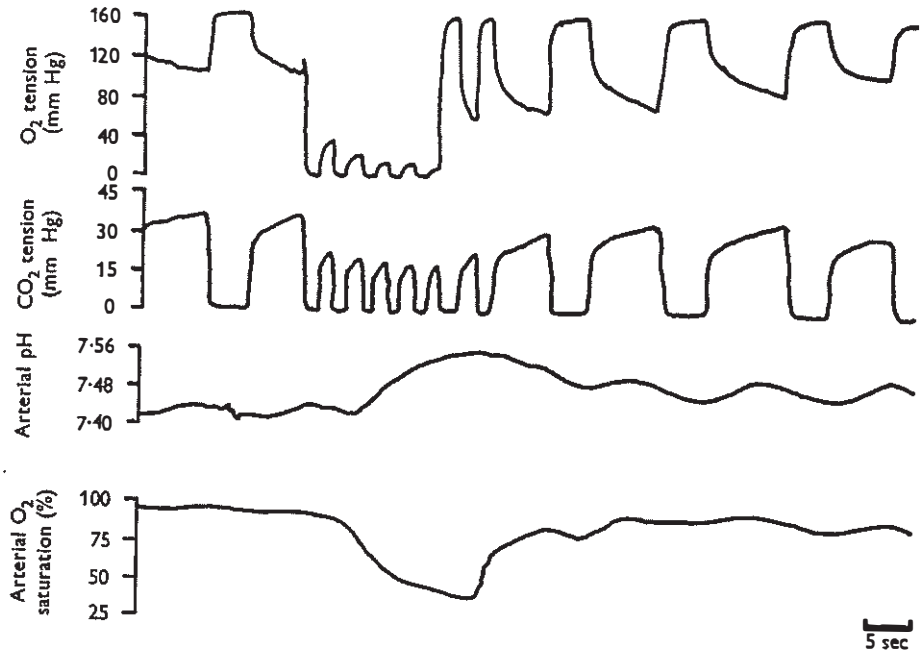

Fig. 2. Respiratory gas tensions and systemic arterial oxygen saturation and pH before, during and after 16 sec over-ventilation with nitrogen. The tensions of oxygen and carbon dioxide were recorded at the lips, whilst the blood was sampled continuously from the brachial artery. Delay time of oxygen saturation record, 0·7 sec of pH record, 1·5 sec.

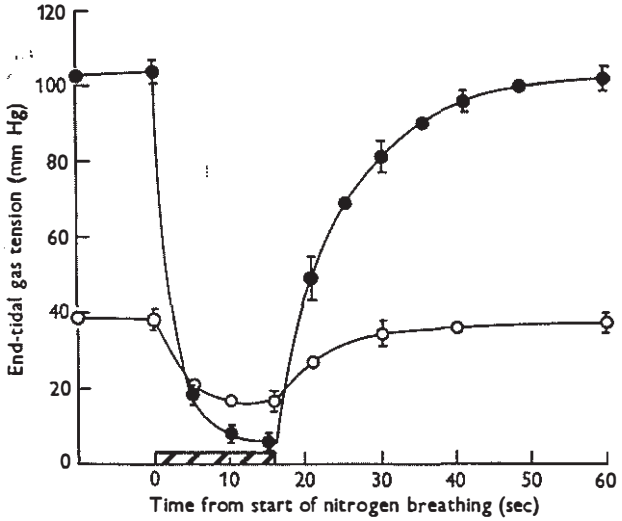

Fig. 3. Effect of over-ventilation with nitrogen upon end-tidal tensions of oxygen (●) and carbon dioxide (○). Each point represents the mean of eighteen values from three subjects; each bar represents ± 1 S.E. of the mean. The period of over-ventilation with nitrogen is indicated by the hatched bar.

typical experimental record of the arterial oxygen saturation and pH is presented in Fig. 2. The arterial oxygen saturation and hydrogen-ion concentration began to fall 4–5 sec after the commencement of nitrogen breathing and both fell very rapidly at first and then more slowly until air breathing was started again at 16 sec. The oxygen saturation then increased rapidly whilst the pH gradually returned to its control value. The mean time courses of the changes of arterial oxygen saturation and pH have been calculated for the nine experiments and these values together with their standard errors are shown in Fig. 4.

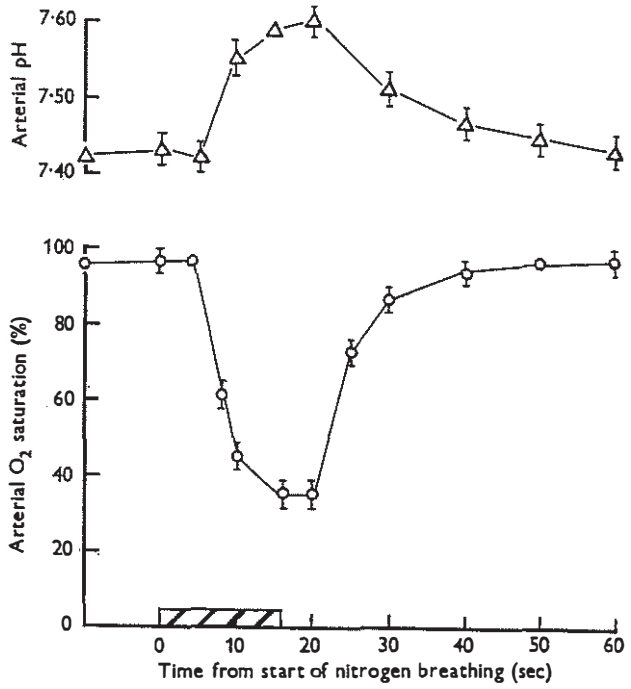

Fig. 4. Effect of over-ventilation with nitrogen upon arterial oxygen saturation (○) and arterial pH (△). Each point represents the mean of nine values from three subjects; each bar represents ±1 S.E. of the mean.

Venous blood oxygen saturation and pH. Blood was sampled from the femoral vein, the pulmonary artery and the right jugular bulb on separate occasions in each of the subjects. The delay in the response of the recording systems was lengthened considerably when intravascular catheters were employed. On none of these occasions did any significant change of pH occur during the period of nitrogen breathing. The mean time courses of the oxygen saturation of the venous blood drawn from these three sites are presented in Fig. 5.

Electroencephalogram changes. The resting e.e.g. shows no specific electrical activity and no change occurred in any experiment until 15–18 sec after the beginning of the period of over-ventilation with nitrogen. When nitrogen over-breathing was carried out for 8–12 sec low voltage

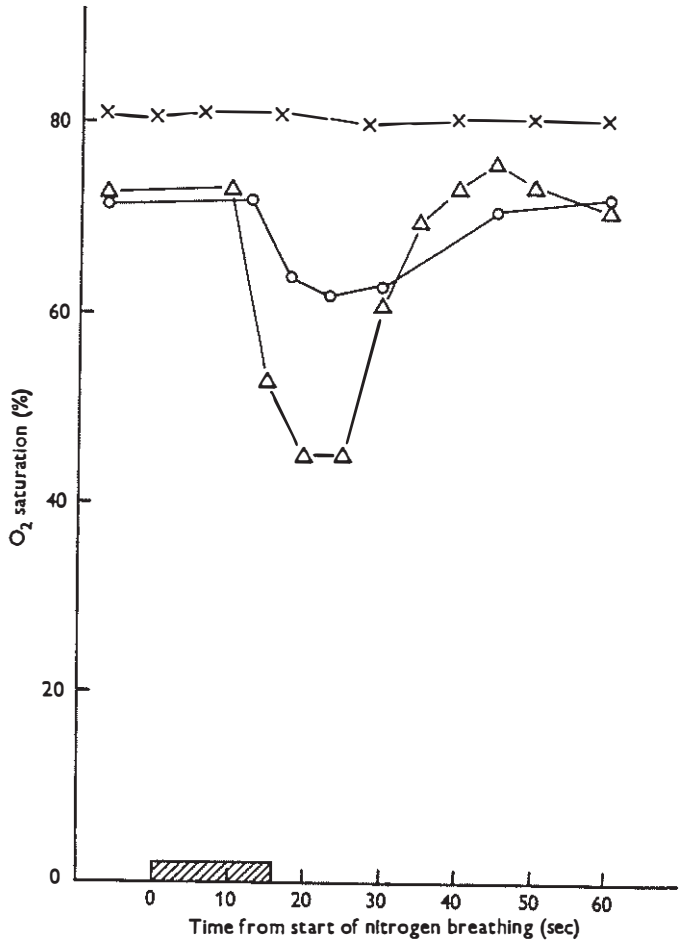

Fig. 5. Effect of over-ventilation with nitrogen upon the oxygen saturation of blood flowing through the femoral (×) and internal jugular (△) veins and the pulmonary artery (○). Each point represents the mean of three values obtained from three subjects.

activity at 11–13 c/s appeared in both channels of the e.e.g. 15 sec after the beginning of the procedure and persisted for 7–9 sec. When the duration of nitrogen over-ventilation was extended to 15–16 sec, similar changes arose in the e.e.g. but they persisted for slightly longer. Occasionally the

11–13 c/s activity was replaced by high-voltage 2–4 c/s activity, which appeared 4–6 sec after the beginning of the change of the e.e.g. This slow activity generally persisted for 4–6 sec. When nitrogen breathing was extended to 18–20 sec the initial fast, low-voltage activity was always replaced by high-voltage 2–4 c/s activity after 5 sec, which lasted for about 10 sec. Control experiments in which a subject over-ventilated for a similar period whilst breathing air produced no change of e.e.g. activity.

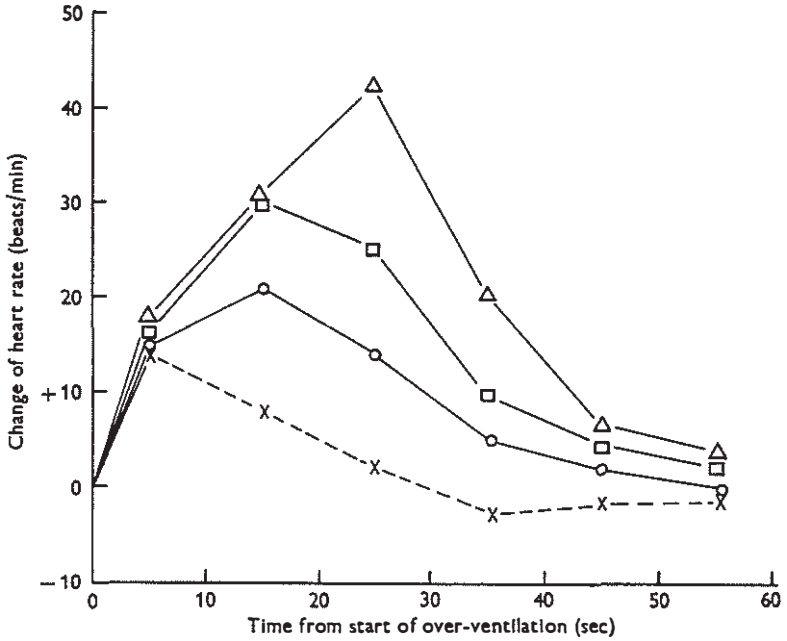

Fig. 6. Effect of over-ventilation with nitrogen for various periods upon the heart rate. △, nitrogen for 17 sec; □, nitrogen for 11 sec; ○, nitrogen for 8 sec; ×, air for 15 sec. Each point represents the mean of three values obtained from three subjects.

Cardiovascular changes. The period of over-ventilation with nitrogen produced a transient acceleration of the heart rate. This commenced at the beginning of the period of over-ventilation and reached a maximum about 30 sec later. The magnitude of the increase varied directly with the duration of the nitrogen over-ventilation. The mean changes of the heart rate for the three subjects when they over-ventilated with nitrogen for various periods are presented in Fig. 6. There were no consistent changes in the shape of the e.c.g. in these experiments. In one subject, however, there was a transient flattening of the 'T' wave, which started 5 sec after the beginning of the nitrogen over-ventilation and persisted for 10 sec. In

several experiments the subjects over-ventilated whilst breathing air. This caused a relatively small and transient increase of heart rate which had subsided 10 sec after the end of the over-ventilation period (Fig. 6).

The period of over-ventilation produced marked respiratory variations of the arterial blood pressure. The mean and pulse pressure were both increased during the deep expiratory efforts and decreased during each inspiration. The mean blood pressure was increased by about 20 mm Hg during the period of over-breathing. Directly the subject ceased over-ventilation the arterial pressure fell and reached a minimum after some 15 sec from the beginning of nitrogen breathing. The minimal value was less than the mean blood pressure before the over-ventilation period. The fall of mean pressure was accompanied by a reduction of the pulse pressure. It was followed by a secondary rise of pressure and an increase of pulse pressure, both of which reached a maximum at about 30 sec after the beginning of the period of over-ventilation with nitrogen. In all, two separate periods of over-ventilation with nitrogen were studied for each of the three subjects and the mean values of arterial pressure before, during and after the period of over-ventilation with nitrogen are presented in Fig. 7. The blood flow through the calf was calculated from the rate at which the circumference of the part increased during each venous-congestion period (Whitney, 1953). The mean value for the calf blood flow obtained in twelve separate periods of over-ventilation with nitrogen in the three subjects are shown in Fig. 7. The flow of blood into the calf was increased during the period of over-ventilation, following which it returned to the resting level, to increase again between 20 and 40 sec after the beginning of over-ventilation.

DISCUSSION

Preliminary experiments in which the subjects over-ventilated with nitrogen for various periods showed that unconsciousness supervened if the duration of this procedure exceeded 16–17 sec. In the majority of these experiments, therefore, the period of over-ventilation with nitrogen was limited to 16 sec. This period of nitrogen over-breathing produced only a transient disturbance of the e.e.g. The low-voltage 8–13 c/s activity was generally associated with a transient dimming of vision and could not be distinguished from that produced by closure of the eyelids. Further, apart from a transient flattening of the 'T' wave on one occasion, no significant change was seen in the e.c.g., although only a standard limb lead (II) was recorded. In view of these findings it was considered that the degree of hypoxia induced by over-ventilation with nitrogen for 15–16 sec was within acceptable limits for resting subjects.

The concentration of oxygen in the gas contained within the respiratory tract at the beginning of the nitrogen breathing period was reduced very rapidly by the very large voluntary increase of pulmonary ventilation. The reduction of the lung volume to a minimum before the first breath of nitrogen was taken decreased the quantity of oxygen to be washed out. The combination of these two manoeuvres resulted in a very rapid fall of end-tidal oxygen tension to 10 mm Hg after 8 sec of over-ventilation. The rate of rise of the end-tidal oxygen tension following the cessation of nitrogen over-ventilation and the return to breathing air was considerably less than the rate at which it had fallen. This difference reflects the reduction of alveolar ventilation associated with the resumption of a more normal breathing pattern.

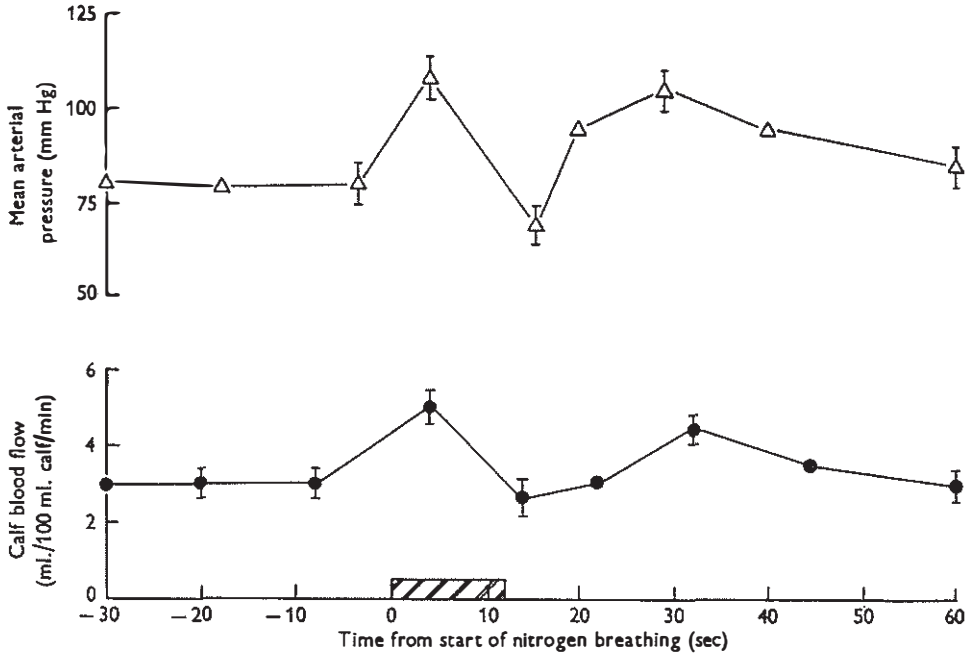

Fig. 7. Effect of over-ventilation with nitrogen upon the mean systemic arterial pressure (△) and the blood flow through the calf (●). The results are from three subjects, each pressure point representing the mean of six values whilst each blood flow point is the mean of twelve values; each bar depicts ±1 S.E. of the mean value.

Arterial oxygen saturation and pH

The delay of 4–5 sec between the beginning of nitrogen breathing and the reduction of the oxygen saturation of the brachial artery blood was a reflexion of the circulation time from the pulmonary capillaries to the sampling point in the systemic arterial tree. A similar delay occurred

between the restitution of air breathing and the subsequent increase of the arterial oxygen saturation. The reduction of the end-tidal oxygen tension to below 10 mm Hg was associated with an arterial oxygen saturation of less than 40 %. The increase of the pH of the arterial blood was related to the fall of the alveolar carbon-dioxide tension and the reduction of the blood oxygen saturation (Christiansen, Douglas & Haldane, 1914). The mean increase of the arterial pH produced by the over-ventilation amounted to 0·18 unit. This gave a calculated value for the minimal arterial carbon-dioxide tension of 22·5 mm Hg as compared with the observed end-tidal value of 17 mm Hg. The changes of arterial oxygen tension produced by over-breathing with nitrogen have been calculated from the simultaneous measurements of the oxygen saturation and pH of the arterial blood by means of standard oxygen dissociation curves (Dill, 1944). The mean time course of the oxygen tension for all the experiments is presented in Fig. 8. together with the curve for the end-tidal oxygen tension. During over-ventilation the end-tidal oxygen tension may be taken as representative of the mean alveolar tension of this gas. When allowance is made for the 4 sec delay between the change of alveolar gas composition and the resultant change of the oxygen tension of the arterial blood at the sampling point, it is apparent that the arterial oxygen tension fell in the same manner as the alveolar oxygen tension until this was less than 16 mm Hg. Beyond this point the systemic arterial oxygen tension was consistently greater than that of the alveolar gas until air breathing was restored. There was a statistically significant difference ($P < 0{\cdot}01$; $n = 9$) between the oxygen tensions of the arterial blood and of the alveolar gas for the last 7 sec of the period of nitrogen breathing. The oxygen tension of the mixed venous blood during nitrogen breathing was between 35 and 40 mm Hg (Fig. 9), and hence the oxygen tension of the alveolar gas was less than that of the blood entering the pulmonary capillaries for nearly the whole period of nitrogen over-ventilation. During this procedure, therefore, there was a reversal of the normal oxygen-tension gradient between the alveolar gas and the mixed venous blood. Since the oxygen saturation of the systemic arterial blood was considerably less than that of the mixed venous blood, oxygen must have passed from the blood flowing through the pulmonary capillaries into the alveolar gas during the latter part of the nitrogen-breathing period. Such a reversal of the normal direction of passage of oxygen across the alveolar capillary membrane has been demonstrated following rapid decompression to high altitude (Luft, Clamann & Adler, 1949; Ernsting & McHardy, 1960) and during rapid ascent following a breath-holding dive to a water depth of 60–100 ft. (18–30 m; Rahn, 1963). In both these situations the oxygen tension of the alveolar gas is reduced rapidly below that of the mixed venous blood.

Venous pH and oxygen saturation

The absence of any detectable change of the pH of the blood sampled from the three venous sites following the period of over-ventilation with nitrogen demonstrated the marked carbon dioxide buffering power of the peripheral tissues and the rapid diffusibility of this gas. The constancy of the venous pH was unexpected, since the reduction of the oxygen saturation of the venous blood would of itself have produced an increase of pH (Christiansen *et al.* 1914). At a constant carbon-dioxide tension the greatest increase of pH due to this mechanism, associated with the decrease of

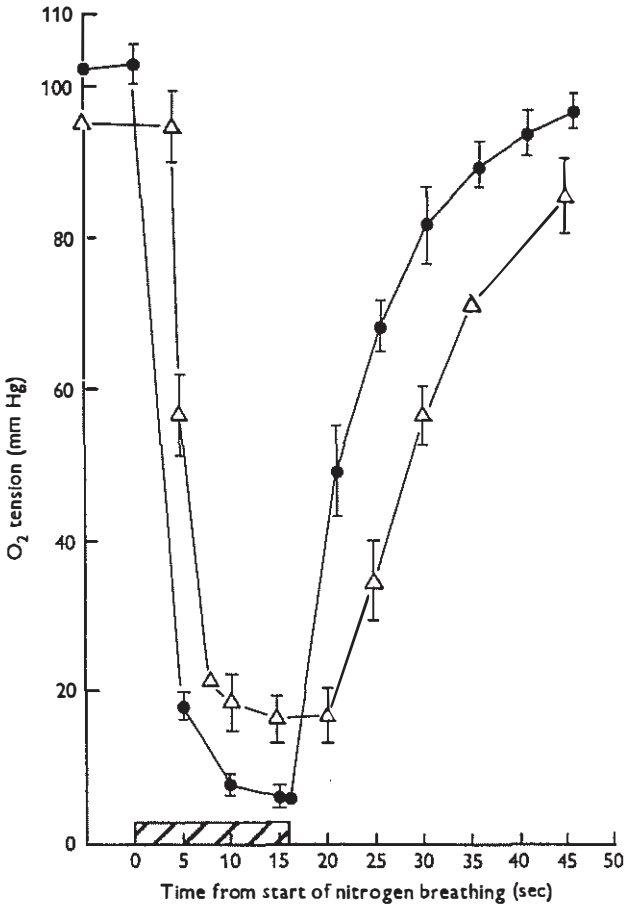

Fig. 8. Effect of over-ventilation with nitrogen upon end-tidal oxygen tension (●) and systemic arterial oxygen tension (△). Each point represents the mean of eighteen end-tidal values and nine arterial values. Each bar denotes ± 1 S.E. of the mean value.

oxygen saturation of the cerebral venous blood by 27 %, was calculated to be of the order of 0·012 unit. The over-all sensitivity of the system used for the measurement of the pH of the venous blood was such, however, that a change of this magnitude might not have been detected.

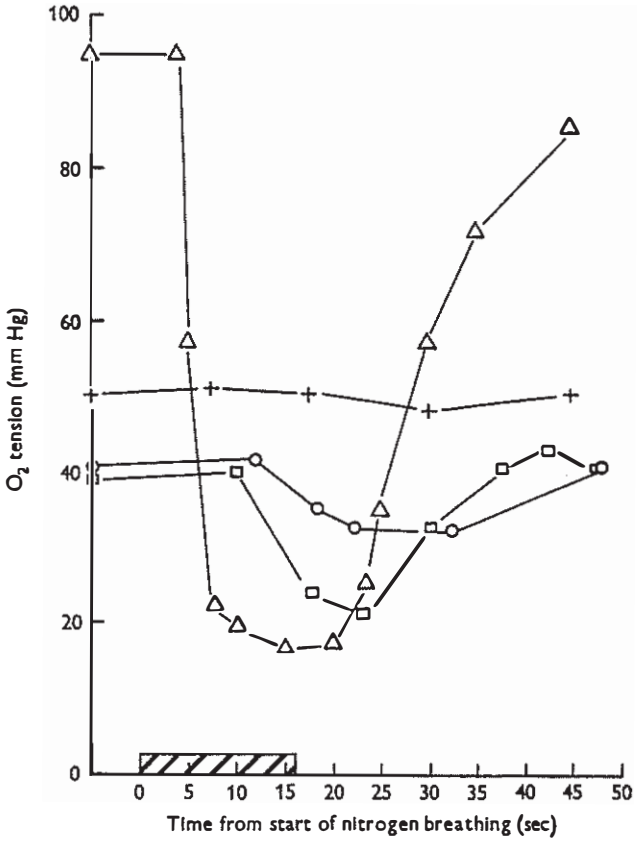

Fig. 9. Effect of over-ventilation with nitrogen upon the oxygen tension of the systemic arterial (△), femoral venous (+), internal jugular (□) and pulmonary arterial (○) blood. Each point represents the mean of the values obtained from three subjects.

The pattern of the reduction of the oxygen saturation of the venous blood produced by the period of nitrogen breathing varies markedly with the site of sampling (Fig. 5). The oxygen content of the jugular venous blood was the first to change and it exhibited the greatest reduction and the most rapid recovery. In contrast the oxygen saturation of the femoral venous blood started to fall last, was reduced by the smallest amount and recovered the most slowly. Mixed venous blood showed changes which

were intermediate between those of the jugular and femoral venous bloods. The maximal fall of the oxygen saturation of the femoral venous blood was half that which occurred in the blood sampled from the pulmonary artery, whilst the maximal reduction of the oxygen content of the jugular blood was more than twice the latter. The changes of the oxygen tension of the blood sampled from these venous sites have been calculated from the measured values of oxygen saturation and pH and the mean curves are presented in Fig. 9, together with the mean curve for the arterial oxygen tension. It is apparent that during the period of severe hypoxia the oxygen tension of the blood flowing from the lower limbs, the brain and the whole body was greater than that of the arterial blood flowing into these regions.

