

Exhibit J

Textbook of Military Medicine

MEDICAL ASPECTS of CHEMICAL and BIOLOGICAL WARFARE

Introduction

Foreword by The Surgeon General

Preface

Patient Flow in a Theater of Operations

Medical Aftermath of the Persian Gulf War

1. Overview: Defense Against the Effects of Chemical and Biological Warfare Agents
 2. History of Chemical and Biological Warfare: An American Perspective
 3. Historical Aspects of Medical Defense Against Chemical Warfare
 4. The Chemical Warfare Threat and the Military Healthcare Provider
 5. Nerve Agents
 6. Pretreatment for Nerve Agent Exposure
 7. Vesicants
 8. Long-Term Health Effects of Nerve Agents and Mustard
 9. Toxic Inhalational Injury
 10. Cyanide Poisoning
 11. Incapacitating Agents
 12. Riot Control Agents
 13. Field Management of Chemical Casualties
 14. Triage of Chemical Casualties
 15. Decontamination
 16. Chemical Defense Equipment
 17. Healthcare and the Chemical Surety Mission
 18. Historical Overview of Biological Warfare
 19. The U.S. Biological Warfare and Biological Defense Programs
 20. Use of Biological Weapons
 21. The Biological Warfare Threat
 22. Anthrax
 23. Plague
 24. Tularemia
 25. Brucellosis
 26. Q Fever
 27. Smallpox
 28. Viral Encephalitides
 29. Viral Hemorrhagic Fevers
 30. Defense Against Toxin Weapons
 31. Staphylococcal Enterotoxin B and Related Pyrogenic Toxins
 32. Ricin Toxin
-

- 33. Botulinum Toxins
- 34. Trichothecene Mycotoxins
- 35. Medical Challenges in Chemical and Biological Defense for the 21st Century

Chapter 8

LONGTERM HEALTH EFFECTS OF NERVE AGENTS AND MUSTARD

FREDERICK R. SIDELL, M.D.*; AND CHARLES G. HURST, M.D.†

INTRODUCTION

Nerve Agents

Mustard

NERVE AGENTS

Polyneuropathy

Muscle Necrosis

Intermediate Syndrome

Neuropsychiatric Effects

Electroencephalographic Abnormalities

Toxicological Studies on Nerve Agents

MUSTARD

Carcinogenesis

Chronic Pulmonary Disease

Chronic Eye Disease

Scarring of Epithelial Surfaces

Central Nervous System

Mutagenesis, Teratogenesis, and Reproductive Toxicity

SUMMARY

* Formerly, Chief, Chemical Casualty Care Office, and Director, Medical Management of Chemical Casualties Course, U.S. Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, Maryland 21010-5425; currently, Chemical Casualty Consultant, 14 Brooks Road, Bel Air, Maryland 21014

† Colonel, Medical Corps, U.S. Army; currently, Special Assistant for Medical Programs, Office of the Deputy Assistant Secretary of Defense, Counterproliferation and Chemical/Biological Matters, Room 3E808, 3050 Defense Pentagon, Washington, D.C. 20301-3050; formerly, Commander, U.S. Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, Maryland 21010-5425

INTRODUCTION

Chemical warfare agents were used extensively in World War I (the United States had approximately 70,000 chemical casualties¹) and have been employed or allegedly employed in a dozen or so conflicts since.² The most recent large-scale use of these weapons was by Iraq in its war with Iran in the late 1980s. During that conflict, Iraq used nerve agents and

symptomatic exposures to mustard over a period of years as a causal factor in an increased incidence of airway cancer. The association between a single exposure to mustard and airway cancer is not as well established. The association between one-time mustard exposure and other chronic airway problems, such as chronic bronchitis, which is based on World War I data, seems more clearly established. In some cases, the long-term damage was probably a continuation of the original insult resulting from insufficient therapy in the preantibiotic era.

Several eye diseases, such as chronic conjunctivitis, appear after an acute, usually severe, insult to the eye. In particular, delayed keratitis has appeared more than 25 years after the acute, severe lesion. Similarly, skin scarring, pigment changes, and even cancer have either followed the initial wound as a continuation of the process (scarring) or later appeared at the site of the lesion.

The production of nonairway cancer by mustard has been demonstrated in animals, but scant evidence exists to implicate mustard as a causative factor in nonairway cancer in humans.

Mustard causes chromosomal breakage and induces sister chromatid exchanges in man and has been classed as a mutagen. No data that implicate mustard as a reproductive toxin in man seem to be available, despite the many thousands of people exposed to mustard in the past 80 years.

REFERENCES

1. Prentiss AM. *Chemicals in War: A Treatise on Chemical Warfare*. New York, NY: McGraw