Cardiovascular effects of profound hypoxia

The limited measurements made in this study demonstrate that the period of over-ventilation with nitrogen produced significant changes in the cardiovascular system. The control experiments in which the subject over-breathed with air make it possible to distinguish two phases in the cardiovascular response. First, during the period in which the pulmonary ventilation was increased there was a moderate rise of heart rate and the arterial pressure and calf blood flow were raised (Fig. 7). Immediately the over-ventilation ceased the arterial pressure and calf blood flow returned to their resting values. These changes occurred when either air or nitrogen was breathed. When the over-breathing was performed with nitrogen the rise of heart rate persisted for considerably longer and there was a secondary increase of arterial pressure and calf blood flow. These secondary changes were absent when air was substituted for nitrogen and were due, therefore, to the severe hypoxia induced by the nitrogen. Throughout each experiment the calf blood flow was directly proportional to the mean systemic arterial pressure. Thus the observed changes of calf blood flow were a result of the concomitant changes of arterial pressure. The secondary changes which occurred after over-ventilation with nitrogen were probably the result of an increase of cardiac output and of systemic arteriolar constriction which were produced reflexly by chemoreceptor stimulation. It is apparent that the arterioles of the calf did not contribute to this vasoconstriction, and the most probable sites for the increase of peripheral resistance were the splanchnic and cutaneous circulations. The rise of the oxygen saturation of the jugular venous blood above the control value when air breathing was restored (Fig. 5) suggests that there was an increase of the over-all cerebral blood flow at this time. In the steady state moderate arterial hypoxaemia, even when accompanied by hypocapnia, is known to produce a dilatation of the cerebral vessels (Kety &

Schmidt, 1948). The rate at which the cerebral vasodilatation develops when arterial hypoxaemia is induced suddenly is not known, but the present experiments suggest that the cerebral vessels respond to a fall of arterial oxygen tension within 20 sec.

Pulmonary gas exchange in profound hypoxia

The arterial oxygen-tension values derived in this study demonstrated that during over-ventilation with nitrogen the oxygen tension of the arterial blood was significantly greater than that of the alveolar gas. The time for which this state existed was only 7–8 sec, although during this period the rates of change of alveolar and arterial oxygen tensions were relatively slow. Furthermore, this length of time is large relative to the average transit time of 0·73 sec (Roughton, 1945; Roughton & Forster, 1957) for a red cell through the pulmonary capillaries lining ventilated alveoli. It would appear, therefore, that the observed difference between systemic arterial and alveolar oxygen tensions cannot be accounted for on the basis of the short period for which the condition existed. Such a difference could be produced by the presence of either a shunt of venous blood into the systemic arterial tree or a higher tension of oxygen in the blood leaving the pulmonary capillaries than in the alveolar gas. Mixed venous blood flowing into the systemic arterial tree without having transversed the capillaries of ventilated alveoli would raise the oxygen tension of the systemic arterial blood above that of the alveolar gas. The effect of the normal quantity of venous admixture upon the arterial oxygen tension would be insignificant, because of the relative steepness of the blood-oxygen dissociation curve over the range concerned here. If, however, the proportion of the cardiac output perfusing ventilated alveoli was reduced during nitrogen breathing, this effect could become significant. In order for this mechanism to account for the total observed oxygen-tension gradient the venous-arterial shunt would have to amount to at least half of the total cardiac output. There is at present no evidence in favour of such a degree of shunting during severe hypoxia. It would appear probable, therefore, that the tension of oxygen in the blood leaving the pulmonary capillaries is considerably greater than that in the alveolar gas during over-ventilation with nitrogen.

Since no measurements were made of the rate of gaseous exchange during the period of over-ventilation with nitrogen it is impossible to examine quantitatively the factors affecting the exchange of oxygen between the pulmonary capillary blood and the alveolar gas. It is of value, however, to compare the effects of over-ventilation with nitrogen with those produced by moderate hypoxia in the steady state. Thus, Lilienthal, Riley, Proemmel & Franke (1946) found that at an alveolar

oxygen tension of 46 mm Hg at rest the difference between the tensions of oxygen in the alveolar gas and the systemic arterial blood amounted to 9·1 mm Hg. They calculated that under these circumstances the oxygen tension of the mixed venous blood was 19 mm Hg less than that of the alveolar gas and that the oxygen tension of the blood leaving the pulmonary capillaries was about 8 mm Hg less than that of the alveolar gas. Although in the nitrogen over-ventilation experiments the oxygen tension gradient between the alveolar gas and the mixed venous blood was reversed, it was of the same order as that which existed in the experiments performed by Lilienthal *et al.* (1946). Furthermore, the mean difference between the oxygen tensions of the arterial blood and the alveolar gas obtained in the present study, which amounted to 11 mm Hg, was only slightly greater than that found in moderate hypoxia by Lilienthal *et al.* (1946). The arterial–alveolar oxygen-tension difference observed in nitrogen over-ventilation experiments was probably due, therefore, to a mechanism analogous to that which was deduced by Lilienthal *et al.* (1946) to be responsible for the existence of an alveolar to end-pulmonary capillary blood-oxygen tension difference in moderate hypoxia. The limited rate at which oxygen was transferred from chemical combination in the pulmonary blood into the alveolar gas under the circumstances which existed in the nitrogen-breathing experiments gave rise to a large oxygen-tension difference between the blood leaving the pulmonary capillaries and the alveolar gas.

Exchange of oxygen between blood and peripheral tissues in profound hypoxia

The reduction in the rate at which oxygen is carried to a part caused by a short period of arterial hypoxaemia depends upon the degree and duration of the desaturation of the arterial blood and the arterial flow to the part. In the resting state the total blood flow to the brain is over twice that to the lower limbs. Thus in the present experiments the deficit of the oxygen supply to the brain was twice that to the lower limbs. The effect of such a deficit in the oxygen supply to a region upon the oxygen content of the blood flowing from it will be determined in part by the relation between the magnitude and nature of its oxygen store and its metabolic oxygen consumption. Where the available oxygen store is small in relation to the oxygen uptake, the venous oxygen saturation will be reduced to a greater extent than when the store is large in relation to the oxygen consumption. Quantitatively the most important oxygen store is that contained by the blood, and the greater proportion of this resides in the small and large veins. Muscle possesses in addition a specific oxygen storage mechanism in the form of oxymyoglobin. The amount of oxygen stored in this manner in man is, however, relatively small (Drabkin, 1950)

and the oxygen tension in muscle must be reduced below 10 mm Hg before a significant proportion of the oxygen held in this form is liberated (Hill, 1936). Finally, all tissues contain oxygen in simple physical solution, although quantitatively this store is relatively small. The brain, in contrast to the lower limbs and the body as a whole, has a high arterial inflow, a high oxygen consumption and a small oxygen store. For a specified transient arterial hypoxaemia all these factors tend to produce a greater fall of the oxygen saturation in the jugular blood than in the blood flowing from the lower limbs.

The pattern of the fall of the saturation of venous blood caused by a transient arterial hypoxaemia will be modified by changes of blood flow into the region and of the capacity of its vascular bed. In the present experiments there were transient changes of calf blood flow during and after the period of hypoxaemia. There was also evidence which suggested that the cerebral blood flow changed, although no direct measurements of this quantity were made. If an increase of blood flow occurred during the period of hypoxaemia, the deficit of the oxygen supply would have been increased. If, however, the increase of blood flow did not occur until the arterial oxygen saturation was rising, it would have produced a more rapid recovery of the venous oxygen saturation, or even a rise to above the control value. Although no direct measurements of the capacity of the vessels of the calf were made, it was noted that the volume of this region was decreased by the period of over-ventilation with nitrogen. Eckstein, Hamilton & McCammond (1958) have shown that the reflex reduction of the distensibility of the capacity vessels produced by over-ventilation is in part due to the hypocapnia and in part a result of the intrathoracic pressure changes associated with the over-ventilation. Such a reduction of the blood content of the calf would have tended to increase the venous desaturation produced by the arterial hypoxaemia.

During the period of over-ventilation with nitrogen, the oxygen tension of the arterial blood was reduced to 20–30 mm Hg below that of the venous blood normally flowing from the regions studied. Thus the oxygen tension of the arterial blood during this period was lower than the mean capillary oxygen tension (Barcroft, 1938) which existed before nitrogen breathing was commenced. Furthermore, during the period of profound hypoxaemia the oxygen tension of the blood flowing from the regions under investigation was greater than that of the arterial blood perfusing them. Although the oxygen content of the blood leaving the tissue capillaries was probably raised by admixture with the blood already present in the venules and veins of the part, it is apparent that during the period of severe hypoxaemia the oxygen tension of the capillary blood was markedly reduced. Thus the diffusion of oxygen into the various tissues from the blood flowing through

them was severely reduced by the period of hypoxia. Indeed, in some areas, especially those with a relatively high capillary blood flow, the capillary oxygen tension may have been reduced below that of the surrounding tissues, so that oxygen actually diffused into the blood as it flowed through them. Thus direct measurements of the oxygen tension of the grey matter of the cerebral cortex in animals breathing air have given values of the order of 18--25 mm Hg (Cater, Garattini, Marina & Silver, 1962), whilst in the present experiments the arterial oxygen tension was reduced to about 17 mm Hg. The effect of a given reduction of the rate at which oxygen diffuses into a tissue upon the cellular oxygen tension will depend upon the relation between the cellular oxygen consumption and the extravascular oxygen store. There is considerable evidence that the cellular oxidative enzyme systems will continue to function normally until the local oxygen tension is reduced to below 5 mm Hg (Keilin, 1930). Thus the cellular metabolic oxygen uptake will probably remain unchanged until severe hypoxia is induced. In the brain, where the only extravascular oxygen store is oxygen dissolved in tissue fluid, and the metabolic oxygen uptake is high, sudden arterial hypoxaemia will produce a very rapid fall of the cellular oxygen tension.

In the present series of experiments it was found that unconsciousness ensued if over-ventilation with nitrogen was continued for longer than 17 sec. A more rapid fall of arterial oxygen tension can be produced by sudden reduction of the environmental pressure to below 140 mm Hg whilst air is breathed. Thus in one series of experiments in which the arterial oxygen tension was reduced to below 20 mm Hg in about 1 sec, unconsciousness ensued 8 sec after the induction of arterial hypoxaemia (Ernsting *et al.* 1960). The delay between a sudden occlusion of the cerebral circulation and loss of consciousness in man also amounts to between 7 and 8 sec (Rossen, Kabat & Anderson, 1943). Thus the time which elapses between a sudden reduction of the arterial oxygen tension to below 20 mm Hg and the onset of unconsciousness is very similar to the interval which occurs between sudden occlusion of the cerebral circulation and loss of consciousness. Kety (1950) has calculated that at any one moment the total oxygen content of the brain and of the cerebral capillary blood is about 7 ml. Thus at the normal level of cerebral oxygen consumption the oxygen tension of the brain following cessation of the supply of this substance would be reduced to zero in about 8 sec. These results suggest that when unconsciousness supervenes following the sudden induction of severe cerebral hypoxia the cellular oxygen tension in many regions of the brain will be virtually zero. This conclusion is in close agreement with the results of calculations made by Thews (1962) with respect to hypoxia of slow onset. His calculations suggest that when the arterial oxygen tension is

reduced to the level which produces unconsciousness, the oxygen tension of the neurones which are furthest from their vascular supply will be of the order of 2–4 mm Hg.

SUMMARY

1. Brief profound hypoxia was induced by voluntary over-ventilation whilst breathing nitrogen. Unconsciousness ensued when this procedure was performed for longer than 16 sec. Voluntary over-ventilation with nitrogen for 16 sec reduced the end-tidal oxygen tension to below 10 mm Hg for 8 sec.

2. Continuous recordings were made of the systemic arterial oxygen saturation and pH during 16 sec of nitrogen over-ventilation. The calculated minimal arterial oxygen tension was 16 mm Hg. There was therefore a reversal of the normal alveolar-arterial oxygen tension difference.

3. The oxygen saturation and pH of venous blood flowing through the jugular bulb, the femoral vein and the pulmonary artery were recorded continuously. The oxygen tension of the jugular blood exhibited the most rapid and most profound reduction when nitrogen was breathed. The femoral-vein oxygen tension exhibited only a very transient and slight fall, whilst the oxygen tension of the blood flowing through the pulmonary artery exhibited a moderate fall.

The author wishes to thank the Director General Medical Services, Royal Air Force, for permission to submit this paper for publication.

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Pathology of hypoxic brain damage in man

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The energy requirements of the brain demand amongst other things adequate supplies of oxygen and glucose. These are provided by the functions of respiration and circulation. Neurons are particularly susceptible to hypoxia since they have an obligative, aerobic, glycolytic metabolism. The adult brain receives about 15 per cent of the cardiac output, or as expressed in terms of blood flow, about 45 ml/100 g/minute in the adult and about twice as much in children (McIlwain, 1966). The respiratory quotient of the brain is almost unity and glucose is the principal source of energy by oxygenation. If the supply of oxygen or glucose is reduced below a critical level consciousness is lost after a few seconds and irreversible brain damage may occur if the 'hypoxia' is more prolonged.

Physiology

The supply of oxygen to the brain depends on the cerebral blood flow (CBF) and the oxygen content of the blood. Cerebral blood flow in turn depends on the cerebral perfusion pressure (CPP) which is defined as the difference between the mean systemic arterial pressure (SAP) and the cerebral venous blood pressure. Blood flow to the brain shows a remarkable capacity for remaining constant, only hypercapnia, hypoxia and extreme hypotension affecting it to any marked extent. The preservation of CBF in response to changes in arterial blood pressure is brought about by autoregulation which can be defined as the 'maintenance of a relatively constant blood flow in the face of changes in perfusion pressure' (Harper, 1972). The mechanism of this autoregulation is still uncertain but it appears to be lost or at least severely impaired in a wide range of acute conditions producing brain damage (Bruce *et al*, 1973; Harper *et al*, 1975). Thus there are many situations in which cerebral autoregulation may be impaired before an episode of hypoxia. The level of CPP at which brain damage is produced is not known in man but in the presence of normal autoregulation the critical level of SAP is about 50 mm Hg (Harper, 1972). In primates with a normal PaO_2, it would appear that brain damage does not occur until the CPP falls to less than 25 mm Hg (Brierley *et al*, 1969).

The energy state of the brain may also be severely reduced in the presence of normal supplies of oxygen and glucose by substances which poison the oxidative enzymes of nerve cells. These considerations form the basis of the various categories of brain hypoxia (Brierley, 1976; Adams, 1976).

Categories of brain hypoxia

1 STAGNANT
(a) Ischaemic is due to local or generalized arrest of blood supply; (b) oligaemic is due to local or generalized *reduction* in blood supply.

2 ANOXIC AND HYPOXIC
(a) Anoxic, an absence of oxygen in the lungs which leads to tissue anoxia; (b) hypoxic, a reduced oxygen tension in the lungs which leads to tissue hypoxia.

3 ANAEMIC
Anaemic is where there is insufficient haemoglobin in the blood to carry the oxygen in chemical combination.

4 HISTOTOXIC
Histotoxic is due to poisoning of neuronal respiratory enzymes.

5 HYPOGLYCAEMIC
Hypoglycaemic is due to a deficiency of the substrate glucose.

6 FEBRILE CONVULSIONS AND STATUS EPILEPTICUS

Hypoxic brain damage

Hypoxic brain damage may occur in any situation where there is an inadequate supply of oxygen or glucose to nerve cells. It is therefore a potential hazard to any patient subjected to general anaesthesia, a severe episode of hypotension, cardiac arrest, status epilepticus, carbon monoxide or

barbiturate intoxication and hypoglycaemic coma. The eventual degree of clinical recovery will be determined by whether or not satisfactory resuscitation can be achieved before permanent brain damage ensues. Crises of this kind are not uncommon in clinical practice but the central question as to 'what duration of anoxia or ischaemia defines the watershed between recovery of the tissue and extensive permanent injury?' has not been critically defined in man (Plum, 1973). Reasons for this include the lack of precise physiological data about a patient's cardiovascular and respiratory status at the time of a crisis since the immediate priority is resuscitation, and the inadequate neuropathological examination of the brains from fatal cases.

Postmortem examination of patients with severe hypoxic brain damage is usually carried out under warrant by the forensic pathologist who often feels obliged to slice the unfixed brain in the mortuary. Under these conditions it is impossible to recognize recent hypoxic brain damage up to and including frank cerebral infarction even when subsequent histological examination shows severe and extensive neuronal necrosis. When the brain has been properly dissected after adequate fixation (up to three weeks' immersion in buffered 10 per cent formol saline) an infarct of about 18 to 24 hours' duration may just be recognizable but even an experienced neuropathologist may fail to identify extensive diffuse hypoxic brain damage if it is less than some three to four days' duration (figs 1 and 2). The extent and severity of hypoxic brain damage can be identified and its distribution analysed only by the microscopical examination of many large, bilateral and representative sections of the brain.[1] It is, however, often possible to establish that a patient has suffered hypoxic brain damage on the basis of a more restricted histological examination provided that the pathologist knows that certain parts of the brain are selectively vulnerable and is familiar with the cytological and histological appearances of ischaemic nerve cell change.

The identification of ischaemic cell change is made difficult in the human brain because of the frequent occurrence of histological artefact. The commonest artefacts are 'dark cells', 'hydropic cells' and 'perineuronal and perivascular spaces' (Cammermeyer, 1961). They are due partly to postmortem handling and to the slow penetration of fixative. Studies in experimental primates and in selected human material have shown that there is an identifiable process, namely ischaemic cell change, which is the neuropathological common denominator in all types of hypoxia.

The earliest histological stage of recent hypoxic neuronal damage in experimental animals in perfusion-fixed material is microvacuolation (Brown and Brierley, 1966; Brierley *et al*, 1971a and b; Meldrum and Brierley, 1973). This rather subtle histological change is difficult to identify in human material so that perhaps the earliest incontrovertible evidence in man of hypoxic brain damage is the second stage, ie, ischaemic cell change. The cell body and nucleus are shrunken and become triangular in shape. The cytoplasm, which usually still contains microvacuoles, stains intensely with eosin and from bright blue to dark mauve with the very useful Luxol fast blue/cresyl violet technique (Adams and Miller, 1970); the nucleus stains intensely with basic aniline dyes. The succeeding stage of ischaemic cell change with incrustations is characterized by

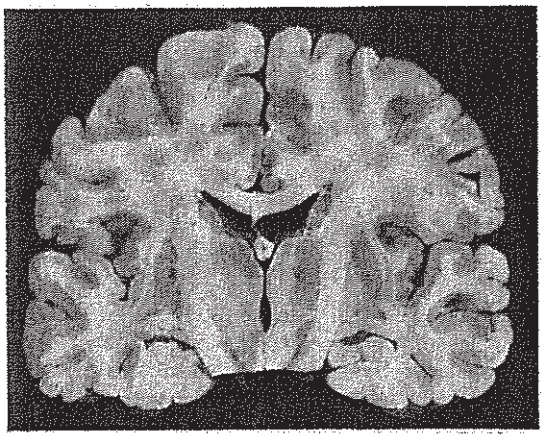

Fig 1 *Coronal section of brain from patient who survived 48 hours after cardiac arrest. There are no macroscopic abnormalities.*

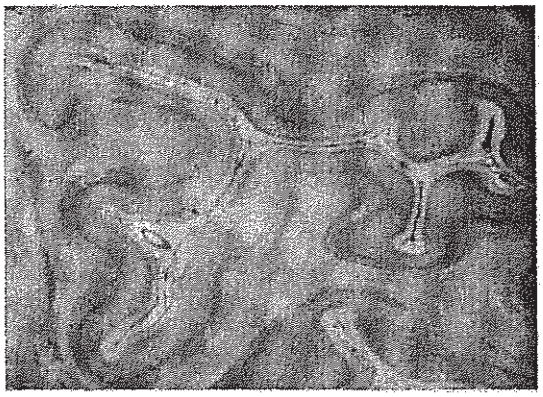

Fig 2 *Same patient as in figure 1. Note subtotal ('laminar') necrosis of the third, fifth and sixth cortical layers with relative sparing of the second and fourth layers (darker staining). Cresyl violet.* × *4.*

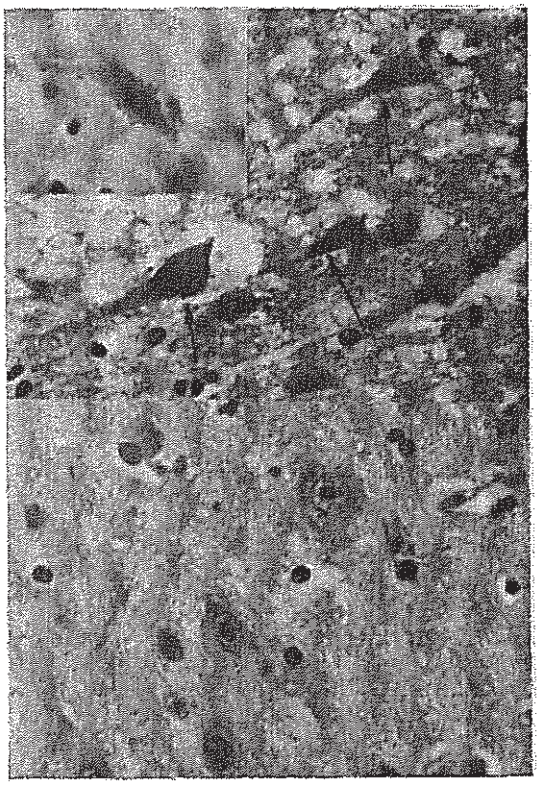

Fig 3

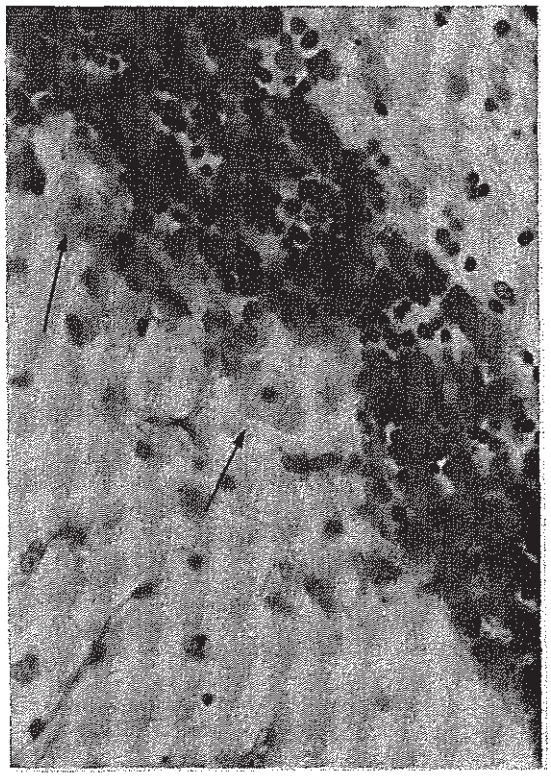

Fig 4

Fig 3 *Bottom: normal cortex. H and E × 500. Top: Ischaemic cell change. The nerve cells are small and triangular and contain hyperchromatic nuclei (arrows). The cytoplasm is intensely eosinophilic. There is also some disintegration of the neuropil. H and E × 500. Top inset: Ischaemic cell change with incrustations. Note the granules on the surface of the cell. H and E × 500.*

Fig 4 *Homogenizing cell change. Note the Purkinje cells with swollen homogeneous cytoplasm and hyperchromatic nuclei (arrows). Cresyl violet. × 500.*

further shrinkage of the nerve cell cytoplasm and the development of small, relatively dense granules lying on or close to the surface of the nerve cell (fig 3). Finally the neuron undergoes homogenizing cell change when the cytoplasm becomes progressively paler and homogeneous and the nucleus smaller. This type of change is most commonly seen in the Purkinje cells (fig 4) of the cerebellum. The time course of ischaemic cell change is relatively constant for neurons according to their size and site so that the interval between a hypoxic episode and death if between two and 18 to 24 hours can be assessed with reasonable accuracy. If the patient survives for more than 24 to 36 hours more advanced changes occur in neurons, and early reactive changes appear in astrocytes, microglia and endothelial cells. After a few days the dead nerve cells disappear and reactive changes become more intense, including the formation of lipid phagocytes, even though the latter may not appear if damage is restricted to neuronal necrosis. When survival is for more than a week or so the damaged tissue becomes rarefied due to loss of myelin and there is a reactive gliosis. Collagen and reticulin fibres are also laid own, the whole appearing as a glio-mesodermal reaction.

The differing susceptibility of nerve cells to hypoxia has been known for many years. According to Jacob (1963), 'in general the nerve cells are the most sensitive followed by oligodendroglia and astrocytes while the microglia and the cellular elements of the vessels are the least vulnerable'. Recent work suggests that local metabolic rather than vascular factors largely determine the pattern of selective vulnerability (Brierley, 1976).

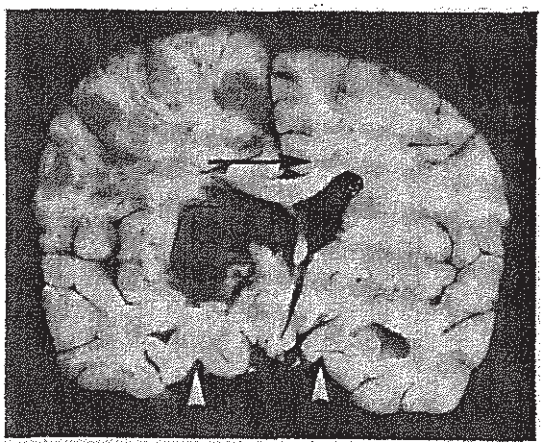

Fig 5 *Coronal section of brain from patient who survived three days after sudden stroke. There is a large recent swollen infarct in territories of left middle and anterior cerebral arteries. Part of the infarct is 'anaemic' and part is 'haemorrhagic'. Note the asymmetry of the lateral ventricles, the displacement of the midline structures to the right, the supracallosal hernia to the right (black arrow) and deep grooving (white arrows) along the line of bilateral tentorial herniae.*

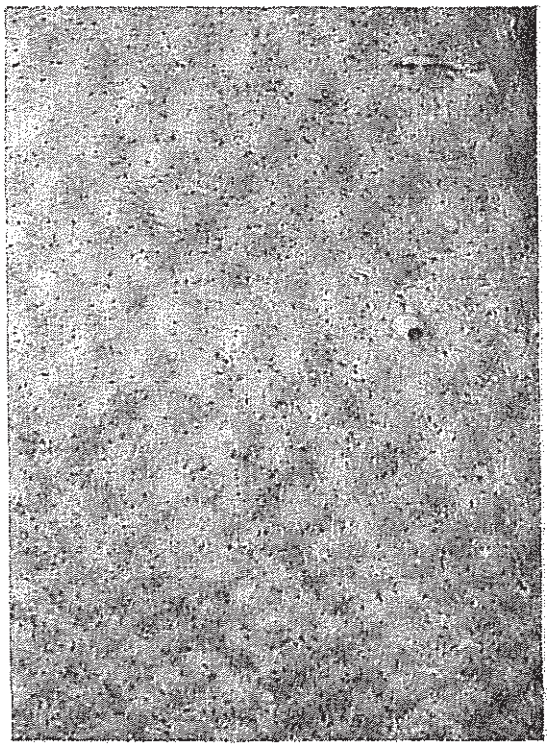

Fig 6 *Recent infarction in cerebral cortex. There is irregular pallor (infarction) of staining of the affected areas. H and E × 15·6.*

1 STAGNANT HYPOXIC BRAIN DAMAGE

This is divided into two main types, viz, ischaemic and oligaemic.

Ischaemic

If the blood flow through an artery is arrested, eg by thrombus or an embolus, an infarct will develop within part or the whole of the distribution of the occluded vessel. The earliest macroscopic change is swelling of the infarct and its edges may be just discernible in the fixed brain within 12 to 18 hours. The lesion may be 'haemorrhagic' or 'anaemic' (fig 5) and at an early stage there is irregular, blotchy pallor of the affected cortex (fig 6). A sharp

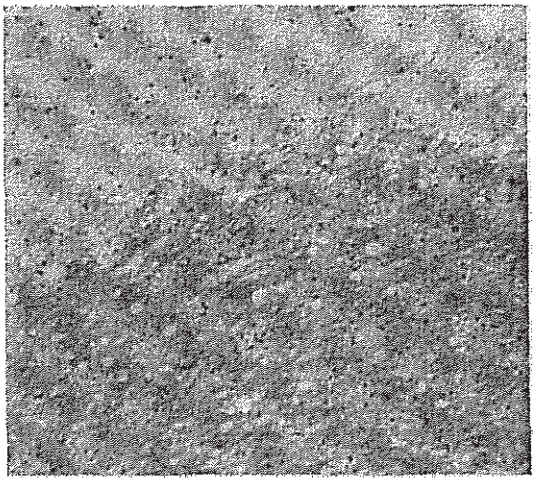

Fig 7 *Recent infarction in white matter. There is a sharply defined border between the abnormal (pale) and normal white matter. H and E × 40.*

and often very irregular line of demarcation between normal and abnormal myelin also appears early, the abnormal myelin staining palely (fig 7). A large infarct may swell sufficiently to constitute a space-occupying mass within 24 to 48 hours (Adams, 1966) resulting in tentorial herniation with secondary distortion of the mid-brain and infarction in the medial occipital (calcarine) cortex. The necrotic tissue is ultimately removed and replaced by a rather shrunken and cystic gliomesodermal scar.

A generalized arrest of blood flow to the brain is most commonly the result of cardiac arrest. This is usually a complication of some surgical procedure under general anaesthesia. Milstein (1956) estimated that about 300 deaths in the United Kingdom were caused by cardiac arrest related to surgery but by 1970 the number of such deaths had dropped to 100

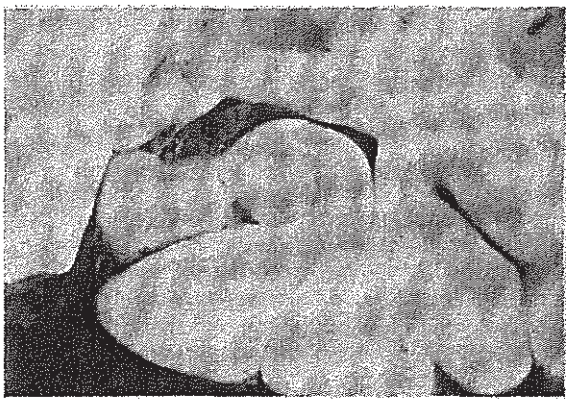

Fig 8a *Normal right Ammon's horn to compare with figure 8b.*

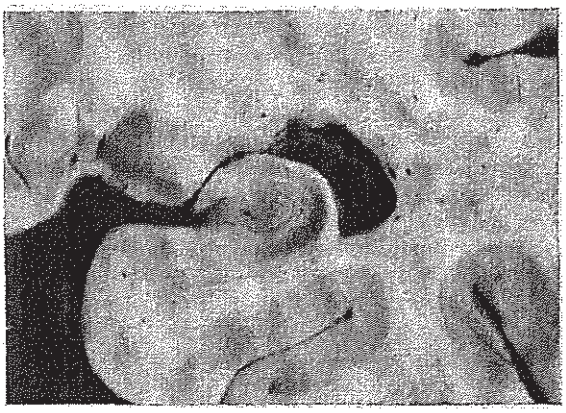

Fig 8b *Right Ammon's horn. Necrosis in the Sommer sector is seen macroscopically.*

Fig 9a *Normal right Ammon's horn. To compare with figure 9b. The arrows delineate the Sommer sector. Cresyl violet.* × 9.

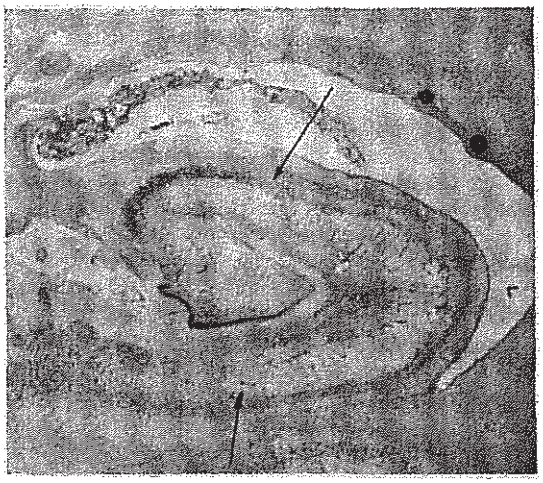

Fig 9b *Right Ammon's horn showing recent selective neuronal necrosis of Sommer sector (between arrows) and in endfolium. Cresyl violet.* × 9.

per annum in England and Wales (Wylie, 1975), the difference in mortality being attributed to better methods of resuscitation.

If cardiac arrest is of abrupt onset and occurs in a patient at normal body temperature, complete clinical recovery is unlikely if the period of arrest is more than five to seven minutes (Brierley, 1972). A short period of cardiac arrest combined with periods of reduced cerebral perfusion pressure before or after the arrest may be as important as the duration of complete arrest (Miller and Myers, 1972) and may lead to accentuation of the ischaemic damage in the arterial boundary zones (Brierley, 1976).

If death occurs within 24 to 36 hours of the arrest, the brain, apart from a variable degree of swelling, may appear normal externally and on section even after adequate fixation. Within 36 to 48 hours it is sometimes possible to identify laminar or patchy discolouration in the depths of sulci, particularly in the posterior halves of the brain and selective necrosis in the Sommer sector of the Ammon's horn (fig 8a and b). Microscopy reveals diffuse neuronal necrosis with a characteristic pattern of selective vulnerability. Ischaemic damage is commonly greater within sulci than at the crests of gyri and is maximal in the third, fifth and sixth layers of the parietal and occipital lobes (fig 2). In the Ammon's horn the Sommer sector and endfolium are the most vulnerable (fig 9a

and b). These changes are sometimes associated with necrosis of the baso-lateral portion of the amygdaloid nucleus. The pattern of damage in the basal ganglia is less constant and tends to be most frequent in the outer halves of the head and body of the caudate nucleus, and in the outer half of the putamen. Damage in the globus pallidus may occur in all types of hypoxia but is especially common in carbon monoxide intoxication. Primary hypoxic damage in the thalamus is most common in the anterior, dorsomedial and ventro-lateral nuclei. In the cerebellum there is characteristically diffuse necrosis of Purkinje cells. Damage to the brain stem nuclei tends to be more severe in infants and young children than in adults.

Patients with severe diffuse brain damage due to cardiac arrest rarely survive for more than a few days (Bell and Hodgson, 1974) but occasionally they may remain alive in a persistent vegetative state for up to six months or longer (Brierley *et al*, 1971; Jennett and Plum, 1972). With increasing survival, the necrotic tissue is replaced by a gliomesodermal scar. When this occurs there may be an appreciable reduction in the weight of the brain and evidence of atrophy of both the cortical gyri and cerebellar folia. In coronal slices ventricular enlargement may be considerable. Whereas the cortex of the parietal and occipital lobes will be reduced to a thin band of discoloured tissue, often with a line of cleavage between it and the underlying white matter, that of the frontal and temporal lobes may appear essentially normal. While the parahippocampal gyri are usually normal, the hippocampi may show the features of Ammon's horn sclerosis. Even when cortical necrosis is severe and survival is for only a few weeks the thalami may appear grossly normal. Eventually evidence of retrograde degeneration will be seen in the corresponding thalamic association nuclei (fig 10).

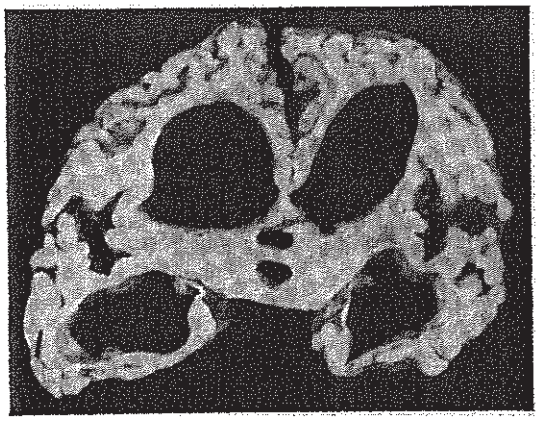

Fig 10 *Coronal section of brain from patient who survived for four years in a persistent vegetative state after cardiac arrest. The cortex is greatly narrowed and there is gross essentially symmetrical enlargement of the ventricles. The Ammon's horns and the thalami are also small.*

Oligaemic

Because of autoregulation a moderate fall in cerebral perfusion pressure does not lead to a reduction in cerebral blood flow. However, when vasodilatation is maximal, autoregulation ceases and the cerebral blood flow will fall parallel to the perfusion pressure. Oligaemic brain damage due to systemic arterial hypotension conforms to one of three patterns (Adams *et al*, 1966), of which the first two types are the most common.

1 Ischaemic damage is concentrated along the boundary zones between the arterial territories of the cerebral cortex and in the cerebellum (fig 11). If the lesions are large and of several days' duration they can be recognized macroscopically provided that the brain is cut in the coronal plane (fig 12a). They vary in size from foci of necrosis in the cortex to large, wedge-shaped lesions extending from the cortex almost to the angle of the lateral ventricle. In the cortex, damage is most frequent and most severe in

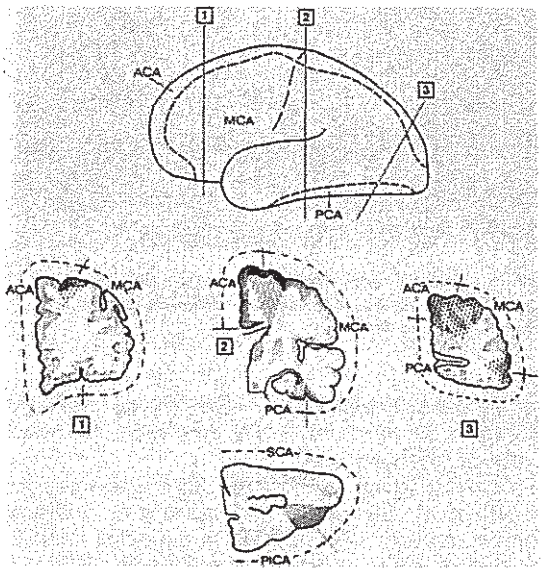

Fig 11 *Diagram to show arterial boundary zones in cerebral and cerebellar hemispheres. The right cerebral hemisphere is shown at three levels, viz, 1 = frontal, 2 = mid-temporal and 3 = occipital. Each boundary zone is stippled. ACA = anterior cerebral artery, MCA = middle cerebral artery, PCA = posterior cerebral artery, SCA = superior cerebellar artery and PICA = posterior inferior cerebellar artery.*

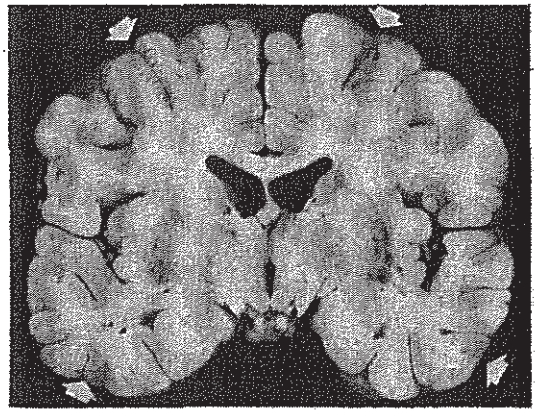

Fig 12a

Fig 12a *Coronal section of brain from patient who survived for 17 days after a myocardial infarct. Note focally haemorrhagic infarcts (arrows) in the boundary zones between the anterior and middle cerebral arterial territories, and between the middle and posterior cerebral arterial territories. Compare distribution of lesions with figure 11.*

Fig 12b *Same case as illustrated in figure 12a. Slices of cerebellar hemispheres to show duskily haemorrhagic infarcts at dorsal angle of each hemisphere, ie, in the boundary zones between the superior and posterior inferior cerebellar arterial territories. Compare with figure 11.*

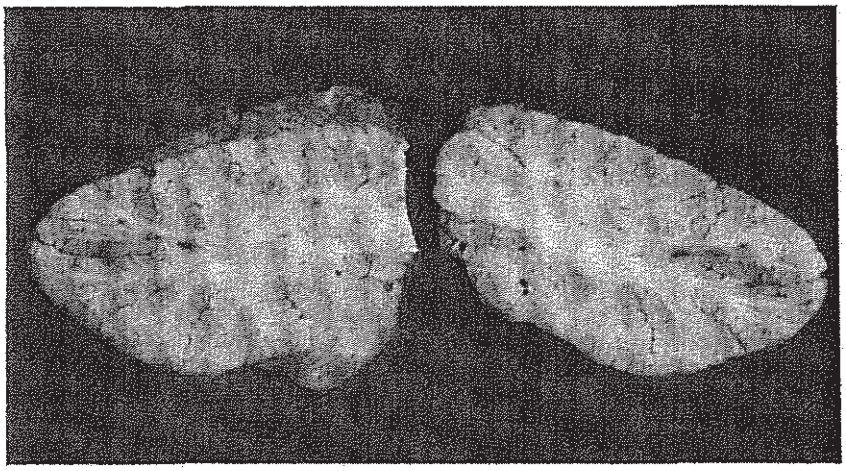

Fig 12b

the parieto-occipital regions, ie, in the common boundary zone between the territories of the anterior, middle and posterior cerebral arteries: it decreases towards the frontal pole along the intraparietal and the superior frontal sulci, ie, between the anterior and middle cerebral arterial territories, and towards the temporal pole along the inferior temporal gyrus, ie, between the middle and posterior cerebral arterial territories. The lesions are usually asymmetrical and may be unilateral, the pattern of ischaemic damage often being determined by atheroma and variations in the calibre of the vessels forming the circle of Willis. In the cerebellum the boundary zone between the territories of the superior and posterior inferior cerebellar arteries lies just beneath the dorsal angle of each hemisphere (fig 12b). There is variable involvement of the basal ganglia particularly in the head of the caudate nucleus and the upper part of the putamen. The Ammon's horn and brain stem are usually not involved. While infarction in the cortical boundary zones may occur in the absence of ischaemic lesions in the basal ganglia and cerebellum the converse is not common.

On the basis of clinical evidence (Adams *et al*, 1966; Adams, 1974) and experimental studies on primates (Brierley *et al*, 1969) this type of brain damage appears to be caused by a major and abrupt episode of hypotension followed by a rapid return to a normal blood pressure. It is often seen after a conscious patient has collapsed as a result of a sudden reduction in cardiac output, viz, due to ischaemic heart disease, and it may occur in the anaesthetized subject during dental or neurosurgical procedures, particularly in the sitting position (Brierley, 1970). More recently it has been described following the use of methylmethacrylic bone cement (Adams *et al*,

1972), in patients undergoing emergency treatment with antihypertensive agents (Graham, 1975) and in patients dying from blunt head injury (Graham *et al*, 1975). Because of the precipitate decrease in arterial pressure there is a transient failure of autoregulation and a severe reduction in CBF in the regions most removed from the parent arterial stems, ie, the boundary zones.

2 Ischaemic damage is generalized in the cortex of the cerebrum and cerebellum, is minor or absent in the hippocampi and is often severe in the thalami. The number of reported cases is small (Brierley and Cooper, 1962; Adams *et al*, 1966) but it would seem that this type of damage appears to be associated with hypotension of a relatively slow onset but of long duration.

3 Ischaemic damage is generalized in the cortex of the cerebrum and cerebellum but with variable accentuation along the arterial boundary zones. The hippocampi are usually spared and there is patchy damage in the basal ganglia. This type of damage appears to be associated with the abrupt onset of hypotension which is responsible for the accentuation of damage within the boundary zones followed by a sustained period of less severe hypotension which causes the diffuse damage.

2 ANOXIC AND HYPOXIC BRAIN DAMAGE

These terms imply that the blood leaving the lungs is either devoid of or has a greatly reduced oxygen content. Hypoxaemia of this severity will occur if there is obstruction of the air passages, after the inhalation of inert gases and in aviation accidents producing decompression. Even though it is still widely believed that brain damage can result from a simple reduction in the oxygen content of arterial blood, there is a lack of critical physiological data about cases purporting to show a correlation between neurological dysfunction and brain damage ascribed to the hypoxaemia. Indeed there is good experimental evidence in Rhesus monkeys and in baboons (Brierley, 1972) that the severity of the hypoxia required to produce brain damage also produces myocardial depression and a reduction in cardiac output. Thus, Brierley concluded that hypoxic hypoxia can produce brain damage only through the medium of a secondary depression of the myocardium, the pattern of damage being similar to that of oligaemic hypoxic brain damage as described above.

3 ANAEMIC BRAIN DAMAGE

This occurs classically in carbon monoxide poisoning. The neurological complications of carbon monoxide poisoning are many (Garland and Pearce, 1967) but there is not a combination of neurological and psychiatric symptoms that can be regarded as the specific consequences of such poisoning since similar symptoms and signs may be encountered after cardiac arrest, hypoglycaemia, etc.

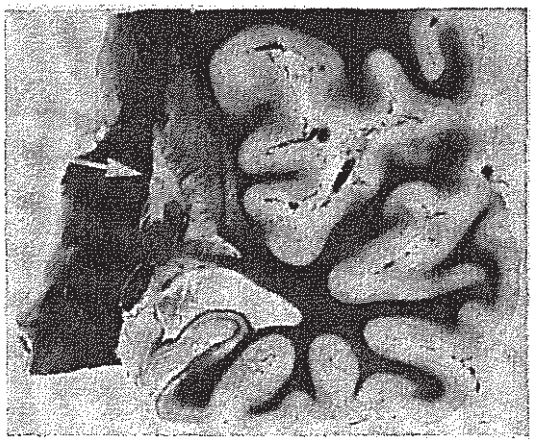

Fig 13 *Carbon monoxide poisoning. There is infarction of the superior pole of the globus pallidus (arrow). Celloidin section—myelin stain.* × *1·6.*

When death occurs within a few hours after poisoning, the organs display the pink/red colour characteristic of carboxyhaemoglobin. When survival is for 36 to 48 hours, the brain shows evidence of congestion, and petechiae are frequently seen in the white matter and the corpus callosum. Although there is a particular predilection for infarction of the globus pallidus in carbon monoxide poisoning (fig 13), there is also neuronal necrosis in other selectively vulnerable regions such as the Ammon's horn and the cerebral and cerebellar cortex.

Changes in the white matter are a common and often conspicuous neuropathological consequence of carbon monoxide poisoning. Damage to white matter tends to occur, particularly in patients who develop delayed signs of intoxication after a period of relative normality following acute poisoning.

Recent experimental work in the Rhesus monkey (Ginsberg *et al*, 1974) has underlined the importance of systemic circulatory factors in the production of brain damage, the concentration of damage in the white matter possibly being due to a combination of a toxic effect of carbon monoxide together with a moderate reduction in blood flow and perhaps an additional acidosis.

4 HISTOTOXIC BRAIN DAMAGE

The histotoxic effects of the cyanide ion and sodium azide are due to the inhibition of cytochrome oxidase. In acute intoxication death ensues rapidly from respiratory failure. In such cases the brain shows

hyperaemia and multiple petechial haemorrhages. In longer surviving cases necrosis has been identified in the lentiform nucleus and in the cortex of the cerebrum and cerebellum (Brierley, 1976). Experimental studies have now shown that brain damage produced by either cyanide (Brierley, 1975) or azide (Mettler and Sax, 1972) cannot be attributed to histotoxic hypoxia alone but results from their secondary effects on respiration and circulation.

5 HYPOGLYCAEMIC BRAIN DAMAGE

Hypoglycaemia in man may lead to permanent brain damage. It may be due to an excess of insulin given either for the treatment of diabetes mellitus or psychosis and in rare instances of islet cell tumour of the pancreas and in examples of idiopathic hypoglycaemia in infants (Brierley, 1976).

In cases of short survival the brain may appear normal. There may be atrophy of the cortex and hippocampi and enlargement of the ventricular system in cases surviving for a number of weeks. Microscopy shows that the brain damage is very similar in type and distribution to that seen in ischaemic hypoxic brain damage, ie, nerve cell loss and a glio-mesodermal reaction in the striatum, the cortex and the hippocampus, except that there is often relative sparing of the Purkinje cells in the cerebellum.

Studies of hypoglycaemia in experimental animals have shown that ischaemic cell change is the principal neuropathological consequence of uncomplicated hypoglycaemia (Meldrum *et al*, 1971; Brierley *et al*, 1971a and b) and in longer surviving animals there is nerve cell loss and a variable glio-mesodermal reaction in the striatum, the cerebral cortex and the hippocampus (Kahn and Myers, 1971). These experiments show that the blood glucose level must fall to about 1 mmol/l (20 mg/100 ml) if uncomplicated hypoglycaemia is to produce brain damage, though a higher level of blood sugar may produce similar damage if complicated by some hypotension, hypoxaemia or epileptic activity. It is therefore quite possible that if a patient has been in hypoglycaemic coma for some time, both oligaemic and hypoxic factors may have contributed to the brain damage.

A different type of neuropathological change has been described in the human infant as a consequence of hypoglycaemia (Anderson *et al*, 1967). Neuronal changes were generalized and included chromatolysis with cytoplasmic vacuolation in some and fragmentation of nuclear chromatin in others. It has, however, been suggested that these appearances could be attributed to autolysis (Brierley, 1976).

6 FEBRILE CONVULSIONS AND STATUS EPILEPTICUS

Status epilepticus may be defined broadly as a convulsive episode lasting over an hour without an intervening period of consciousness (Corsellis and Meldrum, 1976). It has long been recognized as a serious danger to life at any age but it offers a special threat in childhood. The basic neuropathology is that of severe and diffuse ischaemic damage of stagnant hypoxic type in which there is widespread necrosis of the cortex, Ammon's horn, basal ganglia, thalamus, cerebellum and parts of the brain stem (fig 14). Thus status epilepticus, particularly in children, constitutes a medical emergency. Fortunately many patients make an uneventful recovery but some have a permanent intellectual or neurological deficit caused by hypoxic brain damage.

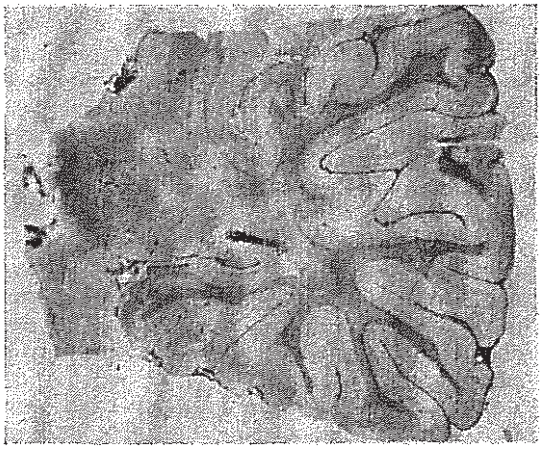

Fig 14 *Status epilepticus. Celloidin section of right temporal lobe from a child who died in coma five days after a series of convulsions. Note widespread neuronal necrosis in cortex and Ammon's horn. There is also some nerve cell loss in the thalamus. Cresyl violet.* × *1·8.*

Experimental studies in subhuman primate (Meldrum and Horton, 1973; Meldrum and Brierley, 1973; Meldrum *etal*, 1973) have emphasized that several factors may contribute to the brain damage, eg, arterial hypotension and hyperpyrexia. Evidence of an impaired neuronal energy metabolism was also found due to a combination of excessive neuronal activity and accumulative effects of secondary changes such as hypoxia, hypoglycaemia, hypotension, etc.

Conclusions

Hypoxic brain damage may occur in diverse clinical situations where there is an inadequate supply of oxygen or glucose to nerve cells. Many patients who experience an episode of severe hypoxia die within a few hours when the pathologist will not be able to

identify any macroscopic abnormalities in the brain. If the patient survives for more than a few hours, however, varying degrees of damage are easily identified, particularly if the brain has been properly dissected after adequate fixation.

The identification of early hypoxic brain damage is made difficult in the human brain because of histological artefact. The earliest clearly identifiable structural damage is selective neuronal necrosis as shown by ischaemic nerve cell change with incrustation formation. If the hypoxic insult is more severe then frank infarction may occur. In each instance the necrotic tissue is replaced by a glio-mesodermal reaction.

The distribution of hypoxic damage is most easily assessed in large representative sections of the brain. It is not usually feasible for the general pathologist to undertake a comprehensive neuropathological analysis in every case of suspected hypoxic brain damage. Fortunately, however, it is possible to establish that a patient has experienced an episode of hypoxia sufficiently severe to produce widespread hypoxic damage by the histological examination of bilateral small blocks from the 'selectively vulnerable areas', namely, the arterial boundary zones, the Ammon's horns, the thalamus and the cerebellum.

My thanks to Professor J. H. Adams for helpful criticism, to Mrs Ann Gentles for typing the manuscript and to Mrs Margaret Murray for photographic assistance.

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Respiratory Acidosis

Respiratory acidosis is primary increase in PCO_2 with or without compensatory increase in HCO_3^-; pH is usually low but may be near normal. Cause is a decrease in respiratory rate, volume (hypoventilation), or both due to CNS, pulmonary, or iatrogenic conditions. Respiratory acidosis can be acute or chronic; the chronic form is asymptomatic, but the acute, or worsening, form causes headache, confusion, and drowsiness. Signs include tremor, myoclonic

Treatment

- Adequate ventilation
- $NaHCO_3$ almost always contraindicated

Treatment is provision of adequate ventilation by either endotracheal intubation or noninvasive positive pressure ventilation (for specific indications and procedures, see Respiratory Failure and Mechanical Ventilation). Adequate ventilation is all that is needed to correct respiratory acidosis, although chronic hypercapnia generally must be corrected slowly (eg, over several hours or more), because too-rapid PCO_2 lowering can cause a posthypercapnic "overshoot" alkalosis when the underlying compensatory hyperbicarbonatemia becomes unmasked; the abrupt rise in CNS pH that results can lead to seizures and death. Any K^+ and Cl^- deficits are corrected.

$NaHCO_3$ is almost always contraindicated, because HCO_3^- can be converted to PCO_2 in serum but crosses the blood-brain barrier slowly, thus increasing serum pH without affecting CNS pH. One exception may be in cases of severe bronchospasm, in which HCO_3^- may improve responsiveness of bronchial smooth muscle to β-agonists.

Key Points

- Respiratory acidosis involves a decrease in respiratory rate and/or volume (hypoventilation).
- Common causes include impaired respiratory drive (eg, due to toxins, CNS disease), and airflow obstruction (eg, due to asthma, COPD, sleep apnea, airway edema).
- Recognize chronic hypoventilation by the presence of metabolic compensation (elevated HCO_3^-) and clinical signs of tolerance (less somnolence and confusion than expected for the degree of hypercarbia).
- Treat the cause and provide adequate ventilation, using tracheal intubation or noninvasive positive pressure ventilation as needed.

Last full review/revision February 2013 by James L. Lewis, III, MD
Content last modified October 2013

Suicide By Asphyxiation Due to Helium Inhalation

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Abstract: Suicide by asphyxiation using helium is the most widely promoted method of "self-deliverance" by right-to-die advocates. However, little is known about persons committing such suicides or the circumstances and manner in which they are completed. Prior reports of suicides by asphyxiation involving helium were reviewed and deaths determined by the North Carolina Office of the Chief Medical Examiner to be helium-associated asphyxial suicides occurring between January 1, 2000 and December 31, 2008 were included in a new case series examined in this article. The 10 asphyxial suicides involving helium identified in North Carolina tended to occur almost exclusively in non-Hispanic, white men who were relatively young (M age = 41.1 ± 11.6). In 6 of 10 cases, decedents suffered from significant psychiatric dysfunction; in 3 of these 6 cases, psychiatric disorders were present comorbidly with substance abuse. In none these cases were decedents suffering from terminal illness. Most persons committing suicide with helium were free of terminal illness but suffered from psychiatric and/or substance use disorders.

Key Words: asphyxia, helium, suicide, right-to-life

(*Am J Forensic Med Pathol* 2010;XX: 000–000)

Publication, in 1991, of the right-to-die manifesto and suicide "how-to" guide, Final Exit: The Practicalities of Self-Deliverance and Assisted Suicide for the Dying,[1] raised a maelstrom of controversy regarding the appropriateness of suicide as a response to terminal or "hopeless" physical illness and exposed divisions within the right-to-die movement itself. In the 1990s, many right-to-die advocates were engaged in public education as to the purported virtues of advanced directives, living wills, and legalized physician-assisted suicide.[2] At the same time, other elements of this movement, including the Self-Deliverance New Technology (NuTech) Group, were developing technologies to "empower people to die on their own terms by controlling the timing and manner of their own death."[2 (p. 8)] NuTech members, including Derek Humphry, author of Final Exit, sought to identify multiple suicide methods that were swift, painless, failure-proof, inexpensive, and nondisfiguring. The group also considered it vital that the method be simple, leave little or no indication that the death was unnatural in nature, and not require a physician's assistance or prescription.[2]

With its detailed descriptions of diverse suicide methods and specific endorsement of the plastic bag asphyxiation method, publication of Final Exit brought an easily understood and generally effective suicide method to the masses. The book was a commercial success, appearing on the New York Times bestseller list and selling more than 1.5 million copies in the decade following its publication. In 2007, Final Exit was named one of the 25 most influential books of the past quarter-century by book critics and editors of USA Today.[3]

Concerns that suicides in nonterminally ill depressed persons might follow exposure to methods elucidated in Final Exit were soon raised,[4] and dramatic increases in plastic bag asphyxial suicides were observed in New York City[5] and the United States[6] in the year following publication of Final Exit. Investigators concluded that "most persons exposed to Final Exit were not terminally ill and had used it as a suicide manual ... (and that) it is likely that a psychiatric disorder would have been diagnosed in most of these people."[5 (p. 1509)]

Efforts by NuTech and others to develop a more effective suicide method and widely disseminate it to the public have continued to the present. In 2000, a supplement to Final Exit was published that presented the first description of helium-assisted plastic bag asphyxiation.[7] Advocates emphasized the enhanced lethality of this approach, reduction in time required for death to occur to less than 5 minutes, and elimination of the need for a sedative prescription. Proponents of the method also noted that materials needed to complete such suicides are readily accessible and that asphyxiation due to helium inhalation is often undetected by autopsy (where findings are typically nonspecific) or toxicological analysis (because special sampling and assay methods are required). Thus, such suicides are likely to remain undetected in cases where the helium delivery apparatus and plastic bag are removed before the death scene is examined and no other information is available implicating death by helium-assisted asphyxiation. Modifications of the helium method were published in 2002[8] and 2009,[9] a DVD including a step-by-step demonstration of the method is available for purchase,[10] and instructional videos depicting the method are accessible on the internet. A schematic of the helium delivery apparatus is presented in Figure 1.[9]

Given the recent development, broad dissemination, and notable lethality of helium-assisted suicide, we endeavored to better understand characteristics of suicides by this method. First, we reviewed findings of extant studies examining suicides by asphyxiation due to helium inhalation. Second, we report new findings from the largest series of these suicides heretofore examined. Results of this investigation may lead to improved identification of helium-assisted suicides by medical examiners, enhanced screening and prevention efforts on the part of physicians and other professionals treating individuals at risk for suicide, and shed new light on unintended deleterious consequences of widespread dissemination of detailed suicide methods to the general public.

MATERIALS AND METHODS

The current report presents findings from 2 related studies. The first is a review of published investigations of suicides by asphyxiation due to helium inhalation. The second is a case series of suicides by asphyxiation due to helium inhalation occurring in North Carolina between 2000 (the year in which the method was first described) and December 31, 2008.

Manuscript received January 19, 2010; accepted March 3, 2010.
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Supported by NIH grants DA15929, DA15556, DA021405 (M.O.H.) and DA007304 (M.T.H.).
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ISSN: 0195-7910/10/0000-0001
DOI: 10.1097/PAF.0b013e3181ed7a2d

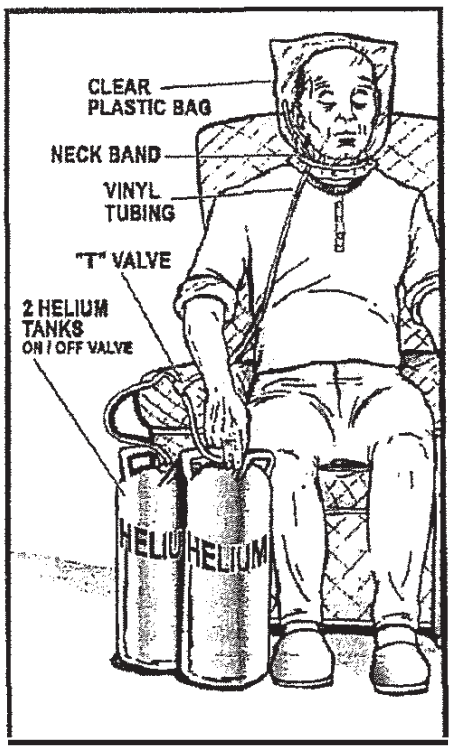

FIGURE 1. Schematic of plastic bag asphyxiation suicide using helium gas in final exit. Reprinted with permission from *Final Exit: The Practicalities of Self-deliverance and Assisted Suicide for the Dying.*[9] (p.4)

Identification of Published Reports

A broad search of the general medical literature was undertaken for any relevant reports addressing suicide by asphyxiation due to helium inhalation. This process entailed searching the PubMed database for the period January 1, 1957 to November 1, 2009 using the search phrase "suicide and helium." Seven pertinent records were identified as follows: 6 English-language case studies[11–16] and a Danish-language case study.[17] A search of EMBASE using the identical approach for the period January 1, 1988 to November 1, 2009 identified the same 7 reports. The 6 English-language reports relevant to this review were published between 2002 and 2007 and present a total of 14 cases.[11–16] The Danish study included a synoptic abstract in English indicating that the decedent was a 35-year-old man who had committed suicide with a plastic bag and helium using a "new and highly lethal technique."[17] The case reports included in this review constitute the entirety of published research on helium-assisted suicide and are presented in Table 1.

Identification of Suicides by Asphyxiation Due to Helium Inhalation in North Carolina

All deaths determined by the North Carolina Office of the Chief Medical Examiner (NCOCME) to be asphyxial suicides due to helium inhalation that occurred between January 1, 2000 and December 31, 2008, were included in this study. These suicides were identified through a search of the manner and cause of death fields of the electronic records maintained by the NCOCME. The presence of helium was confirmed by toxicological testing in 9 of 10 identified cases. Only the first reported case (ie, 2001) was not subjected to toxicological testing for helium. Specimens from suspected helium asphyxiation cases autopsied at the NCOCME are collected in 20 mL headspace vials. In some cases, given that one central laboratory conducts testing for all medical examiner cases in the state, blood samples are delivered to the NCOCME in standard collection vials. Immediately upon arrival, 5 mL of blood from the standard autopsy vial is transferred to a headspace vial for later analysis. Medical records associated with these deaths were manually reviewed and abstracted including the OCME Report of Investigation, State of North Carolina Death Certificate, Report of Autopsy, Toxicology Report, Case Encounter Form, Pathologist's Notes, and Supplemental Report of Cause of Death. On January 5, 2010, the University of North Carolina Institutional Review Board determined that the reported research does not require Institutional Review Board approval under pertinent federal regulations. Characteristics of the 10 cases identified are presented in Table 2.

RESULTS

Review of Published Cases

The first death attributed to suicide by asphyxiation due to helium inhalation reported in the medical literature occurred in September 2000,[11] shortly after the description of the method was published. Several investigators asserted that suicides by the helium method had not been seen in their localities prior to publication of the 2000 Supplement to Final Exit.[11,12,15,16]

The 14 decedents whose cases were presented in the 6 published reports ranged in age from 19 to 81 (M age = 50.0, SD = 21.8, median = 48.5). Between these extremes, decedents were approximately evenly divided between those in their 20s, 30s, 40s, 60s, and 70s. Medical and psychiatric histories were scant or entirely unreported for some cases, but revealed a history of depression, prior suicide attempt(s), paranoid schizophrenia, or some combination thereof in 4 (25.6%) cases. In 4 (25.6%) additional cases, psychiatric dysfunction may have contributed to the suicide, given that 3 of these decedents were determined to be in good health (ages 49, 49, and 76) and one mentioned the recent death of his wife as a reason for his suicide in a note left at the death scene. In 5 other cases (including 4 decedents in their 20s or 30s), no medical or psychiatric histories were reported. A terminal disease process was present in only 2 of 14 (14.3%) cases. In 2 (14.3%) additional cases involving men ages 71 and 78, "failing health" and "unspecified health problems" were possible contributing factors. Medical disorders were not implicated in 10 of 14 (71.4%) suicides.

In all reported cases, routine toxicological testing did not reveal the presence of helium and manner and cause of death determinations relied heavily on death scene investigations. Autopsy findings tended to be absent or nonspecific in the 12 cases that involved an autopsy.

In 8 cases (57.1%), a suicide note was found, and in 4 cases (28.6%) right-to-die literature was found at the death scene.

A number of helium delivery devices were employed. Five cases involved use of a mask; 4 of these cases were reported in 2002 or 2003, before plastic bag asphyxiation (without use of a mask) became preferred by advocates of the helium method.[8] Characteristics of the plastic tubing used, use of rubber bands and Velcro straps to secure plastic bags to the neck, types of helium canisters employed, and use of multiple plastic bags in 1 case were consistent with published descriptions of helium-assisted suicide.[8]

Characteristics of Suicides by Asphyxiation due to Helium Inhalation in North Carolina

Asphyxial suicides in North Carolina involving helium inhalation tended to occur almost exclusively in non-Hispanic, white

TABLE 1. Published Case Reports of Suicides by Asphyxia Due to Helium Inhalation

Authors/Date/ Location	Characteristics of Decedent	Medical/Psychiatric History	Helium-Delivery Apparatus	Death Scene	Autopsy Findings	Toxicology Findings
Ogden and Wooten (2002), South Carolina[11]	Woman, 60, white, suffering from adenoid cystic carcinoma with related eye involvement and diplopia. Death occurred 9/2000	History of depression and a prior suicide attempt. Unclear whether depression/suicide attempt antedated carcinoma diagnosis.	Found with surgical mask over face and clear plastic bag over head. Next to body was refillable industrial tank of helium. Clear plastic tube led from plastic bag to helium tank valve.	Decedent discovered on living room floor of home with suicide note and copy of her will. The book Final Exit, Final Exit videotape, and Spring 2000 Hemlock society newsletter were found on a nearby coffee table.	Does not appear an autopsy was conducted. It was noted at death scene that decedent's skin color was unremarkable and no external signs of poisoning were observed.	Blood/urine tests for medications and psychoactive substances were negative.
Gilson et al. (2003) Tucson, Arizona[12]	Cases 1 and 2: man, 49 and woman, 48, who were common-law married.	No specific information presented; decedents were reportedly in good health. Motivation for suicide unclear.	Each decedent had 3 plastic bags over their heads, which were secured by elastic straps around their necks.	Couple found lying supine by police on floor of master bedroom in their residence. Couples' attorney had called police after receiving a mailed suicide note. No right-to-die materials found.	Remarkable only for early decompositional changes.	Unremarkable for both decedents.
	Cases 3 and 4: husband, 78; wife, 76	Husband reportedly in "failing health" and "depressed"; wife in "good health" other than a recent minor elective surgery.	Both decedents were wearing filter cartridge-style masks attached to helium tanks with plastic tubing.	Couple found dead in bed by neighbor. Suicide notes were found close to bodies. Notes referring to the Hemlock society were found in apartment. No other right-to-die materials found.	External exams unremarkable. Internal exams not performed per family's wishes.	Negative for ethanol, medications, and illicit drugs for both decedents.
Gilson et al. (2003) Tucson, Arizona (continued)	Case 5: man, 81	Advanced squamous cell carcinoma of throat, cachectic.	Plastic bag over head with plastic tube running from inside plastic bag to helium tank.	Found by daughter in bed. Family unable to provide information as to whether "right-to-die" literature or suicide note were found at death scene.	Not clear that an autopsy was conducted.	Blood and urine tests were negative, but it was not clear what substances were assayed.
	Case 6: man, 71	Decedent mentioned unspecified health problems and the recent death of his wife as principal reasons for his suicide.	Plastic bag over head secured with elastic band and Velcro strap at neck. Plastic tube from helium tank connected to the mask inside plastic bag.	Found expired in chair in living room of home by police. A suicide note found, but no right-to-die literature.	External exam unremarkable except for decomposition.	Toxicology tests not performed due to decomposition.
	Case 7: man, 25	Medical history unknown; motivation for suicide unclear.	Plastic bag over head with plastic tube running from helium tank to bag with tube passing through a sink where warm water was running.	Found dead in empty bathtub of his apartment by landlord. Right-to-die literature and suicide note were not found.	Unremarkable except for decompositional changes.	Remarkable only for ethanol (234 mg/dL) in decomposition fluid.
Gallagher et al. (2003), Indiana[13]	Woman, 19, well-nourished	History of prior suicide attempts (number and nature not described). No description of medical history. Had searched methods of suicide on the internet.	Decedent wore air filter gas mask coated with a substance similar to correction fluid. A helium tank obtained from a local supply company was attached via clear plastic tubing to the mask. Duct tape sealed mask to skin of face covering nose and mouth.	Decedent found supine in backseat of car with helium tank on floor and valve between knees. Many signed suicide notes and a page from the "Church of Euthanasia" website entitled "How to kill yourself" were left in an envelope on the driver's seat. A hand-written map to a local general store was also found in the envelope with a list including tubing, mask and duct tape. A letter was found in decedent's residence describing where her body was located.	Conjunctival petechial hemorrhages bilaterally. Nares and oral cavity contained frothy white edema fluid. R lung = 670 g; L lung = 620 g. Lungs congested with severe pulmonary edema. No evidence of trauma, injury, or explanation for death other than helium inhalation.	Routine toxicology unremarkable. Presents a method by which specimens can be collected and analyzed for the presence of helium.
Auwaerter et al. (2007) Freiburg, Germany[14]	Man, 23	No information presented.	A helium gas canister was connected to a plastic bag with polypropylene tubing. The bag was over the decedent's head and affixed to neck with a rubber band.	Decedent was found dead in "lying" position in unidentified location. A nearly empty bottle of tequila, blister pack of travel sickness medication, and pack of Ibuprofen tablets were found.	Nonspecific findings included "an aqueous swelling of the brain and of the lungs and an acute hyperemia of the kidneys." No evidence of severe illness or injury.	Routine tests revealed a BAC of 0.9 mg/g; diphenhydramine in heart serum (0.81 μg/mL) and urine (2.2 μg/mL). Ibuprofen found in urine and gastric content. A positive test for helium by novel assay method was reported.

(*Continued*)

TABLE 1. *(Continued)*

Authors/Date/ Location	Characteristics of Decedent	Medical/Psychiatric History	Helium-Delivery Apparatus	Death Scene	Autopsy Findings	Toxicology Findings
Grassberger & Krauskopf (2007) Vienna, Austria[15]	Case 1: man, 28	History of paranoid schizophrenia; otherwise, no medical history reported.	Found with plastic bag over head sealed at neck with duct tape. A 10 L tank of party balloon helium was connected to the bag via plastic tubing.	Decedent found expired in his apartment reclining in a chair. Mouth contained frothy white edema fluid. A suicide note was left which named his mental illness as the primary reason for his suicide. No right-to-die literature found in domicile.	External exam unremarkable. Engorgement of right atrium and ventricle, pulmonary edema, and a few subpleural petechiae.	Blood/urine tests for 6 classes of illicit drugs were negative. Not clear whether ethanol was assayed.
	Case 2: man, 39	Not reported	Plastic tubing led from industrial helium tank into plastic mask.	Found expired in an empty bathtub wearing a plastic mask over face. Right-to-die literature and suicide note were found.	Autopsy remarkable. only for early decompositional changes.	Tests of decomposition fluid identified a BAC of 1 mg/L.
	Case 3: man, 39	Not reported.	Plastic bag over head connected via plastic tubing to a 10 L helium tank affixed to neck with rubber band.	Found supine on floor of his apartment with plastic bag over head. A suicide note was found.	External/internal exams unremarkable except for advanced decompositional changes.	Negative except for traces of benzodiazepines in urine.
Schon & Ketterer (2007) Bern, Switzerland[16]	Man, 64, white	Not reported	A gas canister labeled "helium" was found on a table at side of room opposite from where body was found. The helium canister was not connected to the 17 L blue plastic garbage bag that was found over the decedent's head. In addition to the plastic ribbon used to tie the bag, the decedent had inserted a rubber band into the bag's collar. The bag was secured tightly around decedent's neck.	Decedent found expired in hotel room lying supine on bed with garbage bag over head. No alcohol bottles, medications or drug paraphernalia were found. A rental receipt for the helium canister was found, but no suicide note or self-help materials. An inquiry at the decedent's home town revealed that another person in the area had committed suicide using the same method within the same week.	No external injuries/petechial hemorrhages found, except for a ligature mark impression attributed to a rubber band around neck. Nose, mouth, and airways filled with frothy reddish fluid. Lungs/brain edematous. Internal organs acutely congested. Pulmonary emphysema and hypertrophy/ dilation of right atrium/ventricle noted. No other potential causes of death were identified.	No obvious evidence of alcohol/drug abuse, but no toxicology assays performed.

TABLE 2. Characteristic of Suicides by Asphyxiation due to Helium Inhalation in North Carolina: 2000–2008

Year of Death	Characteristics of Decedent	Medical/Psychiatric History	Helium-Delivery Apparatus	Death Scene Description	Autopsy Findings	Toxicology Exam Findings
2001	Man, 47, never-married, white (non-Hispanic) graduate school education	Long history of depression treated by his physician. Depression listed as a contributing cause of suicide. Little information available about medical or psychiatric history or acute precipitants of suicide.	Plastic bag over head, secured with velcro tie around neck. Plastic tubing was taped to top of head, extended down left arm under shirt sleeve and exited at left cuff. The tubing was connected to a T-valve and attached to 2 helium tanks.	Found in living room of his home by a co-worker and police. Two bottles of temazepam and a will and suicide note found at scene.	Early decompositional changes noted at death scene; no autopsy conducted.	Trace levels of 7-aminoclonazepam, and temazepam (0.016 mg/L) were identified in a 1 mL sample of vitreous humor.
2003	Man, 31, married, white (non-Hispanic), 13 yr of education	Suicide note mentioned "chronic pain" as a reason for suicide. However, medical and psychiatric history are not known.	Clear blue, thin plastic bag over head secured with 2 large yellow rubber bands around neck. Clear plastic tube taped to inside of plastic bag, extending out of bag, looping around left arm and connected to helium tank.	Decedent found in his apartment. Had left a suicide note describing how he planned the suicide. No medications found in apartment.	Pathological diagnosis: bilateral pulmonary congestion. No significant external/internal injuries. Lungs: R lung: 750 g; L lung: 640 g. Parenchyma of both lungs show extensive congestion w/o obvious consolidation or focal lesions. Brain: 1500 g. Leptomeninges thin, delicate and congested. Cerebral hemispheres unremarkable w/mild generalized edema w/o evidence of herniation. Microscopic exams of lungs, kidneys, and brain show vascular congestion. No evidence of injury.	Two 8.0 mL aortic blood samples were positive for helium as was one lung sample. No ethanol detected in an 18.0 mL aortic blood sample.
2005	Man, 37, married, white (non-Hispanic); 16 yr of education	Medical and psychiatric history and acute precipitants of suicide are unclear.	Found with white plastic trash bag around head with tube hooked to helium tank valve at one end and the other end within the plastic bag. Tubing was connected to the helium tank with electrical tape. The bag was secured to neck with bag tie, which was knotted in a bow knot on right anterior neck. A clear vinyl plastic tube extended into the bag through a hole made in the rear of the bag space, held in place by black electrical tape.	Death occurred in motel. Decedent found supine in bed. Medications found at scene were an OTC sleep aid, Ibuprofen, and hydrocodone. Receipts from a local hardware store were found for helium tank, tubing, and tape No suicide note or right-to-die materials were found.	Pathological diagnoses: pulmonary vascular congestion and edema, slight diffuse cerebral swelling, moderate coronary atherosclerosis. R lung: 920 g; L lung 700 g. Lungs on section demonstrate marked vascular congestion Bronchial branches contain clear fluid and intra-alveolar edema. Brain: 1500g with mild diffuse swelling and narrowing of sulci. No evidence of acute trauma.	10 mL aortic blood sample revealed trace levels of cyclobenzaprine and propoxyphene and was positive (0.91 mg/L) for diphenhydramine. and helium. Diphenhydramine was believed to have contributed to the death. No ethanol or organic bases were identified.
2005	Man, 21, never married, white (non-Hispanic) 12 yr of education	History of symptoms, treatment, and hospitalization for paranoia/suicidal ideation. Not clear whether patient suffered from psychotic illness.	Plastic bag over head with elastic strap securing bag around neck. An empty helium canister found on floor beside decedent. A cylinder of helium and plastic tubing were found in decedent's bedroom closet.	Found in bedroom at parent's home sitting in chair. The following medications were found in home: Trazodone (100mg), Geodon (80mg), Risperdal (3mg), Trileptal (300mg), and Zoloft (50mg).	Pathological diagnosis: pulmonary vascular congestion and edema, cerebral edema, and early decompositional changes. R lung: 640 g; L lung: 590 g Brain: 1,500 g, microscopic lung sections show variable degrees of pulmonary vascular congestion and intra-alveolar hemorrhage.	Post-mortem exam revealed an ethanol level of .40 mg/dL and the presence of helium in 15.0 mL and 5.0 mL aortic blood samples, respectively.
2005	Man, 39, never married, white (non-Hispanic), 12 yr of education	No history of suicide attempts per family. Little information available about medical or psychiatric history and acute precipitants of suicide.	Found with plastic bag over head secured with a metal clip to hold bag tight around neck. Plastic tubing ran from a nearby helium tank to the back of the plastic bag. Duct tape covered front of bag and had 0.5 cm circular hole in it. Tube was connected to helium tank, which was turned on and near decedent's hand.	Found lying supine in bed at home by mother. No suicide note left, but insurance policy and will were found on coffee table.	Final anatomic diagnosis: congestion of lungs with early pulmonary edema. Brain: 1,325 g. Vessels over right hemisphere congested. R lung: 610 g; L lung: 560 g Lungs boggy with congestion. Microscopic sections show that alveolar spaces were partially filled with clear edema fluid.	Positive for helium in 4.0 mL subclavian vessel blood sample, but negative for ethanol in 17.0 mL subclavian blood sample.

(*Continued*)

TABLE 2. *(Continued)*

Year of Death	Characteristics of Decedent	Medical/Psychiatric History	Helium-Delivery Apparatus	Death Scene Description	Autopsy Findings	Toxicology Exam Findings
2005	Man, 34, unmarried, white (non-Hispanic); 9 yr of education	History of alcohol dependence and bipolar disorder. Prior psychiatric treatment for both disorders. Was living in car and taking Zoloft.	Had clear plastic bag over head with tubing connecting it to a helium tank. A velcro closure secured the bag around neck.	Found dead in driver's seat of a car parked in the yard of a relative's house. A picture of his girlfriend was found on dashboard.	Pathological diagnoses: pulmonary edema and vascular congestion; atherosclerotic coronary artery disease, focal, mild to moderate. R lung: 960 g; L lung 820 g. Lungs heavy and congested. Lung sections revealed areas of atelectasis, pulmonary edema, and collections of pigment-laden intra-alveolar macrophages.	20.0 mL and 6.0 mL aortic blood samples were positive for ethanol (70 mg/dL) and helium, respectively. Ethanol was listed as a contributing cause of suicide.
2006	Woman, 60, never married white (non-Hispanic), 12 yr of education	Obese (5'9", 303 lbs). No medical or psychiatric history information available except that EKG leads were found on right lower leg, left lower leg and left arm. No acute precipitants of suicide were identified.	Decedent had clear plastic bag over head with 1/2 inch plastic tubing attached to helium tank in back car seat and inside of plastic bag. A tan elastic band was used to secure bag to neck. The plastic tubing was taped to lower margin of plastic bag.	Decedent found in front passenger seat of car in motel parking lot where she had stayed. Letters to different people and "a very organized" suicide note were found in car. Note referred to pgs. 132–137 in Final Exit 3rd edition which describe helium-assisted suicide. Decedent had set e-mail to respond to messages with "Return to Sender due to Suicide."	Pathological diagnoses: Plastic bag over head with evidence of helium inhalation; pulmonary vascular congestion (R lung: 430 g; L lung: 400 g); decomposition. Sectioned lungs showed vascular congestion with patchy intra-alveolar edema. No evidence of acute trauma.	A 20-mL-blood sample from pleural cavity was positive for helium and ethanol (40 mg/dl). Elevated BAC may have been partially or totally due to decomposition.
2007	Man, 41, married (but recently separated from wife), white (non-Hispanic), 14 yr of education	Previously disabled in motor vehicle accident with neck and back injuries. Was reportedly depressed due to recent separation from wife and pending sale of home. Wife reported that decedent was taking prescribed antidepressants, Neurontin, Oxycontin, and Vicodin.	Clear blue plastic bag covered head and was wrapped with duct tape. Black tubing was connected at one end to the inside of bag and at the other end to a 65lb helium tank used to fill balloons for parties.	Found expired at home sitting in chair in basement. No suicide note left.	No autopsy.	A 13.0 mL subclavian blood sample was negative for ethanol, but positive for helium.
2007	Man, 45, never married, white (non-Hispanic)	History of alcohol and drug abuse and diabetes. Decedent has been very depressed per family's report. Family noted a history of social, medical and emotional problems. Was taking Coumadin, Clonidine, Aspirin, Verapamil, Atenolol, and Lovastatin.	Clear plastic bag was found over head. Two black tubes led from helium tank into the plastic bag. Had purchased these materials at local hardware store. The helium tank was from a party store balloon-filling kit.	Found sitting in chair in parent's home. Patient was pulseless and not breathing. The book Final Exit was lying open and face down on the bed. A suicide note was left describing how severely depressed the decedent had felt and apologizing for the suicide.	No autopsy, but blue nail beds and burst capillaries in lower legs bilaterally were observed at death scene.	19.0 mL subclavian blood sample was negative for ethanol and positive for helium.
2008	Man, 56, married, white (non-Hispanic), 12 yr of education	History of depression and substance abuse.	Decedent had a bag over his head with a tube attached to it and to a helium tank positioned on car passenger seat.	Found in car in garage at home by wife with car running and exhaust piped into the vehicle. A suicide note was found.	No autopsy.	18.0 mL subclavian blood sample was positive for helium and negative for ethanol. Carbon monoxide detected at <5.0% saturation.

OTC indicates over-the-counter; BAC, blood alcohol concentration; EKG, electrocardiogram.

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men who were relatively young (M age, 41.1; SD, 11.6; range, 21–60; median, 40.0). In 6 of 10 cases, decedents suffered from significant psychiatric dysfunction; in 3 of these 6 cases, psychiatric problems were present comorbidly with substance abuse. Medical histories identified chronic pain, disability, and chronic pain associated with injuries suffered in a motor vehicle accident, and diabetes (with probable coronary artery disease in 3 decedents). One decedent was found with electrocardiogram leads attached to her body, but autopsy and toxicological findings were negative for potential explanations for the death other than helium-assisted suicide. In none of the 10 cases were decedents suffering from terminal illness.

Helium delivery devices were consistent with those recommended in Final Exit (eg, use of T-valves, 2 helium tanks, Velcro and other neck fasteners), and all were associated with use of a plastic bag rather than mask.[8] In 5 cases, a suicide note was found; in 2 cases, a will was left; in 1 case, insurance papers were left; and in 2 cases, right-to-die materials were found.

Autopsies were performed in a majority of cases and typically revealed evidence of pulmonary vascular congestion and mild cerebral edema. Ethanol and diphenhydramine were considered contributing causes of death in 1 case each.

DISCUSSION

Despite reports identifying a plethora of prosuicide internet sites providing detailed instructions in methods of suicide including helium-assisted asphyxiation,[18] media accounts of helium-assisted suicides,[19–21] and the recent arrests of Final Exit Network members for allegedly assisting in asphyxial suicides involving helium,[22] scientific investigations of such suicides are largely absent from the medical literature. This dearth of information is unfortunate given the tragic consequences of such acts and because it is possible that suicides by the helium method are underestimated and increasingly common for reasons described later in the text.

The methods by which helium-assisted suicides are carried out have been carefully detailed and widely publicized and the approach is promoted as simple, painless, and quick.[8] Materials needed for helium-assisted suicides are easily obtained and inexpensive. One well-known internet vendor currently sells disposable helium tanks for less than $50, and reports that customers who bought helium tanks also often bought the book Final Exit.[23] Unless there is a high index of suspicion for helium involvement in a death, the death may be erroneously attributed to natural causes or underlying illness because standard toxicological assays are unlikely to detect helium and autopsy findings are generally nonspecific.[14,16] Standard toxicological assays using GC/MS employ helium as the carrier gas and therefore cannot detect helium unless another gas (eg, nitrogen) is substituted for the helium. Auwaeter et al[14] and Gallagher et al[13] developed useful methods of collecting, preserving, and analyzing gas samples taken from decedents' for qualitative detection of helium. In all North Carolina cases, helium-delivery devices were found at the death scene, and toxicological testing was conducted in 9 of 10 cases. However, it is possible that an unknown number of such suicides went undetected, if and when helium-delivery devices and plastic bags were removed from the death scene prior to investigation. The author of Final Exit states that a person may choose to leave right-to-die materials to be found to make an ethical statement that they are committing "rational suicide" or, conversely, make plans to have the helium delivery apparatus and plastic bag removed following their death if they prefer to keep the suicidal nature of the death concealed.[8] Toxicological testing for helium has been conducted at the NCOCME in suspected cases since 2003 by a novel testing procedure using a dual cell thermal conductivity detector.[24]

Of particular concern, are recent national reports of notable increases in the prevalence of suicide due to suffocation (a category that includes deaths by plastic bag asphyxiation with or without helium assistance as well as hanging and strangulation) since the 1990s and especially since 2000.[25–27] Such increases have been observed in respondents of widely varying ages, including adolescents, and both genders. Observers have noted that the reasons for these increases are poorly understood, that declining rates of suicide observed in the 1990s have been largely reversed, and that recent increases in suicides due to suffocation account for most of the recent overall increases in rates of suicide.[28] It is possible that greater awareness of the plastic bag asphyxiation method and the enhanced lethality of the method when used with helium may account for the significant increases in suicides due to suffocation reported since 2000.

Given the national growth in adolescent, young adult, and adult suffocation suicides since 2000,[25,26] and relatively young age, psychiatric dysfunction, and absence of terminal illness characteristic of many identified cases, it is possible that many persons committing suicide by the helium method are neither hopelessly nor terminally ill, but rather psychiatrically disordered. Although the author of Final Exit cautions readers to be certain they are hopelessly ill, and not just depressed and to talk to their doctor,[8] depressive illness and substance dependency often impair the very capacities required to make these assessments and undertake these actions.

Prospective studies are needed to better understand the prevalence, incidence, predictors, and characteristics of asphyxial suicides due to helium inhalation. It is important to learn more about decedents' medical and psychiatric histories and the circumstances in which depressed and/or suicidal persons encounter descriptions of the helium method (eg, internet demonstrations of the process). At present, professionals working with persons at risk for suicide should routinely assess whether patients have read or viewed instructional materials describing specific methods of suicide such as helium-assisted plastic bag asphyxiation. Inquiries of this nature do not increase subsequent risk for suicide and can provide critically important information to guide appropriate preventative actions where indicated.[29,30] Medical examiners should also increase their index of suspicion for suicides by asphyxiation associated with helium inhalation. Medical ethicists and the general public may also want to carefully weigh the unintended adverse consequences of widely disseminated suicide methods likely to appeal to some depressed persons (irrespective of their physical health status or age) against the putative benefits associated with making these methods more widely known and available.

ACKNOWLEDGMENTS

The authors thank P. Barnes, Administrative Services Manager, and other staff of the North Carolina Office of the Chief Medical Examiner for their assistance.

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Report on Study of Methods of Execution &
Recommendations for Procedures

Submitted by: Louisiana Department of Public Safety & Corrections

February 18, 2015

House Resolution 142 of the 2014 Regular Legislative Session was enrolled and signed by the Speaker of the House on June 5, 2014 to study and make recommendations relative to the different forms of execution and the methods of execution to determine the best practices for administering the death penalty in the most humane manner.

The Secretary of the Louisiana Department of Public Safety and Corrections, James Le Blanc, chaired this work and held an organizational meeting on July 22, 2014 to organize a study committee to conduct this work. At that time, he assigned the following individuals to serve on the committee:

Burl Cain, Warden, Louisiana State Penitentiary
William Kline, Executive Counsel, DPS&C Legal Department
Seth Smith, Chief of Operations, DPS&C Office of Adult Services
Stephanie LaMartinere, Assistant Warden, Louisiana State Penitentiary
Bruce Dodd, Deputy Warden, Louisiana State Penitentiary
James Hilburn, Attorney, Shows Cali & Walsh, LLP
Jeff Cody, Attorney, Shows Cali & Walsh, LLP
Angela Whittaker, Executive Mgmt Officer, DPS&C Secretary's Office

The committee met on the following dates:

August 11, 2014: Planning meeting to develop resource and research needs of the group.

September 2, 2014: Report and discussion on research findings.

October 31, 2014: Report and discussion regarding identifying experts and discussion on additional research compiled.

December 4, 2014: Report and discussion regarding research and protocol options and drafting the required written report.

January 8, 2015: Review of research and draft report and consensus on recommendations for protocol options.

January 22, 2015: Review and approval final report.

Background:

Capital punishment, or the death penalty, is a sentence used in the justice process whereby an offender is put to death as punishment for a crime he/she committed. The death penalty in the United States is a legal sentence and states determine whether the death penalty will be used as a form of punishment for crimes committed within their borders.

In Louisiana, the death penalty may be applied in cases involving first degree murder, a violation of La. R.S. 14:30, in circumstances such as:

(1) The murder was committed during the commission of or attempt of, a specified felony such as aggravated kidnapping, second degree kidnapping, aggravated escape, aggravated arson, aggravated rape, forcible rape, aggravated burglary, armed robbery, assault by drive-by shooting, first degree robbery, second degree robbery, simple robbery, terrorism, cruelty to juveniles, or second degree cruelty to juveniles.

(2) The murder was committed while the defendant was engaged in "ritualistic acts."

(3) The murder was committed for pecuniary gain or pursuant to an agreement that the defendant would receive something of value.

(4) The defendant caused or directed another to commit murder, or the defendant procured the commission of the offense by payment, promise of payment, or anything of pecuniary value.

(5) The defendant has been convicted of, or committed, a prior murder, a felony involving violence, or other serious felony.

(6) The capital offense was committed by a person who is incarcerated, has escaped, is on probation, is in jail, or is under a sentence of imprisonment.

(7) The defendant was a drug dealer or has prior convictions involving the distribution of a controlled substance.

(8) The victim was under the age of 12 years.

(9) The victim was 65 years or older.

(10) The victim was a fireman, peace officer, or correctional officer engaged in his lawful duties.

(11) The victim was a witness in a prosecution against the defendant, gave material assistance to the state in any investigation or prosecution of the defendant, or was an eyewitness to a crime alleged to have been committed by the defendant or possessed other material evidence against the defendant.

(12) The murder was especially heinous, atrocious, cruel or depraved (or involved torture).

Before a jury may impose the death penalty it must consider whether there were any mitigating circumstances against imposing the death penalty. Louisiana Code of Criminal Procedure Art. 905.5 provides for the following mitigating circumstances:

(a) The offender has no significant prior history of criminal activity;

(b) The offense was committed while the offender was under the influence of extreme mental or emotional disturbance;

(c) The offense was committed while the offender was under the influence or under the domination of another person;

(d) The offense was committed under circumstances which the offender reasonably believed to provide a moral justification or extenuation for his conduct;

(e) At the time of the offense the capacity of the offender to appreciate the criminality of his conduct or to conform his conduct to the requirements of law was impaired as a result of mental disease or defect or intoxication;

(f) The youth of the offender at the time of the offense;

(g) The offender was a principal whose participation was relatively minor;

(h) Any other relevant mitigating circumstance.

Pursuant to La. R.S. 15:569 and 570, every sentence of death executed on or after September 15, 1991, shall be by lethal injection, that is, by the intravenous injection of a substance or substances in a lethal quantity into the body of the offender until such person is dead.

Including Louisiana, there are currently 34 states that authorize the death penalty. Most all of these states have adopted lethal injection as the primary means of implementing the death penalty. While 18 of those states have solely authorized lethal injection as the execution method, the rest of the states that impose the death penalty have also set forth alternative methods of execution such as electrocution, lethal gas, hanging, and the use of firing squads. The methods of execution for each such state are set forth in the chart below.

Research from Other Capital Punishment States:

State	Lethal Injection	Electrocution	Gas Chamber	Hanging	Firing Squad	Methods and Alternatives	Lethal Injection Drugs
Alabama	x	x				Lethal injection, unless inmate affirmatively selects electrocution	500 mg - midazolam hydrochloride; 600 mg - rocuronium bromide; 240 milliequivalents - potassium chloride
Arizona	x		x			Lethal injection; inmate sentenced on or before 11/15/92 may choose lethal injection or lethal gas	midazlam/ hydromorphone
Arkansas	x	x				Lethal injection, but electrocution if lethal injection declared unconstitutional	Statute specifies a barbituate preceded by a benzodiazepine
California	x		x			Lethal gas or lethal injection may be chosen by inmate; if inmate fails to choose either method, then lethal injection	
Colorado	x					Lethal injection	Statute specifies sodium thiopental or equivalent
Connecticut	x					Lethal injection	
Delaware	x					Lethal injection	
Florida	x	x				Lethal injection, unless inmate affirmatively selects electrocution; if both deemed unconstitutional, then any constitutional method	
Georgia	x					Lethal injection	
Idaho	x					Lethal injection	
Indiana	x					Lethal injection	
Kansas	x					Lethal injection	
Kentucky	x	x				Lethal injection; inmates sentenced on or before 3/31/98 may choose lethal injection or electrocution	

State	Lethal Injection	Electrocution	Gas Chamber	Hanging	Firing Squad	Methods and Alternatives	Lethal Injection Drugs
Louisiana	x					Lethal injection	midazlam/hydromorphone
Mississippi	x					Lethal injection	Statute specifies an ultra short-acting barbituate in combination with a paralytic agent
Missouri	x		x			Lethal gas or lethal injection	
Montana	x					Lethal injection	Statute specifies an ultra-fast-acting barbituate in combination with a chemical paralytic agent
Nebraska	x					Lethal injection	
Nevada	x					Lethal injection	
New Hampshire	x			x		Lethal injection; but may be by hanging if lethal injection deemed "impractical"	Statute specifies an ultrashort-acting barbituate in combination with a chemical paralytic agent
New Mexico	x					Lethal injection, but only for crimes committed prior to July 1, 2009; otherwise, capital punishment repealed	
North Carolina	x					Lethal injection	
Ohio	x					Lethal injection	midazlam/ hydromorphone
Oklahoma	x	x			x	Lethal injection; but electrocution if lethal injection held unconstitutional; if both lethal injection and electrocution held unconstitutional, then firing squad	midazlam/ hydromorphone

State	Lethal Injection	Electrocution	Gas Chamber	Hanging	Firing Squad	Methods and Alternatives	Lethal Injection Drugs
Oregon	x					Lethal injection	Statute specifies an ultra-short-acting barbituate in combination with a chemical paralytic agent and potassium chloride
Pennsylvania	x					Lethal injection	Statute specifies an ultrashort-acting barbituate in combination with chemical paralytic agents
South Carolina	x	x				Electrocution, but inmate may choose lethal injection; if fails to choose either, then lethal injection; but if convicted prior to date of statute, then electrocution unless chooses lethal injection; if lethal injection held unconstitutional, then electrocution	
South Dakota	x					Lethal injection	
Tennessee	x	x				Lethal injection; but offender, whose capital offense occurred prior to 1/1/99, may choose electrocution; if those methods deemed unconstitutional, then use any constitutional method	
Texas	x					Lethal injection	
Utah	x				x	Lethal injection; but firing squad if court determines inmate has a right to this alternative; if lethal injection is held unconstitutional, then firing squad	Statute specifies that one of the intravenous injections shall be sodium thipoental or equivalent

State	Lethal Injection	Electrocution	Gas Chamber	Hanging	Firing Squad	Methods and Alternatives	Lethal Injection Drugs
Virginia	x	x				Inmate may choose lethal injection or electrocution; if refuses to choose, then lethal injection	
Washington	x			x		Lethal injection, unless inmate chooses hanging	
Wyoming	x		x		*	Lethal injection; if lethal injection is held unconstitutional, then lethal gas. *Wyoming Senate recently approved legislation that allows for the use of a firing squad. Concurrence is pending by the House.	Statute specifies an ultra-short-acting barbituate, alone or in combination with a chemical paralytic agent and potassium chloride

It may be noted that the basis for utilizing a particular method of execution is not necessarily uniform among the states that offer more than one execution method. In some states, lethal injection is the primary execution method unless it should be declared unconstitutional, in which case the statute next provides for an alternate method, or a series of alternate methods in the event a successive method should be deemed unconstitutional. In other states, the condemned inmate is actually given a choice between lethal injection and another alternate method of execution.

In Louisiana, between 1919 and May 21, 1957, executions were conducted by the local parish law authorities. Prior to August 6, 1941, the penalty in Louisiana was carried out by hanging. The last hanging in Louisiana was on March 7, 1941. Between August 6, 1941 and June 9, 1961, executions were performed by electrocution in the electric chair. Between 1941 and 1957, a portable electric chair was transported from parish to parish in order that the death penalty could be administered in the parish where the crime was committed. After 1957, the State became responsible for administering the death penalty. Prior the reinstatement of capital punishment, the last death in the electric chair was on June 9, 1961.

In 1967, there was a rising tide of litigation against the death penalty. Federal courts suspended all executions pending a final decision by the U.S. Supreme Court. In 1972, the U.S. Supreme Court struck down all capital punishment laws as unconstitutional. All individuals under death sentenced at that time were re-sentenced to life in prison.

Effective October 1, 1976, the new Louisiana death penalty statute was adopted. The state's death penalty law was again revised in 1978, specifying that the sentencing judge must sign the death warrant rather than the governor. Capital punishment was reinstated in Louisiana on June 29, 1979.

In 1990, the legislature approved the use of lethal injection for those sentenced after January 1, 1991. In 1991, the legislature provided that every death sentence executed after September 15, 1991 would be by lethal injection. Since the reinstatement of the death penalty in 1979, there have been 28 executions performed, 20 by electrocution and 8 by lethal injection. The last one was on January 7, 2010.

The death penalty has risen to the forefront of national headlines recently due to the shortage of drugs historically used in the lethal injection process. States continuing to carry out executions have been forced to obtain drugs from other sources or substitute drugs normally used in the process. The alternatives have provided inmates with new grounds for appeal as they request transparency regarding execution methods.

To date, Louisiana has 85 offenders in custody who have been sentenced to death.

Study:

This study was conducted by reviewing available scientific, technical and safety literature related to various methods of execution. It is not intended to express an opinion about Louisiana's law for administration of capital punishment.

Lethal Injection Protocols:

Through February 2011, Louisiana had in place a three drug protocol which included 3 gm sodium thiopental, 50 mg pancuronium bromide and 240 meq potassium chloride.

In February 2011, after lawsuits, international trade restrictions and raw materials shortages complicated the market for drugs used in executions and the lack of availability of sodium thiopental, a decision was made to modify the three 3 drug protocol to use pentobarbital in lieu of sodium thiopental. This decision was based on experiences in Oklahoma using pentobarbital and the use of it being upheld in the United State District Court in the Western District of Oklahoma. Base on the change, the protocol then called for 1 gm of Pentobarbitol, 50 mg pancuronium bromide and 240 meq potassium chloride.

In January 2014, the protocol was again updated to provide two options for lethal injection. They are:

A) 5 gm of Pentobarbital or
B) 10 mg of Midazolam and 40 mg of Hydromorphone

Recommended Protocols:

A. Lethal Injection

We are recommending for consideration a lethal injection protocol that calls for the use of a one drug protocol utilizing 5 gm of Pentobarbital injected intravenously (IVP). This protocol has been used in numerous states, including Texas, as a one drug method. The availability of this drug to Departments of Corrections is however severely hampered and there could be issues obtaining a supply of Pentobarbitol or any other drug to be used for lethal injection. Drug suppliers have refused to sell drugs to the prison systems for use in executions and other entities have refused to sell to Louisiana DOC. It is this committees understanding that suppliers have threatened providers with no longer supplying the drugs to their businesses if they in turn sell to correctional agencies for the purpose of lethal injection. As a result, suppliers fear the backlash of bad publicity to their businesses if involved in providing the drugs to correctional agencies.

This committee also recommends reconsideration of a bill that combines the language from the original and amended versions of House Bill 328 of the 2014 Legislative Session authored by Representative Lopinto. The attached draft legislation (Appendix A) amending LA R.S. 15:569 outlines what is needed to allow for the recommendations within this report and will provide for the confidentiality of information related to the execution of a death sentence. The amended version of the prior bill stated that "The name, address, qualifications, and other identifying information of any person or entity that manufactures, compounds, prescribed, dispenses, supplies or administers the drugs or supplies utilized in an execution shall be confidential, shall not be subject to disclosure, and shall not be admissible as evidence or discoverable in any action of an kind in any court or before any tribunal, board, agency, or person. The same confidentiality and protection shall also apply to any person who participates in an execution or performs any ancillary function related to an execution and shall include information contained in any department records, including electronic records, that would identify any such person." Such legislation would provide some security to those tasked to and involved in carrying out the state's order to execute an individual as punishment for a qualifying crime.

It should also be noted that the U.S. Supreme Court will consider in April whether a multi-drug protocol used in recent lethal injections in other states violates the Constitution with regard to cruel and unusual punishment.

B. Induced Hypoxia via Nitrogen

It is the recommendation of this study group that hypoxia induced by the inhalation of nitrogen be considered for adoption as an alternative method of administering capital punishment in the State of Louisiana.

It is important to note that the recommendation would induce hypoxia, which is a deficiency of oxygen reaching the tissues of the body. In nitrogen induced hypoxia, there is no buildup of carbon dioxide in the bloodstream so the subject passes out when the blood oxygen falls too low. The research reviewed suggests that this method would be the most humane method and would not result in discomfort or cruel and unusual punishment to the subject.

Though the exact protocol and nitrogen delivery device have not been finalized, it has been determined that a Gas Chamber would not be used. Options for the nitrogen delivery device include a mask or a device similar to an oxygen tent house (small clear oxygen tent covering only the head and neck area). Research as to the best method of delivery is ongoing.

Oklahoma has recently filed similar legislation to allow for induced hypoxia (refer to Appendix B). Also, you will find attached the Executive Summary (Appendix C) of the research conducted in Oklahoma that supports this method as a humane method which does not require the assistance of licensed medical professionals. We have also attached the documents (Appendix D) which make up the research used in Oklahoma by this committee in developing this recommendation. This method is believed to be simple to administer and nitrogen is readily available.

Conclusion:

This committee submits this study response to House Resolution 142 of the 2014 Regular Legislative Session to make recommendations to consider relative to the different forms of execution and the methods of execution upon agreement that the above considerations represent the best practices for administering the death penalty in the most humane manner. There are two sides to the debate on the death penalty. Proponents believe that the death penalty reduces crime and provides safe communities, while also honoring the victim and those left behind who grieve a loss. Opponents believe that the cost of capital punishment doesn't justify the outcome, that it does not deter crime, and that there are social injustices that are not addressed that make justice system inequitable. As a whole, this committee takes no stand on either side of this debate, but submits this response based on the request for this study and the research and materials available to the group.

We close reminding readers that many are directly impacted by the process of capital punishment: the victim, the victim's friends and family; law enforcement; the judiciary, the prosecutor, the defense attorney, the jurors, the public, the offender, the offender's family, and the staff tasked to carry out the protocol, to name just a few. We understand that the decision to act on these recommendations for consideration is an enormous task before you that cannot be taken lightly. We trust that we have provided the information you needed to consider Louisiana's options.

Amendment to LSA-R.S. 15:569

Appendix A

**Delete current Sections A and B; rewrite statute to read as follows:

Section 1. R.S. 15:569 is hereby amended to read as follows:

§569. Place for execution of death sentence; manner of execution; confidentiality

Every sentence of death executed in this state on or after August 1, 2015, shall be conducted by either of the following methods:

(1) Lethal injection, which is the intravenous injection of a substance or substances in a lethal quantity into the body of a person convicted until such person is dead. Execution by lethal injection shall be permitted in accordance with procedures developed by the department.

(2) Induced hypoxia via nitrogen or an inert gas, which is the administration of gas in a lethal quantity upon the body of a person convicted until such person is dead. Execution by nitrogen or inert gas shall be permitted in accordance with procedures developed by the department.

A. The method of execution shall be chosen by the secretary of the department based upon the availability of the department to administer the lethal injection or induced hypoxia.

B. Every sentence of death imposed in this state shall be executed at the Louisiana State Penitentiary at Angola. Every execution shall be made in a room entirely cut off from view of all except those permitted by law to be in that room.

C. No licensed health care professional shall be compelled to administer the lethal injection or induced hypoxia.

D. The name, address, qualifications, and other indentifying information of any person or entity that manufactures, compounds, prescribes, dispenses, supplies, or administers the drugs or supplies utilized in an execution shall be confidential, shall not be subject to disclosure, and shall not be admissible as evidence or discoverable in any action of any kind in any court or before any tribunal, board, agency, or person. The same confidentiality and protection shall also apply to any person who participates in an execution or performs any ancillary function related to an execution and shall include information contained in any department records, including electronic records, that would identify any such person.

E. The provisions of the Administrative Procedure Act, R.S. 49:950, et seq., shall not apply to the procedures and policies concerning the process for implementing a sentence of death.

Appendix B

STATE OF OKLAHOI

1st Session of the 55th Legislature (2015)

HOUSE BILL 1879 By: Christian

AS INTRODUCED

An Act relating to criminal procedure; amending 22 O.S. 2011, Section 1014, which relates to the manner of inflicting punishment of death; providing alternative method for inflicting punishment of death; and providing an effective date.

BE IT ENACTED BY THE PEOPLE OF THE STATE OF OKLAHOMA:

SECTION 1. AMENDATORY 22 O.S. 2011, Section 1014, is amended to read as follows:

Section 1014. A. The punishment of death shall be carried out by the administration of a lethal quantity of a drug or drugs until death is pronounced by a licensed physician according to accepted standards of medical practice.

B. If the execution of the sentence of death as provided in subsection A of this section is held unconstitutional by an appellate court of competent jurisdiction or is otherwise unavailable, then the sentence of death shall be carried out by nitrogen hypoxia.

C. If the execution of the sentence of death as provided in ~~subsection~~ subsections A and B of this section is held unconstitutional by an appellate court of competent jurisdiction or is otherwise unavailable, then the sentence of death shall be carried out by electrocution.

~~C.~~ D. If the execution of the sentence of death as provided in subsections A ~~and~~, B and C of this section is held unconstitutional by an appellate court of competent jurisdiction or is otherwise unavailable, then the sentence of death shall be carried out by firing squad.

SECTION 2. This act shall become effective November 1, 2015.

55-1-6354 GRS 01/20/15

PROVINCE OF ONTARIO

CITY OF BURLINGTON

AFFIDAVIT OF LARRY D. SASICH, PharmD, MPH, FASHP

Comes now the Affiant, Larry D. Sasich, who, being first duly sworn by an officer authorized by law to administer oaths, deposes and states as follows:

1. My name is Larry Sasich, PharmD, MPH, FASHP. I am over the age of twenty-one and competent to testify to the truth of the matters contained herein. The factual statements I make in this affidavit are true and correct to the best of my knowledge and experience. The opinions I express in this statement are made to a reasonable degree of scientific certainty.

2. I am a Consultant specializing in drug safety and efficacy issues. My background, experience and qualifications, in part, include:

   a. Serving as a consultant to the Saudi Food and Drug Authority, Riyadh, Saudi Arabia.

   b. Serving as Chairperson of the Department of Pharmacy Practice at the LECOM School of Pharmacy in Erie, Pennsylvania, from 2007 to 2009;

   c. Serving as a consultant to Public Citizen Health Research Group, Washington, D.C., and

   d. Serving as a Consumer Representative on the Science Board of Food and Drug Administration's, an advisory committee to the FDA Commissioner.

3. I have a Masters in Public Health, Epidemiology and Public Policy from George Washington University and a Doctorate of Pharmacy from University of the Pacific. I have completed a residency in nuclear pharmacy from the University of New Mexico. I have also been elected a Fellow in the American Society of Health-System Pharmacists (FASHP). I have also been appointed on the Science Board to the Commissioner of the Food and Drug Administration.

4. I have also authored publications and/or presented analysis on drug safety issues. A complete list of my publications and presentations are listed in my Curriculum Vitae, which is appended to this statement.

5. I have previously been qualified in Mr. Warren Hill's case by the Fulton County Superior Court as an expert in pharmacy, public health, compounding pharmacies and drug safety, and Food and Drug Administration standards and, in that capacity, testified via affidavit and live testimony in the case about the use and practice of compounding pharmacies in the United States and, specifically, the many risks associated with the use of compounded drugs in lethal injections.

6. I have reviewed materials provided by the Office of the Georgia Attorney General and Georgia Department of Corrections (DOC) in response to a request by the Georgia Resource Center for information pertaining to the DOC's

lethal injection protocol and lethal injection drugs. I am aware that Georgia law shields from public scrutiny the identity of the manufacturer of lethal drugs, any middlemen or supply chain handlers, prescribing or other physicians involved in the execution process, pharmacists, compounding pharmacies, and so on. I have also reviewed the Georgia Supreme Court's recent opinion in *Owens, et al. v. Hill*, Supreme Court Case No. S14A0092, 2014 Ga. LEXIS 400 (May 19, 2014), which involves this case.

7. I have been asked by Mr. Hill's counsel to offer supplemental testimony to address some of the Georgia Supreme Court's assumptions, as set forth in the *Hill* opinion, about the level of risk associated with using compounded drugs to implement judicial lethal injections. Some of the information set forth below may be redundant of my previous testimony, but I reiterate this information to provide context.

I. The Risks of Using Compounded Drugs

8. The oversight of compounding pharmacies in the United States at this time is at best haphazard. That the FDA reports serious issues with some compounding pharmacies[1] does not indicate that compounding pharmacies as an

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[1] *See infra* note 3 and Attachments A, B, and C.

industry are subject to consistent, meaningful regulation by the FDA. To the contrary, given the FDA's limited oversight over compounding pharmacies, many instances of noncompliance with GMP guidelines likely go undetected and/or unreported.

9. As I testified previously, it is essential that compounding pharmacies use ingredients manufactured by FDA-registered and inspected manufacturers in order to ensure the quality of the final product. If poor quality ingredients are used, even the best compounding practices will not build quality and suitability into the final product. To the contrary, the safe production of injectable pentobarbital, or other drugs compounded from a non-sterile Active Pharmaceutical Ingredient (API) is technologically too difficult to do outside of Food and Drug Administration ("FDA") regulated facilities that must comply with federal Good Manufacturing Practice ("GMP") guidelines.

10. GMP guidelines are in place to eliminate the substantial risk of serious harm that results when API s and drugs are produced or compounded in the guidelines' absence. That is, the GMP guidelines are in place to prevent the preventable. APIs and drugs produced by manufacturers or compounding pharmacies that do not follow GMP guidelines pose a concrete, substantial risk of serious pain and suffering for those to whom the resulting drugs are administered.

Indeed, by definition, an API or drug produced outside compliance with GMP guidelines is adulterated.[2]

11. In Mr. Hill's case, there is no evidence that the pentobarbital selected for use in the non-traditional compounding of that drug for lethal injection has been produced in an FDA-registered and inspected facility. The API used in compounding pharmacies may come from the grey market, having been produced in non-FDA-registered, non-FDA inspected facilities. The ability to trace raw APIs used in compounding back to the original manufacturers for information on quality, packaging, storage, shipment conditions and chains of custody from a chemical's cradle to grave is incredibly difficult.

12. APIs often come from plants in China or India, which may or may not be registered with or have records of inspection by the United States FDA. Plants

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[2] 21 U.S.C. § 351 (a)(2)(B) ("A drug or device shall be deemed to be adulterated . . . if it is a drug and the methods used in, or the facilitated or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drugs meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.") (internal citation removed). *See also* U.S. Dept. of Health and Human Services, FDA, and Center for Drug Evaluation and Research, *Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing Cross-Contamination*, (Current Good Manufacturing Practices, Apr. 2013), available at http://www.fda.gov/downloads/Drugs/Guidances/UCM246958.pdf.

in China have been identified in which pesticides are manufactured using the same equipment as is used to make APIs.

13. The use of non-sterile and potentially contaminated APIs creates a serious risk of harm, including reactions from bacterial, fungal and endotoxin contamination. The presence of adulterants or growing organisms (like bacteria and fungus) may also accelerate chemical degradation resulting in a product that is sub-potent. The presence of growing organisms may also alter the final pH, with the potential to create instability and/or incompatibility with human blood.

14. A larger than expected moisture content of APIs risks inaccurate weighing that may also result in a product that is sub-potent.

15. Counterfeit or substandard ingredients, and/or poor practice on the part of drug compounders, often results in drugs which are contaminated or sub-potent and which do not have the strength, quality or purity represented on their labeling. The harm associated with the use of such contaminated or sub-potent drugs is not speculative. Indeed, the risk is demonstrated and extremely high.[3]

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[3] *See, e.g.*, Attachment A – Form FDA-483 Inspection Report of Downing Labs (July 16, 2014) (stating that the "inspection revealed sterility failures in 19 lots of drug products intended to be sterile, endotoxin failures in three lots of drug products, and inadequate or no investigation of these failures"), also available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM405669.pdf;

16. Several studies, including a survey conducted by the FDA in 2001, have reported a high prevalence of quality problems with various compounded drugs, including sub-potency and contamination. A follow-up survey of compounded drug products was conducted by the FDA in 2006. The results showed that 33% of compounded drugs failed analytical testing using rigorously defensible testing methodology. Testing by the Missouri Board of Pharmacy, which is the only state that regularly tests compounded drugs, revealed that compounded drugs fail tests for potency and purity on average around 25% of the time, an unacceptable failure rate consistent with rates observed by FDA. This is an extremely high failure rate, further supported by recent FDA inspection observations related to absent or limited sampling and testing of compounded drug products that would serve to identify substandard products prior to distribution.

Attachment B – FDA Warning Letter to Grandpa's Compounding Pharmacy, Inc. (May 2, 2014) (warning that the pharmacy "poses a significant contamination risk" as a result of "serious deficiencies in [its] practices for producing sterile drug products and flaws in the design of [its] aseptic processing areas."), also available at http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2014/ucm396239.htm; Attachment C – FDA Warning Letter to Sichuan Pharmaceutical Co., Ltd. (September 9, 2011) (identifying "significant deviations from Current Good Manufacturing Practice . . . for the manufacture of APIs," including a "failure to have appropriate procedures in place to prevent cross-contamination."), also available at http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm272791.htm.

17. Pharmacies compounding injectable pentobarbital, or other compounded drugs, may purchase APIs, of unknown quality from an unknown source. The Certificates of Analysis that accompany the APIs to the compounding pharmacy are of unknown origin and may be produced by unknown contract-testing laboratories whose competence has been questioned.

18. Compounded injectable pentobarbital, or other compounded drugs, may contain endotoxins which can induce an inflammatory response that manifests as a painful reaction, fever, and increased heart and respiratory rates that can cascade to organ failure and a painful death.[4] Contract-testing laboratories have failed to detect endotoxins in products they have tested.

19. Compounded drugs may have partial or complete lack of effect due to ingredient tampering or controlled drug diversion after analytical testing, circumstances that would be expected to prolong the execution process.

20. Compounded drugs that are super-potent may result in a person experiencing suffocation and gasping for breath.

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[4] *See* Attachment A and accompanying FDA Alert (warning that endotoxins like those found in samples at Downing Labs "cause a wide variety of serious reactions such as fever, shock, changes in blood pressure, and in other circulatory functions").

21. Compounded drugs contaminated by endotoxins or exotoxins will result in painful reactions.

22. Compounded drugs may be contaminated by solid particulate matter or precipitates, which are not necessarily visible to the naked eye or easily identifiable by the person preparing the compound. Compounded drugs that have solid particulate matter of any kind will contaminate the solution or precipitate out of solution during intravenous injection and present a substantial risk of pain and suffering upon injection of the solution.

23. Compounded drugs with improper pH levels can produce a burning sensation upon injection.

24. Because there is inadequate oversight of both compounding pharmacies and the contract-testing laboratories used by compounding pharmacies, the State of Georgia does not know with certainty what is contained in the pentobarbital sodium injection, or other compounded drugs, that will be injected into Mr. Hill.

II. The Use of Contaminated Pentobarbital in Prior Executions Illustrates the High Risk of Needless Suffering Posed by Use of Compounded Pentobarbital in Lethal Injections

25. As I read the Georgia Supreme Court's opinion in the *Hill* case, part of the basis of the decision to vitiate the temporary injunction was the conclusion

that the use of compounded pentobarbital posed an insignificant or completely speculative risk of pain and suffering in the executed inmate. However, in my opinion, recent executions demonstrate that this risk is not speculative, but rather very real and very significant.

26. For example, on January 9, 2014 Oklahoma prisoner Michael Lee Wilson was executed under a three-drug protocol that used a pentobarbital injection produced by an unknown compounding pharmacy. Media witnesses reported that within 20 seconds of receiving the injection, Mr. Wilson cried that he felt his "whole body burning."[5]

27. It is my opinion that Mr. Wilson's reaction is consistent with contaminated pentobarbital sodium injection. Because of common problems with safety procedures of compounded pharmacies and testing laboratories, and the lack of adequate oversight by federal and state authorities, the injection used in Mr. Wilson's execution could have contained cross-contaminates to which he was

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[5] Associated Press, *"I Feel My Whole Body Burning," Says Oklahoma Death Row Inmate During Execution*, Jan. 10, 2014, http://www.foxnews.com/us/2014/01/10/feel-my-whole-body-burning-says-oklahoma-death-row-inmate-during-execution/. *See also* Charlotte Alter, *Oklahoma Convict Who Felt "Body Burning" Executed With Controversial Drug*, TIME, Jan. 10, 2014, http://nation.time.com/2014/01/10/oklahoma-convict-who-felt-body-burning-executed-with-controversial-drug.

allergic; bacteria; and endotoxins. The injection could have had an altered pH due to contaminates. Additionally, because of this lack of oversight no one knows for sure what was injected into Mr. Wilson.

28. The October 15, 2012, South Dakota execution of Eric Robert used compounded pentobarbital. According to reports,[6] Mr. Robert appeared to clear his throat, gasped heavily and snored. Over a ten-minute period his skin turned a purplish hue. During the course of his execution, he opened his eyes and they remained open until his death. It took 20 minutes for the state to declare Mr. Robert dead. Mr. Robert's heart continued to beat ten minutes after he stopped breathing.

29. It is my opinion that the events observed during Mr. Robert's execution are consistent with the administration of a compounded drug that was contaminated or sub-potent.

30. If Georgia proceeds with the execution of Mr. Hill using compounded pentobarbital or some other compounded drug, Georgia will be injecting a drug of unknown composition into Mr. Hill, which is highly likely to be contaminated or

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[6] *See e.g.*, Dave Kolpack and Kristi Eaton, *S. Dakota Executes Inmate Who Killed Prison Guard*, Associated Press, October 16, 2012, http://bigstory.ap.org/article/sd-death-row-inmate-be-executed-monday-0.

whose quality is otherwise compromised. Doing so carries a substantial risk of causing Mr. Hill unnecessary and lingering pain and suffering.

FURTHER AFFIANT SAYETH NAUGHT,

LARRY D. SASICH

Sworn to and subscribed before me
this 24 day of July, 2014.

NOTARY PUBLIC

Attachment A

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
4040 North Central Expressway, Suite 300 Dallas, TX 75204 (214) 253-5200 Fax:(214) 253-5314 Industry Information: www.fda.gov/oc/industry	06/03/2014 - 07/16/2014* FEI NUMBER 3010087152

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Kristi A. Kubosh, Pharm. D., R.Ph., Pharmacist in Charge

FIRM NAME	STREET ADDRESS
Downing Labs, LLC	4001 McEwen Rd Suite 110
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Dallas, TX 75244-5020	Producer of Sterile Drug Products

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

There is a failure to thoroughly review the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

Specifically,

A. SOP #9.040 entitled, "Sterility Testing of a Finished Preparation" (Effective date: 6/2012) documents that an investigation should be conducted in the event that contamination is observed.

My review of approximately (b)(4) Logged Formula Worksheets for the period between 4/16/2013 and 6/23/2014 revealed that your firm had sterility or endotoxin failures for 22 different lots of drug product. In each case, the investigations were either absent or incomplete.

All lots which failed testing for sterility or endotoxin were destroyed with the exception of the following:

- Cyanocobalamin, lot #N04302014@14

Lot #N04302014@14 was originally (b) (4) on 5/2/14. Subsequent testing for sterility failed (Test dated 6/2/14) and the lot was re-sterilized by (b) (4) on 6/3/14. Subsequent testing for endotoxin and sterility met specifications. The lot is currently being held in inventory pending distribution.

- Folic Acid, lot #N04172014@20 (Production date: 4/30/14, BUD: 10/28/14)

Lot #N04172014@20 was (b) (4) on 4/30/14. Subsequent testing for sterility failed as noted on testing record dated 6/2/14. The lot is being held in quarantine pending destruction.

Each batch with the failed result is identified in the following table:

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Stephen D. Brown, Investigator Darla J. Christopher, Investigator	07/16/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
4040 North Central Expressway, Suite 300 Dallas, TX 75204 (214) 253-5200 Fax:(214) 253-5314 Industry Information: www.fda.gov/oc/industry	06/03/2014 - 07/16/2014* FEI NUMBER 3010087152

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Kristi A. Kubosh, Pharm. D., R.Ph., Pharmacist in Charge

FIRM NAME	STREET ADDRESS
Downing Labs, LLC	4001 McEwen Rd Suite 110
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Dallas, TX 75244-5020	Producer of Sterile Drug Products

Product	Lot #	Mfd. Date	BUD	Sterility Test Result/Day Positive	Organism(s)	Endotoxin Result/Date	Investigation
HCG 5 K Lyophilized 5000 U Powder Injectable	N05082014@30	5/9/14	12/12/14	Negative	N/A	Failed endotoxin (Result of 150.75EU/vial versus spec of (b)(4) /vial)	Yes
Cyanocobalamin 30 mL Buffered 1 mg/mL Injectable	N04302014@14	5/2/14	11/1/14	Positive/Day 14	*Afipia felis*	<0.05 EU/mL	No
Folic Acid 30 mL 10 mg/mL Injectable	N04172014@20	4/30/14	10/28/14	Positive/Day 12	*Afipia felis*	<5.00 EU/mL	No
HCG 5 K Lyophilized 5000 U Powder Injectable	N04082014@14	4/17/14	10/15/14	Positive/Day 5	*Staphylococcus haemolyticus*	4.50 EU/Vial	Yes
Cyanocobalamin 30 mL Buffered 1 mg/mL Injectable	N03272014@7	3/27/14	9/23/14	Positive/Day 4	*Afipia felis*	<0.05 EU/mL	No
Green Tea (EGCG) 10 mL 10 mg/mL Injectable	N01202014@8	2/10/14	8/9/14	Negative	N/A	Failed endotoxin (Result of 252.64 EU/ml)	Yes
L-Carnitine 30ml 500mg/ml	N12202013@8	1/29/14	7/28/14	Negative	N/A	Failed endotoxin (Result 476.19EU/ml versus spec of (b)(4) U/ml)	Yes
Terbutaline/ Betamethasone 5 mL 0.05/0.01 mg/mL Injectable	N12202013@4	12/23/13	6/22/14	Positive/Day 10	*Methylobacterium brachiatum*	Not tested	Yes
Procaine 30 mL 10% Inj	N12182013@1	12/19/13	6/18/14	Positive/Day 8	*Propionibacterium acnes*	Not tested	Yes
Methylcobalamin Buffered 30 mL 5 mg/mL Inj	N11042013@1	12/16/13	6/15/14	Positive/Day 5	*Staphylococcus epidermidis*	Not tested	Yes
Magnesium Chloride Hexahydrate 30 mL 200 mg/mL Injectable	N11042013@14	11/14/13	5/13/14	Positive/Day 6	*Staphylococcus epidermidis*	Not tested	Yes
DMPS B-Complex 10ml	N10172013@20	11/6/13	2/1/14	Positive/Day 4	*Bacillus amyloliquefaciens* *Methylotrophicus*	Not tested	Yes
Ascorbic Acid (Corn) 50 mL 500 mg/mL Injectable	N10172013@19	10/30/13	4/29/14	Positive/Day 13	*Propionibacterium acnes*	Not tested	Yes
Hyaluronidase 10 mL 150 U/mL Injectable	N09042013@14	10/15/13	1/31/14	Positive/Day 4	*Staphylococcus epidermidis*	Not tested	Yes
Dexpanthenol 30 mL 250 mg/mL Injectable	N09032013@14	9/3/13	2/2/14	Positive/Day 3	Not tested	Not tested	Yes
Calcium Gluconate 50 mL 5% Injectable	N08152013@20	8/22/13	2/23/14	Positive/Day 13	*Bacillus fastidiosus*, *Bacillus simplex*, *Nocardia nova*	Not tested	Yes

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Product	Lot #	Mfd. Date	BUD	Sterility Test Result/Day Positive	Organism(s)	Endotoxin Result/Date	Investigation
Riboflavin (R5P) 30 mL 10 mg/mL Inj	N08212013@5	8/21/13	2/17/14	Positive/ Day 5	*Cupriavidus metallidurans*	Not tested	Yes
TPM IV Base#2 Concentrate 50 mL SDV Inj	N07122013@14	8/19/13	1/8/14	Positive/Day 7	*Roseomonas mucosa*	Not tested	Yes
L-Glutathione for Inhalation 10 X 4 mL Soln for Neb	N08142013@3	8/14/13	2/10/14	Positive/ Day 3	*Staphylococcus epidermidis*	Not tested	Yes
Ascorbic Acid (Corn) 50 mL 500 mg/mL Injectable	N07172013@26	8/8/13	1/13/14	Positive/Day 12	*Propionibacterium acnes*	Not tested	Yes
Folic Acid 10 mL 5 mg/mL Injectable	N06112013@27	6/11/13	12/8/13	Positive/Day 2	*Delftia acidovorans*	Not tested	Yes
L-Proline 30 mL 50 mg/mL Injectable	N06052013@19	6/3/13	12/2/13	Positive/Day 10	*Corynebacterium afermentans lipophilum*	Not tested	Yes

Some examples where an investigation was absent include the following:

1. Cyanocobalamin 1mg/ml Buffered, lot #N04302014@14 (Production date: 5/2/14, Beyond Use Date: 11/1/14)

Your contract laboratory determined that this lot failed sterility and the contaminating organism was *Afipia felis*. No investigation was performed.

2. Folic Acid 10mg/ml, lot #N04172014@20 (Production date: 4/30/14, Beyond Use Date: 10/28/14)
Your contract laboratory determined that this lot failed sterility and the contaminating organism was *Afipia felis*. No investigation was performed.

3. Cyanocobalamin 1mg/ml Buffered, lot #N03272014@7 (Production date: 3/27/14, Beyond Use Date: 9/23/140
Your contract laboratory determined that this lot failed sterility and the contaminating organism was *Afipia felis*. No investigation was performed.

Some examples where an investigation was incomplete consist of the following:

1. Green Tea (EGCG) 10ml 10mg/ml Injectable, lot #N01202014@8 (Production date: 2/10/14, Beyond Use date: 8/9/14)

Lot #N01202014@8 failed the test for endotoxin with a result of 252.64 EU/ml as documented on a Certificate of Analysis dated 2/26/14 from the contract laboratory.

Your investigation identified the possible root causes as 1)(b) (4) 2) aseptic technique, or endotoxin in the API.

However, your firm's investigation was incomplete in that:

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a. The raw material, EGCG, was identified as a possible source of endotoxin contamination but was never tested.

b. (b) (4) was identified as a possible source of the contamination but was not investigated.

c. Aseptic technique was also included as a possible source of the contamination but was not investigated.

d. There was no assessment of (b) (4) (glassware) which have not been validated.

2. L-Carnitine 500mg/ml for Injection, lot #N12202013@8 (Production date: 1/29/14, Beyond Use Date: 7/28/14)

Lot #N12202013@8 failed the test for endotoxin with a result of 476.19 EU/ml as documented on a Certificate of Analysis dated 3/19/14 from the contract laboratory.

Your investigation identified possible root causes as 1) presence of endotoxin or gram negative bacteria in the API, and 2) excessive time between preparation and (b) (4)

Your firm's investigation was incomplete in that:

a. The testing of the raw material, L-Carnitine, which was identified as a possible source of contamination was not conducted.

b. Excessive time between preparation and (b) (4) was identified as a possible cause but was not investigated.

c. The investigation did not include an assessment of (b) (4) (glassware) which have not been validated.

d. The investigation did not extend to all impacted batches. Per your Pharmacist in Charge, the L-Carnitine, lot (b) (4) which was used in L-Carnitine, lot #N12202013@8 was also used in the product, Lipotocin Plus 10 ml for Injection, lot #N01042014@2 (Production date: 1/9/14 Beyond Use Date: 7/8/14) which was sent to consignees.

3. Human Chorionic Gonadotropin 5000IU Lyophilized, lot #N04082014@14 (Production date: 4/17/14, Beyond Use Date: 10/15/14)

Lot #N04082014@14 failed the test for sterility as documented on a Certificate of Analysis issued by the contract laboratory (Organism: *Staphylococcus haemolyticus).*

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FIRM NAME Downing Labs, LLC	STREET ADDRESS 4001 McEwen Rd Suite 110
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Your investigation identified aseptic technique by the technician as the probable root cause but failed to include an evaluation of the following areas:

(b) (4)
Room pressurization
Laminar flow operation
Assessment of container closure
Sanitization procedures (Room, equipment, product containers, etc.)
Evaluation of other lots compounded by the same technician

B. SOP #9.030 entitled, "Particulate Testing for Sterile Preparations" (Date: 1/2013) provides guidance for the evaluation of vials of sterile, injectable drug products for particulates. My review of (b) (4) lots of drug products manufactured between 4/16/2013 and 6/23//2014 revealed that at least 185 lots had fibers or particulates. No investigations have been conducted.

In each case, your firm conducted a 100% inspection by (b) (4) Vials identified as containing fibers and/or particulates were then removed and discarded. However, this method has not been shown effective to detect fibers or particulates in amber vials.

The remaining vials from each lot were then distributed to consignees. Some examples consist of the following:

- Methylcobalamin, lot #N01162014@21
- DMSO, lot #N01082014@1
- Cyanocobalamin, lot #N01062014@11

C. Investigations have not been conducted for sterile, injectable drug products which were rejected due to precipitation or particulates. Some examples consist of the following:

1. Thiamine HCl 30ml 100mg/ml Injectable, lot #N02212014@10 (Production date: 2/25/2014, BUD: 8/24/2014): Particulates
2. M.I.C.A. 126 50ml Preserved 25/50/50/5/50/25 mg/ml Injectable, lot #N12272013@6 (Production date: 1/2/2014, BUD: 7/1/2014): Precipitation

D. A "Sterilizer Test Report" dated 2/27/14 issued by (b) (4) indicated that a gram stain confirmed spore growth in one or more test strips and control strips for a test conducted on 2/19/14. No investigation was conducted.

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Dallas, TX 75244-5020	Producer of Sterile Drug Products

OBSERVATION 2

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established.

Specifically,

A) Media Fills

SOP #7.007.3 entitled, "Media Fill for High Risk Compounding " (Date: 4/17/14) documents, in part, that a total of (b) (4) ml vials (b) (4) for positive controls and (b)(4) for product) will be used to conduct media fills.

1) The media fills were not representative of actual production processes in that:

a. The media fills failed to simulate a lot with the maximum number of vials (i.e. Cyanocobalamin, lot #N04302014@14: (b) (4) vials)
b. The number and type of interventions was not included.
c. The aseptic assembly of equipment (e.g., at start-up, during processing) was not included.

2) The (b) (4) tubes of media used as positive controls with the media fills were not inoculated with a known number/type of organisms. Instead, the (b) (4) tubes were exposed to the environment (undefined), capped and then incubated for (b)(4) days.

3) Media fills for lyophilized products were not conducted (i.e. Human Chorionic Gonadotropin and Sermorelin)

B) (b) (4) validation

Your firm failed to validate the (b) (4) used for the sterilization of injectable drug products. Some examples of (b) (4) utilized by your firm consist of the following:

(b) (4)

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(b) (4)

My review of approximately (b) (4) production records for the period between 4/16/2013 and 6/23/2014 revealed that integrity testing was not documented as being performed on (b) (4) for approximately (b) (4) lots.

D) (b) (4) Sterilization

Your firm failed to validate the (b) (4) used to sterilize injectable drug products and drug product components such as vials and stoppers.

Your firm currently uses the following (b) (4) for the sterilization of drug products and components:

(b) (4)

Some examples of sterile, injectable drug products which were terminally sterilized include the following:

- DMSO 50 mL 99% Injectable, lot #N01082014@1 (Production date: 1/20/2014, Beyond Use Date: 7/19/2014)
- Hyaluronic Acid 10 mL X-Link 10 mg/mL Injectable, lot #N05092014@1 (Production Date: 5/12/2014 Beyond Use Date: 11/1/2014)
- Vitamin A 10 mL 50,000 IU/mL Injectable, lot #N04142014@8 (Production Date: 4/14/2014 Beyond Use Date: 10/11/2014)

In addition, your firm uses (b) (4) of drug products which are (b) (4). The (b) (4) does not meet the USP standards for (b) (4) and is not tested to ensure the absence of endotoxins.

E) Qualification of ISO 5 processing area modifications

Your firm failed to re-qualify the ISO 5 and 7 processing areas after major modifications to the areas. For example, on 4/7/14, your vendor conducted major repairs in the ISO 5 and ISO 7 areas to include the re-positioning of four HEPA filters in the ISO 5 area and re-location of the lyophilizer from the ISO 7 cleanroom to the ISO 5 area. There was no documentation to indicate that cleaning was performed in the controlled areas after the repairs were made.

A re-qualification of the ISO 5 and ISO 7 areas did not occur until 5/21/14. Between 4/7/14 and 6/2/14, your firm

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compounded approximately (b)(4) lots of injectable drug products of which at least (b)(4) have been distributed.

Some examples include the following:

- Lidocaine HCl 50ml 1% Injectable, lot #N 05122014@12, (Production date: 5/13/14 Beyond Use Date: 11/11/14)
- Procaine Potassium Buffered 50ml 2% Injectable, lot #N04142014@5 (Production date: 5/13/14, Beyond Use Date: 11/10/14)
- Magnesium Chloride Hexahydrate 50ml 200mg/ml Injectable, lot #N04302014@17 (Production date: 5/12/14 Beyond Use Date: 11/10/14)

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OBSERVATION 3

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

Specifically, environmental monitoring is not representative of the clean room environment during aseptic processing operations. For example,

A) Viable air sampling is performed in the ISO 5 and ISO 7 areas once every (b) (4) when the rooms are being re-certified by your outside contractor.

B) Surface samples are obtained randomly (b) (4) in the clean room. The areas to be sampled are not identified.

C) Routine monitoring for clean room personnel is performed once every (b) (4) and there is no monitoring of gowns,

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arms, face masks or other areas of the technician.

D) Growth promotion testing is not performed on incoming prepared media (i.e. (b) (4) [redacted]") used for environmental sampling.

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OBSERVATION 4

Aseptic processing areas are deficient regarding systems for maintaining any equipment used to control the aseptic conditions.

Specifically,

A. There is no assurance that the air quality inside the ISO 5 area is adequately maintained. Currently, the ISO 5 area is separated from the ISO 7 cleanroom by a plastic curtain which descends approximately 30" from the ceiling. The latest cleanroom qualification dated 5/21/14 failed to include documentation to demonstrate that laminarity can be adequately maintained between the ISO 5 and ISO 7 areas.

On 6/3/2014, we observed that the sides of the plastic curtain which enclose the ISO 5 area inside the ISO 7 cleanroom were absent. I was told by management that the sides were removed on 6/2/2014 based on recommendations from the HVAC vendor since they were opaque and needed to be clear. The ISO 5 area was not recertified after this modification.We also observed on 6/3/14 that the product, HCG K Lyophilized 5000 U Powder Injectable, lot #05232014@2, was being processed within the uncertified ISO 5 area.

In addition, your firm manufactured the following drug products on 6/19/2014 and 6/23/2014 using the uncertified ISO 5 area:

- AMP Buffered 10ml 25mg/ml Injectable, lot #06192014@3 (Production date: 6/19/14, BUD: 12/16/2014)
- Methylcobalamin Buffered 30ml 1mg/ml Injectable, lot #06172014@14 (Production date: 6/23/14, BUD: 12/21/2014)
- Magnesium Sulfate 50ml 50% Injectable, lot #06132014@9 (Production date: 6/23/14, BUD: 12/21/2014)

Each lot was (b) (4) [redacted] in the ISO 5 area and then (b) (4) [redacted]. The Pharmacist in Charge told me that the lots were (b) (4) [redacted] since the firm had identified rationale in literature. In addition, I was told that the ISO 5 area was uncertified and that the firm was only compounding products which could be (b) (4) [redacted]. The three lots are being held in quarantine pending the completion of testing for sterility and endotoxin.

B. Your firm checks and documents the differential pressure between the ISO 7 and ISO 8 areas (b) (4) [redacted]. There are no requirements for additional monitoring.

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OBSERVATION 5

Each batch of drug product purporting to be sterile and pyrogen-free is not laboratory tested to determine conformance to such requirements.

Specifically, my review of approximately (b) (4) lots manufactured between 4/16/2013 and 6/23/2014 revealed that endotoxin testing had not been performed for approximately 180 of the (b) (4) lots of injectable drug products distributed. Some examples where testing for endotoxin was not performed consist of the following:

- Taurine 30ml 50mg/ml, lot #N12182013@13 (Production date: 1/22/14, Beyond Use date: 7/21/14)
- Methylcobalamin Buffered 10ml 1mg/ml, lot #N01162014@20 (Production date: 1/23/14 Beyond Use date: 7/22/14)
- Thioctic Acid 30ml 25mg/ml, lot #N12202013@5 (Production date: 1/23/14 Beyond Use date: 7/19/14)

OBSERVATION 6

Equipment and utensils are not maintained at appropriate intervals to prevent malfunctions and contamination that would alter the safety, identity, strength, quality or purity of the drug product.

Specifically, your firm has never conducted preventive maintenance on the (b) (4) or lyophilizer used for the processing of injectable drug products. My review of the operators' manuals for the (b) (4) and one lyophilizer revealed that specific maintenance is required to ensure optimal operation. Some examples of the recommended maintenance consist of the following:

A. (b) (4)

The lyophilizer is used for the production of two products, HCG 5 K Lyophilized 5000 U Powder Injectable and Sermorelin /GHRP-6/GHRP-2 3/3/3 mg per vial Injectable. Some examples of lots distributed include the following:

- Sermorelin/GHRP-6/GHRP-2 3/3/3 mg per Vial Injectable, lot #N03112014@9 (Production Date: 3/11/2014 Beyond Use Date: 9/7/2014)
- HCG 5 K Lyophilized 5000 U Powder Injectable, lot #N03182014@10 (Production Date: 3/27/2014 Beyond Use Date:

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9/23/2014)

The operating manual recommends the following maintenance:

1. (b) (4)

2. (b) (4)

B. (b) (4)

1.

- (b) (4)

- (b) (4)

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OBSERVATION 7

Adequate lab facilities for testing and approval or rejection of drug products are not available to the quality control unit.

Specifically, your firm has not authorized your contract laboratory to conduct suitability testing for all drug products tested for sterility as confirmed by management. Review of approximately (b) (4) testing records for the period between 4/16/2013 and 6/23/14 revealed that at least 80% of the records included a statement from the contract laboratory documenting that the sterility test did not meet all the requirements for sampling and/or method suitability specified in USP <71>. Some examples consist of the following:

- L-Glutamine 30ml 30mg/ml Injectable, lot #N05122014@8 (Production date: 5/13/14, Beyond Use Date: 11/11/14)
- Hyaluronic Acid 10ml X-Link 10mg/ml Injectable, lot #N05092014@1 (Production date: 5/12/14 Beyond Use Date: 11/1/14)
- Procaine 50 ml Buffered 1% 10mg/ml Injectable, lot #N05082014@23, (Production date: 5/9/14, Beyond Use Date: 11/7/14)

OBSERVATION 8

There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

Specifically,

A. Your firm utilizes a (b) (4) (b) (4) for the lyophilization of injectable drug products. Your firm has failed to validate the different cycles used for the lyophilization of the drug products, Human Chorionic Gonadotropin Lyophilized 5,000 Units Powder and Sermorelin. Some examples of specific cycle parameters consist of the following:

Freezing	Duration	HCG (Human Chorionic Gonadotropin)	Sermorelin
(b) (4) (b) (4)	(b) (4)		(b) (4) (b) (4)

SEE REVERSE OF THIS PAGE

EMPLOYEE(S) SIGNATURE
Stephen D. Brown, Investigator
Darla J. Christopher, Investigator

DATE ISSUED
07/16/2014

FORM FDA 483 (09/08) PREVIOUS EDITION OBSOLETE INSPECTIONAL OBSERVATIONS PAGE 12 OF 15 PAGES

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
4040 North Central Expressway, Suite 300 Dallas, TX 75204 (214) 253-5200 Fax:(214) 253-5314 Industry Information: www.fda.gov/oc/industry	06/03/2014 - 07/16/2014* FEI NUMBER 3010087152

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Kristi A. Kubosh, Pharm. D., R.Ph., Pharmacist in Charge

FIRM NAME	STREET ADDRESS
Downing Labs, LLC	4001 McEwen Rd Suite 110
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Dallas, TX 75244-5020	Producer of Sterile Drug Products

(b) (4)

THIS IS A REPEAT OBSERVATION FROM THE PREVIOUS INSPECTION CONDUCTED BETWEEN 3/18/2013 AND 4/16/2013.

OBSERVATION 9

Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the room to produce aseptic conditions.

Specifically,

A. There is no documentation to indicate that the plastic curtain separating the ISO 5 and ISO 7 areas has ever been cleaned or sanitized.

B. Your firm has not conducted disinfectant effectiveness studies to demonstrate that the disinfectants used to clean the walls, floors, ceilings, and work surfaces in the ISO 5 and ISO 7 areas can sufficiently reduce bioburden. Currently, your firm utilizes the following disinfectants in the ISO 5 and ISO 7 areas:

(b) (4)

C. Your firm uses non-sterile wipes in the ISO 5 and ISO 7 areas for the cleaning and sanitization of surfaces.

THIS IS A REPEAT OBSERVATION FROM THE PREVIOUS INSPECTION CONDUCTED BETWEEN 3/18/2013 AND 4/16/2013.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Stephen D. Brown, Investigator Darla J. Christopher, Investigator	07/16/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Dallas, TX 75244-5020	Producer of Sterile Drug Products

OBSERVATION 10

Clothing of personnel engaged in the manufacturing of drug products is not appropriate for the duties they perform.

Specifically, the goggles used by technicians in the ISO-5 clean room are not sterile and are not disinfected prior to use.

THIS IS A REPEAT OBSERVATION FROM THE PREVIOUS INSPECTION CONDUCTED BETWEEN 3/18/2013 AND 4/16/2013.

OBSERVATION 11

There is no written testing program designed to assess the stability characteristics of drug products.

Specifically,

A) Your firm has no documentation to justify the Beyond Use Date of injectable drug products of 180 days. My review of approximately (b) (4) lots of drug products manufactured between 4/16/13 and 6/23/14 revealed that your firm produced approximately (b) (4) different sterile, injectable drug products with Beyond Use Dates (BUDs) up to 180 days, to include preserved and preservative free drug product units which are intended for single use but not labeled accordingly. For example,

- Phosphatidylcholine 50ml, 5/2.5% Injectable, lot #N05092014@8, BUD 180 days.
- Lipotocin 10 ml Injectable, lot #N04302014@8, BUD 180 days.

B) Your firm has not conducted anti-microbial effectiveness testing to determine whether Benzyl Alcohol, Methylparaben, or Benzalkonium Chloride effectively inhibit microbial growth in sterile injectable drug products through BUD. My review of approximately (b) (4) lots of sterile drug products for the period between 4/16/2013 and 6/23/2014 revealed that your firm manufactured drug products containing these preservatives with BUDs of 180 days. For example,

- B12 3ml (Hydroxo 12.5mg/ml + Cyano 12.5mg/ml) 25mg/ml Injectable, lot #N05082014@22 (BUD: 180 days) Contains: Benzyl Alcohol
- Biotin 30 ml (Preserved) 10mg/ml Injectable, lot #N01282014@10 (BUD 180 days) Contains: Methylparaben
- Acetyl-L-Carnosine Eye Drop 15ml Modified 5% Ophthalmic, lot #N03282014@7 (BUD 180 days) Contains: Benzalkonium Chloride

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Stephen D. Brown, Investigator SB Darla J. Christopher, Investigator	07/16/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
4040 North Central Expressway, Suite 300 Dallas, TX 75204 (214) 253-5200 Fax:(214) 253-5314 Industry Information: www.fda.gov/oc/industry	06/03/2014 - 07/16/2014* FEI NUMBER 3010087152

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Kristi A. Kubosh, Pharm. D., R.Ph., Pharmacist in Charge

FIRM NAME	STREET ADDRESS
Downing Labs, LLC	4001 McEwen Rd Suite 110
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Dallas, TX 75244-5020	Producer of Sterile Drug Products

THIS IS A REPEAT OBSERVATION FROM THE PREVIOUS INSPECTION CONDUCTED BETWEEN 3/18/2013 AND 4/16/2013.

OBSERVATION 12

Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the identity and strength of each active ingredient prior to release.

Specifically, your firm has not conducted potency testing for any drug products manufactured and distributed. My review of approximately (b) (4) lots of sterile drug products manufactured between 4/16/2013 and 6/23/2014 revealed that potency testing had not been conducted for any lots.

THIS IS A REPEAT OBSERVATION FROM THE PREVIOUS INSPECTION CONDUCTED BETWEEN 3/18/2013 AND 4/16/2013.

OBSERVATION 13

Master production and control records lack complete manufacturing and control instructions.

Specifically, your firm does not consistently document the model/lot number of the (b) (4) used in the sterilization of injectable drug products. For example, Lipotocin 10ml for Injection, lot #N04302014@18 (Production date: 5/5/14, Beyond Use Date: 11/3/14).

THIS IS A REPEAT OBSERVATION FROM THE PREVIOUS INSPECTION CONDUCTED BETWEEN 3/18/2013 AND 4/16/2013.

*** DATES OF INSPECTION:**
06/03/2014(Tue), 06/04/2014(Wed), 06/05/2014(Thu), 06/06/2014(Fri), 06/10/2014(Tue), 06/11/2014(Wed), 06/12/2014(Thu), 06/13/2014(Fri), 06/17/2014(Tue), 06/18/2014(Wed), 06/19/2014(Thu), 06/20/2014(Fri), 06/24/2014(Tue), 06/25/2014(Wed), 06/26/2014(Thu), 07/02/2014(Wed), 07/03/2014(Thu), 07/14/2014(Mon), 07/15/2014(Tue), 07/16/2014(Wed)

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Stephen D. Brown, Investigator Darla J. Christopher, Investigator	07/16/2014

FDA alerts health care professionals not to use sterile drugs from Downing Labs (aka NuVision Pharmacy)

[7/18/2014] The U.S. Food and Drug Administration is alerting health care professionals and consumers not to use drugs marketed as sterile produced by Downing Labs LLC, also known as NuVision Pharmacy, in Dallas, as they may be contaminated.

Health care professionals should immediately check their medical supplies, quarantine any sterile drug products from NuVision, and not administer them to patients. Administration of a non-sterile drug product intended to be sterile may result in serious and potentially life-threatening infections or death.

NuVision's products were distributed nationwide. Most of the product labels include: NuVision Pharmacy, Dallas TX. 75244 1-800-914-7435.

FDA investigators inspected NuVision and observed insanitary conditions that result in a lack of sterility assurance of purportedly sterile drug products produced by the company, which puts patients at risk (Form FDA-483 issued July 16, 2014). The inspection revealed sterility failures in 19 lots of drug products intended to be sterile, endotoxin failures in three lots of drug products, and inadequate or no investigation of these failures. Endotoxins are substances found in certain bacteria that cause a wide variety of serious reactions such as fever, shock, changes in blood pressure, and in other circulatory functions.

Patients who have received any drug product produced by NuVision and have concerns should contact their health care professional.

FDA is not aware of recent reports of illness associated with the use of these products. FDA asks health care professionals and consumers to report adverse events or quality problems associated with the use of NuVision's products to FDA's MedWatch Adverse Event Reporting program by:

- Completing and submitting the report online at MedWatch Online Voluntary Reporting Form
- Downloading and completing the form (PDF - 1.22MB), then submitting it via fax at 1-800-FDA-0178

For more information:

- FDA press release, April 15, 2013: FDA issues alert about lack of sterility assurance of drug products from ApotheCure, Inc. and NuVision Pharmacy and of forthcoming recall
- FDA Form 483 issued April 16, 2013
- FDA press release, May 18, 2013: FDA expands alert to health care providers about lack of sterility assurance of all sterile drug products from NuVision Pharmacy
- FDA recall request, July 26, 2013
- FDA press release, Aug. 16, 2013: FDA reminds health care providers not to use sterile products from NuVision Pharmacy

Attachment B

Grandpa's Compounding Pharmacy, Inc. 5/2/14

Department of Health and Human Services

Public Health Service
Food and Drug Administration

San Francisco District
1431 Harbor Bay Parkway
Alameda, CA 94501-7070
Telephone (510) 337-6700

Warning Letter

WL: 423162

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

May 2, 2014

Daniel R. Wills
General Business Manager
Grandpa's Compounding Pharmacy, Inc.
7563 Green Valley Road
Placerville, CA 95667-3917

Dear Mr. Wills:

Between September 3, 2013 and September 10, 2013, U.S. Food and Drug Administration (FDA) investigators conducted an inspection of your facility, Grandpa's Compounding Pharmacy, Inc., 7563 Green Valley Road, Placerville, CA 95667-3917. During the inspection, FDA's investigators were accompanied by California State Board of Pharmacy (BOP) inspectors. At that time, the investigators noted that you were not receiving valid prescriptions for individually-identified patients for a portion of the drug products you were producing. In addition, the investigators observed serious deficiencies in your practices for producing sterile drug products and flaws in the design of your aseptic processing areas, which could lead to contamination of the products, potentially putting patients at risk. For example, we observed that the air supply duct work for the cleanroom consists of, in part, a **(b)(4)** held together, in part, with duct tape. We also observed that the cleanroom contained an in-wall air conditioner bringing outside air into the room where aseptic manipulations are occurring. These items are difficult to clean and could allow for air to enter the cleanroom that has unacceptable microbial and particulate levels. Furthermore, we observed operators with exposed wrist and forearm skin engaging in aseptic manipulations. In addition, we observed that your firm uses tap water and a**(b)(4)** to clean and depyrogenate containers and closures; these are not suitable to depyrogenate the containers and closures intended for injectable drug products. Therefore, your products may be produced in an environment that poses a significant contamination risk. These observations and others were noted on a Form FDA 483, issued on September 10, 2013. We acknowledge receipt of your firm's response to the Form FDA 483 dated September 20, 2013, in which your firm stated it would cease all sterile compounding.

Based on this inspection, it appears that you are producing drugs that violate the Federal Food, Drug, and Cosmetic Act (FDCA).

A. Compounded Drugs Under the FDCA

At the time FDA inspected your facility, there were conflicting judicial decisions regarding the applicability of section 503A of the FDCA [21 U.S.C. § 353a], which exempts compounded drugs from several key statutory requirements if certain conditions are met.[1] Nevertheless, receipt of valid prescriptions for individually-identified patients prior to distribution of compounded drugs was relevant for both section 503A of the FDCA and the agency's Compliance Policy Guide 460.200 on Pharmacy Compounding (CPG) (2002), which was then in effect (CPG) (2002).[2] During the inspection, investigators observed that your firm does not receive valid prescriptions for individually-identified patients for a portion of the drug products you produce. Based on this factor alone, those drugs were not entitled to the statutory exemptions for compounded drugs described in section 503A of the FDCA and did not qualify for the agency's exercise of enforcement discretion set forth in the CPG.[3]

Since FDA inspected your facility, Congress enacted and the President signed into law the Compounding Quality Act (CQA)[4], which amended FDCA section 503A by eliminating the advertising restrictions that had been the basis for conflicting judicial decisions. The CQA otherwise left section 503A intact, and so clarified that the remainder of section 503A, including the requirement of valid prescriptions for individually identified patients, is applicable in every federal judicial circuit. Accordingly, the drugs you compound without valid prescriptions for individually identified patients are not entitled to the exemptions in section 503A.[5]

In addition, we remind you that there are a number of other conditions that must be satisfied to qualify for the exemptions in section 503A of the FDCA.[6]

B. Violations of the FDCA

The drug products that you manufacture and distribute without valid prescriptions for individually-identified patients are misbranded drugs in violation of section 502(f)(1) [21 U.S.C. § 352(f)(1)] of the FDCA. In addition, your sterile drug products are prepared, packed, or held under insanitary conditions whereby they may have been contaminated with filth, or whereby they may have been rendered injurious to health. As such, all sterile products you manufacture are adulterated within the meaning of section 501(a)(2)(A) [21 U.S.C. § 351(a)(2)(A)] of the FDCA. Furthermore, because you manufacture and distribute drugs without valid prescriptions for individually-identified patients, the manufacture of those drugs is also subject to FDA's Current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations (CFR), Parts 210 and 211. FDA investigators observed significant CGMP violations at your facility, causing such drug product(s) to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA [21 U.S.C. § 351(a)(2)(B)].

Misbranded Drug Products

Because the drug products for which you have not obtained valid prescriptions for individually-identified patients are intended for conditions that are not amenable to self-diagnosis and treatment by individuals who are not medical practitioners, adequate directions cannot be written for them so that a layperson can use these drug products safely for their intended uses. Consequently, their labeling fails to bear adequate directions for their intended uses, causing them to be misbranded under section 502(f)(1) of the FDCA [21 U.S.C. § 352(f)(1)], and they are not exempt from the requirements of section 502(f)(1) of the FDCA (*see*, *e.g.*, 21 C.F.R. § 201.115). It is a prohibited act under section 301(k) of the FDCA [21 U.S.C. § 331(k)] to do any act with respect to a drug, if such act is done while the drug is held for sale after shipment in interstate commerce of the components used to make the drug and results in the drug being misbranded.

Adulteration Charges

Additionally, FDA investigators noted that your sterile drug products were prepared, packed, or held under insanitary conditions, whereby they may have become contaminated with filth or rendered injurious to health, causing your drug products to be adulterated under section 501(a)(2)(A) of the FDCA [21 U.S.C. § 351(a)(2)(A)]. Examples of these conditions include an air supply system that is composed of, in part, a **(b)(4)** held together, in part, with duct tape; an in-wall air conditioner; operators performing aseptic manipulations with exposed wrist and forearm skin; and the use of tap water and a **(b)(4)** to clean and depyrogenate containers and closures intended for injectable drug products.

FDA investigators also noted CGMP violations at your facility, causing the drug products for which you have not obtained valid prescriptions for individually-identified patients to be adulterated under section 501(a)(2)(B) of the FDCA [21 U.S.C. § 351(a)(2)(B)]. The violations include, for example:

1. Your firm failed to establish an adequate air supply filtered through high-efficiency particulate air filters under positive pressure in the aseptic processing areas (21 CFR 211.42(c)(10)(iii)).

2. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

3. Your firm failed to ensure that manufacturing personnel wear clothing appropriate to protect drug product from contamination (21 CFR 211.28(a)).

4. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv)).

5. Your firm does not have, for each batch of drug product purporting to be sterile and/or pyrogen-free, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product (21 CFR 211.167(a)).

It is a prohibited act under section 301(k) of the FDCA [21 U.S.C. § 331(k)] to do any act with respect to a drug, if such act is done while the drug is held for sale after shipment in interstate commerce of the components used to make the drug and results in the drug being adulterated.

C. Corrective Actions

We are aware that the California State BOP issued a Notice of Violation and Embargo Notice to your firm on September 6, 2013. Additionally, on September 10, 2013, the California State BOP issued another Embargo Notice to recall all sterile drug products due to a lack of viable sterility and endotoxin testing, ordered your firm to immediately cease and desist the compounding of injectable sterile drug products (effective until October 31, 2013), and cancelled your firm's sterile compounding license. In a letter to the BOP dated September 16, 2013 (and referenced in your response to the Form FDA 483 dated September 20, 2013), you agreed to voluntarily relinquish your State of California Sterile Compounding License (LSC 99109) to the BOP.

In your September 20, 2013 response to the Form FDA 483, you stated that you had decided at that time to no longer continue sterile compounding. In addition, you stated that your lawyer was "looking over the observations and may have a further response, but he is currently on vacation." No other responses from your firm have been received by FDA since that time. In your letter to the California State BOP dated September 16, 2013, you stated you would continue to compound products that do not require you to have the licensed sterile compounding permit, as well as all other operations as a retail pharmacy.

FDA strongly recommends that if you decide to resume production of sterile drugs, your management immediately undertake a comprehensive assessment of your manufacturing operations, including facility design, procedures, personnel, processes, materials, and systems. In particular, this review should assess your aseptic processing operations. A third party consultant with relevant sterile drug manufacturing expertise could be useful in conducting this comprehensive evaluation.

As noted above, your firm has manufactured and distributed drug products without valid prescriptions for individually-identified patients, and the manufacture of such drugs is subject to FDA's drug CGMP regulations, 21 CFR Parts 210 and 211. Before resuming such operations, you should fully implement corrective actions that meet the minimum requirements of 21 CFR Part 211 in order to provide assurance that the drug product(s) produced by your firm conform to the basic quality standards that ensure safety, identity, strength, quality, and purity.

In addition, if you resume sterile compounding, you should also correct the violations of FDCA section 502(f)(1) noted above.

D. Conclusion

The violations cited in this letter are not intended to be an all-inclusive statement of violations at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence or the occurrence of other violations. It is your responsibility to ensure that your firm complies with all requirements of federal law and FDA regulations.

If you decide to resume sterile drug operations, you should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice, including, without limitation, seizure and injunction.

Within fifteen working days of receipt of this letter, please notify this office in writing if you have taken specific steps to correct violations, or you may inform us that you do not intend to resume production of sterile drugs. If you intend to resume production of sterile drugs in the future, please include an explanation of each step being taken to prevent the recurrence of violations, as well as copies of related documentation. If you do not believe that the products discussed above are in violation of the FDCA, include your reasoning and any supporting information for our consideration. In addition to taking appropriate corrective actions, you should notify this office prior to resuming production of any sterile drugs in the future. Your written reply should be addressed to:

Lawton Lum
Director, Compliance Branch
U.S. Food and Drug Administration
1431 Harbor Bay Parkway
Alameda, CA 94502

If you have questions regarding any issues in this letter, please contact Mr. Russell Campbell, Compliance Officer, at 510-337-6861.

Sincerely,
/S/

Kathleen M. Lewis, J.D.
District Director

cc:
Virginia Herold, Executive Officer
California State Board of Pharmacy
1625 N Market Street
Sacramento, CA 95834

---

[1] *Compare Western States Med. Ctr. v. Shalala*, 238 F.3d 1090 (9th Cir. 2001) *with Medical Ctr. Pharm. v. Mukasey*, 536 F.3d 383 (5th Cir. 2008).

[2] The CPG set forth a non-exhaustive list of factors that FDA considered in determining whether to take enforcement action when the scope and nature of a pharmacy's activities raised concerns. This CPG has been withdrawn in light of new legislation. See below.

[3] *See* 21 U.S.C. § 353a(a) (granting compounded drugs statutory exemptions if, among other things, "the drug product is compounded for an identified individual patient based on the . . . receipt of a valid

prescription order or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient . . . .”); CPG at 2 (“FDA recognizes that pharmacists traditionally have extemporaneously compounded and manipulated reasonable quantities of human drugs upon receipt of a valid prescription for an individually-identified patient from a licensed practitioner. This traditional activity is not the subject of this guidance.”).

[4] Drug Quality and Security Act, Public Law 113-54, 127 Stat. 587 (Nov. 27, 2013).

[5]The CQA contains a number of other provisions, including new exemptions and requirements for compounders seeking to operate as outsourcing facilities. A discussion of the CQA and the agency’s plans to implement the new law may be found at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm.

[6] For example, section 503A also addresses anticipatory compounding, which includes compounding (not distribution) before receipt of a valid prescription order for an individual patient. We are not addressing anticipatory compounding here.

!

Attachment C

Sichuan Pharmaceutical Co., Ltd. 9/9/11

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring MD 20993

Warning Letter

VIA UPS MAIL

WL: 320-11-019

September 09, 2011

Mr. Wang Gouping
General Manager
Sichuan Pharmaceutical Co., Ltd.
No. 189 Hualong Road
Pengzhou, Sichuan, China 611930

Dear Mr. Gouping:

During our June 23 to 29, 2010 inspection of your active pharmaceutical ingredient (API) manufacturing facility, Sichuan Pharmaceutical Co., Ltd. located at No. 189 Hualong Road, Pengzhou, Sichuan, China, an investigator from the Food and Drug Administration (FDA) identified significant deviations from Current Good Manufacturing Practice (CGMP) for the manufacture of APIs. These deviations cause your API(s) to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 351(a)(2)(B)] in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

We have reviewed your firm's response of August 05, 2010 and December 13, 2010, and note that it lacks sufficient corrective actions.
Specific deviations observed during the inspection include, but are not limited, to the following:

1. Failure to have appropriate procedures in place to prevent cross-contamination.

   From September 2008 to July 2009 your firm manufactured **(b)(4)** API in workshop **(b)(4)**, which is adjacent to workshops **(b)(4)** and **(b)(4)** where you manufactured **(b)(4)** API and **(b)(4)** injection, respectively. However, you failed to have adequate controls and monitoring program to prevent cross-contamination between these adjacent workshops.

In addition, your firm manufactures a **(b)(4)** API (**(b)(4)** (API) in a facility that was previously used to manufacture **(b)(4)** without conducting adequate decontamination, renovation, and activation of the facility. Your firm has failed to conduct adequate assessment of the cross-contamination risks.

Please note that analytical testing of a product for possible contamination with **(b)(4)** is not sufficient to ensure adequate conditions for **(b)(4)** manufacture. In your response to this letter include your plans for decontamination, renovation, and reactivation (if appropriate) of your facility including the decontamination agent, decontamination plans, analytical methodology for environmental and product testing, and the data obtained to support the effectiveness of the decontamination plan.

The deviations detailed in this letter are not intended to be an all-inclusive statement of deviations that exist at your facility. You are responsible for investigating and determining the causes of the deviations identified above and for preventing their recurrence and the occurrence of other deviations. If you wish to continue to ship APIs to the United States, it is the responsibility of your firm to ensure compliance with all U.S. standards for CGMP and all applicable U.S. laws and regulations.

Additionally, your firm is neither registered nor has it listed every API in commercial distribution in the United States with FDA, as required by 21 C.F.R. § 207.40 and section 510(i) of the Act [21 U.S.C. § 360(i)]. Information on how to register and list is available at the following internet website:http://www.fda.gov/cder/drls/registration_listing.htm. You must complete the required registration and listing and provide evidence that you have fulfilled these requirements in your response to this letter.

Until all corrections have been completed and FDA has confirmed corrections of the deviations and your firm's compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as an API manufacturer. In addition, failure to correct these deviations may result in FDA refusing admission of articles manufactured at Sichuan Pharmaceutical Co., Ltd. located at No. 189 Hualong Road, Pengzhou, Sichuan, China into

the United States. The articles are subject to refusal of admission pursuant to section 801(a)(3) of the Act [21 U.S.C. § 381(a)(3)] in that the methods and controls used in their manufacture do not appear to conform to Current Good Manufacturing Practice within the meaning of section 501(a)(2)(B) of the Act [21 U.S.C. § 351(a)(2)(B)].

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct deviations. Include an explanation of each step being taken to prevent the recurrence of deviations and copies of supporting documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the date by which you will have completed the correction.

Additionally, your response should state if you no longer manufacture or distribute **(b)(4)** API and provide the date(s) and reason(s) you ceased production. Please identify your response with FEI # 3002808073.

If you have questions or concerns regarding this letter, contact Milva E. Meléndez, Compliance Officer, at the below address and telephone number.

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Manufacturing and Product Quality
Division of International Drug Quality
White Oak, Building 51
10903 New Hampshire Ave
Silver Spring, MD 20993
Tel: (301) 796-0662
Fax: (301) 847-8741

Sincerely,

/Steven Lynn/
Steven Lynn
Director
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

!

IN THE CIRCUIT COURT OF PULASKI COUNTY, ARKANSAS
FIFTH DIVISION

JASON MCGEHEE,
STACEY JOHNSON,
JACK JONES,
BRUCE WARD,
KENNETH WILLIAMS,
MARCEL WILLIAMS
ANDREW SASSER,
DON DAVIS, and
TERRICK NOONER,

Plaintiffs,

v.

RAY HOBBS, in his official capacity
Director, Arkansas Department of Correction, and
ARKANSAS DEPARTMENT OF CORRECTION,

Defendant.

AFFIDAVIT OF DAVID B. WAISEL, M.D.

1. My name is Dr. David Waisel and I am a practicing anesthesiologist at Boston Children's Hospital in Boston, MA, and an Associate Professor of Anaesthesia at Harvard Medical School. I received my Medical Degree from Medical College of Pennsylvania in 1989. I have been practicing clinical anesthesiology for over twenty years. Over the years, I have authored several articles pertaining to anesthesiology that were published in various publications.

2. Counsel for the plaintiffs in this case asked me to opine on the effects and uses of barbiturate and benzodiazepine drugs. I have consulted with counsel on a *pro bono* basis and am not being compensated for my work in this case.

3. Barbiturates are a class of drugs that act to depress a person's central nervous system. The clinical uses of barbiturates are wide ranging, from treating anxiety or insomnia symptoms to treating seizure disorders to anesthetizing patients for surgery.

4. The term barbiturate describes a number of different drugs. Barbiturates are classified depending on the length of time of the drug's onset and how long those effects last. Generally, barbiturates

can be classified as ultra-short-acting, short-acting, intermediate-acting, or long-acting. There is a substantial difference between the way an ultra-short-acting barbiturate acts in the body as compared to a long-acting barbiturate. For example, an ultra-short-acting barbiturate produces a rapid onset in the body (typically within seconds). Depending on the dosage, a person administered an ultra-short-acting barbiturate will lose consciousness within seconds. While ultra-short-acting barbiturates take effect rapidly upon intravenous administration, the drugs start to wear off relatively quickly. Comparatively, a long-acting barbiturate may take considerably longer to take effect in the body, as well as may stay in the body for a significantly longer time. So while "barbiturates" is a word to describe a type of drug, barbiturate drugs themselves are diverse and have different effects on the body.

5. The duration of a barbiturate, meaning how long the drug works in the body (as explained above), is measured in the "half-life" of the drug. The half-life of a drug is the period of time required for the body to reduce the amount of the drug in the body by one-half. The half-life of a drug is useful to determine how long it will take the body to process the drug out of its system. So for example, ultra-short-acting barbiturates will begin to work very quickly in the body and will leave the body quickly; long-acting barbiturates will take comparatively longer to take effect in the body and longer to leave the body.

6. Like barbiturates, benzodiazepines depress (or slow down) a person's central nervous system. Benzodiazepines specifically enhance the effect of the $GABA_A$ (gamma-aminobutyric acid) receptor in the brain, which affects the physical functioning of the brain and can cause sedation, induce sleep, inhibit anxiety, prevent seizures, or relax muscles. Benzodiazepines are like alcohol in that they both bind to the $GABA_A$ receptor and can produce a similar cognitive effect: feelings of sedation or relaxation, an altered consciousness, a lack of judgment or insight, or tiredness. Benzodiazepines are used frequently to treat anxiety and induce amnesia.

7. Depending on the dose given, benzodiazepines can produce paradoxical effects. A paradoxical effect (or reaction) is when a drug produces an effect that is opposite of what is expected. For example, a person administered a sedative to calm them down may respond with the paradoxical effect of causing the patient to become more anxious, more talkative, aggressive or violent.

8. Benzodiazepines may produce paradoxical reactions. Depending on the dose administered, some individuals administered a benzodiazepine show signs of agitation, excitement, acute anxiety, anger, impulsivity and gross motor and behavioral disturbances. The cause of these reactions are unclear, although several risk factors have been identified, including a history of alcoholism and psychiatric or personality disorders, especially disorders characterized by poor impulse control.

9. I hold these opinions to a reasonable degree of medical certainty.

Dated this 26 day of AUGUST, 2013.

David B. Waisel, MD.

Sworn to and subscribed before me on this 26th day of AUGUST, 2013.

Notary

REBECCA D. BRENNAN
Notary Public
Massachusetts
Commission Expires Aug 15, 2019

SWORN DECLARATION OF SPENCER J. HAHN

STATE OF ALABAMA)
)
COUNTY OF MONTGOMERY)

I, Spencer J. Hahn, a resident of Montgomery, Alabama, hereby declare, under penalty of perjury, the following:

1. I am an Assistant Federal Defender in the Capital Habeas Unit of the Federal Defenders for the Middle District of Alabama, in Montgomery, Alabama, where I have worked since October 1, 2014. I have been licensed to practice law since 2004.

2. Ron Smith designated me and our Executive Director, Christine Freeman, to witness his execution. This declaration contains my observations of what occurred immediately before, during, and after Ron's execution.

3. At approximately 10:20 p.m., Christine and I, along with members of the press (including Kent Faulk) who had been waiting in a van next to our transport car, were escorted into the witness room. While waiting, I had noticed two people in an Etowah County Medical Examiner vehicle; they remained outside.

4. I asked the corrections officer who drove us if anyone from the victim's family was present, and was told that someone was. Once inside the witness room, I heard a radio transmission that witnesses were being taken to room 8, followed by footsteps and the shadows of feet passing our (closed) door. Whoever was in room 8 was allowed to leave before we did, as I heard a similar radio transmission about room 8, and saw the reverse of what I saw after the first message. They left and entered through the other end of the hall from us and the press.

5. The Warden read the death warrant to Ron, offered him a chance to make any final statement ("No, ma'am"), and the Warden left the room.

6. Shortly thereafter, the second guard left the room, and the prison chaplain approached Ron, held his right hand, and kneeled in front of him for a minute or so. As the prison chaplain approached, Ron appeared to be mouthing, repeatedly, what I believe was the Lord's Prayer.

7. The midazolam began around 10:30 p.m. The first thing I noticed was that Ron ran his tongue around his lips several times, as if he had a dry mouth. Then, at 10:31:55 p.m. (according to the clock above his gurney) Ron began having difficulty breathing, including regular asthmatic-sounding barking coughs every ten seconds or so. He also lifted his head and looked around, moved his arms, clenched his left hand, and moved his lips in what appeared to be an attempt to say something. Ron's eyes never closed, and he moved and coughed regularly throughout approximately the next fifteen minutes.

8. Both before and after the first consciousness check, it was obvious Ron was still awake, as he was still moving his head, hands and arms, coughing, and attempting to speak. He reacted to the arm pinch by moving his arm toward his body (away from the source of pain).

9. Sometime before the administration of the second dose of midazolam, I heard raised voices coming from the Commissioner's room. Although I couldn't make out the words, the tone indicated panic or, at the very least, extreme stress.

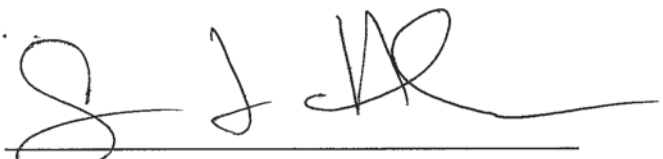
10. Ron again began to exhibit the signs he did after the first dose of midazolam. After several more minutes, a second consciousness check was done, during which Ron continued to move and his eyes remained open. While touching his left eyelid, the guard pushed it closed, but it opened as soon as he removed his finger.

11. Ron moved his right arm after the second consciousness check. Shortly thereafter, they must have administered the paralytic, as Ron's breathing became very shallow and he stopped moving. His eyes remained open, with the left eye opening further as his breathing became imperceptible.

12. The curtains were closed without anyone having approached Ron and, when I stood to leave, I, on my tiptoes, looked over the top of the curtain, and saw no signs of the EKG or anyone checking Ron. Leaving the building, I noticed that both members of the medical examiner's office were still in their truck.

I hereby declare, pursuant to 28 U.S.C. 1746, under penalty of perjury, that the foregoing is true and correct to the best of my knowledge and belief.

Dated this 13th day of December, 2016.



Spencer J. Hahn
Assistant Federal Defender

IN THE UNITED STATES COURT OF APPEALS
FOR THE EIGHTH CIRCUIT

No. 16-3072

In re: Missouri Department of Corrections, Petitioner

M7, Petitioner – Intervenor

Richard Jordan and Ricky Chase, Respondents.

On Petition for Writ of Mandamus to the United States District Court
for the Western District of Missouri – Jefferson City
(2:16-MC-09005)

RESPONDENTS' MOTION FOR LEAVE TO FILE TRANSCRIPT UNDER SEAL

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RESPONDENTS' MOTION FOR LEAVE TO FILE TRANSCRIPT UNDER SEAL

Richard Jordan and Ricky Chase, Respondents in the above-captioned mandamus proceeding, move this Court for leave to file a portion of the transcript of the hearing before District Judge Bough under seal. The transcript, attached to the paper copy of this motion, is designated "Exhibit 4-B" in Respondents' pleadings in opposition to the petitions for mandamus and rehearing filed by the Missouri Department of Corrections ("MO-DOC") and M7. In support of this motion, Respondents represent the following to the Court:

1. On July 1, 2016, the United States District Court for the Western District of Missouri conducted a hearing on MO-DOC's motion to quash a subpoena duces tecum and notice of deposition served upon MO-DOC by Respondents.

2. A portion of the hearing was sealed with only MO-DOC and Respondents' attorneys present in the courtroom.

3. On September 20, 2016, the district court entered a Protective Order sealing the transcript of the *in camera* portion of the July 1 hearing. Doc. 38, *Missouri Department of Corrections v. Jordan et al.*, case no. 2:16-mc-09005.

4. Under the terms of the Protective Order, the transcript of the *in camera* portion of the transcript can only be filed in the Eighth Circuit Court of Appeals under seal.

5. In addition to the sealed transcript, Respondents submit a brief Argument Regarding Matters in Sealed Transcript, setting forth the relevance of the sealed transcript to the issues before this Court.

6. Respondents believe that this Motion may be made publically available on PACER. See Local Rule 25A(g).

WHEREFORE, PREMISES CONSIDERED, Respondents request that this Court grant leave to file the sealed portion of the July 1 transcript and the Argument Regarding Matters in Sealed Transcript under seal.

Respectfully submitted,

/s/ James W. Craig
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Attorneys for Respondents

CERTIFICATE OF SERVICE

I hereby certify that I have served a copy of this Motion on all parties by electronic mail. This pleading is not filed via the Electronic Case Filing system of the United States Court of Appeals for the Eighth Circuit.

This, the 30th day of September, 2016.

/s/ James W. Craig

IN THE UNITED STATES COURT OF APPEALS
FOR THE EIGHTH CIRCUIT

No. 16-3072

In re: Missouri Department of Corrections, Petitioner

M7, Petitioner – Intervenor

Richard Jordan and Ricky Chase, Respondents.

On Petition for Writ of Mandamus to the United States District Court
for the Western District of Missouri – Jefferson City
(2:16-MC-09005)

RESPONDENTS' ARGUMENT REGARDING MATTERS IN SEALED TRANSCRIPT

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RESPONDENTS' ARGUMENT REGARDING MATTERS IN SEALED TRANSCRIPT

On July 1, 2016, the United States District Court for the Western District of Missouri conducted a hearing on MO-DOC's motion to quash a subpoena duces tecum and notice of deposition served upon MO-DOC by Respondents. A portion of the hearing was sealed with only MO-DOC and Respondents' attorneys present in the courtroom. The sealed transcript is designated as "Exhibit 4-B" in the Respondents' oppositions to the motions filed by the Missouri Department of Corrections ("MO-DOC") and M7, MO-DOC's anonymous drug vendor.

During the in camera portion of the hearing, counsel for MO-DOC discussed matters set forth in the privilege log which had been submitted to the district court ex parte. Respondents' counsel did not have access to the ex parte privilege log.

MO-DOC's counsel focused the Court's attention on Request No. 2 of the subpoena duces tecum under consideration in the district court. That request seeks production of "All drug labels and package inserts for any drug purchased or obtained by the Department, from 2010 to the present, for use in lethal injection executions."[1] MO-DOC counsel stated:

> I'm primarily focused on request number 2 for documents about pentobarbital . . . if identified whether or not there is a responsive document to that request, that answers the question of whether it is or is not manufactured or

[1] Exhibit 3 to Respondents' Opposition at 5.

> compounded pentobarbital because manufactured pentobarbital has that information, and compounded pentobarbital does not have a package insert.
>
> So by merely saying that there exists a document that proves it's manufactured or proves that it's compounded, that answers the question does Missouri use compounded or manufactured pentobarbital.[2]

Thereafter, the district court stated "there are three responses that list No. 2."[3] Counsel for MO-DOC agreed.[4]

Thus, there is evidence that at some point after 2010, MO-DOC purchased manufactured pentobarbital for use in lethal injection executions. All parties agree that pentobarbital can be purchased in one of two forms: either compounded by a licensed pharmacy from the active pharmaceutical ingredients for the chemical; or manufactured by a pharmaceutical company under FDA-approved and monitored practices. Akorn Pharmaceuticals is the sole licensed manufacturer of pentobarbital.[5] Akorn has instituted a policy restricting the sale of Nembutal to corrections departments for use in executions.[6]

The sale of manufactured pentobarbital by M7 or another vendor to MO-DOC would violate the property and contractual rights of Akorn to determine how its

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[2] Exhibit 4-B at 8-9.
[3] Id. at 10.
[4] Id.
[5] See Exhibit D (May 13, 2016 article) to Exhibit 15 (Declaration of Comptroller DiNapoli) to Respondent's Opposition.
[6] Exhibit B to Exhibit 15 to Respondents' Opposition.

product is used. For the reasons set forth in the Oppositions filed by Respondents in the public record, mandamus should be denied if this Court, or the district court, finds that MO-DOC and M7's attempt to safeguard the confidentiality of the identity of MO-DOC's lethal injection drug vendors would facilitate the violation of the rights of Akorn and its shareholders.

Respectfully submitted,

/s/James W. Craig
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Attorneys for Respondents

CERTIFICATE OF SERVICE

I hereby certify that I have served a copy of this Argument on all parties by electronic mail. This pleading is not filed via the Electronic Case Filing system of the United States Court of Appeals for the Eighth Circuit.

This, the 30th day of September, 2016.

/s/ James W. Craig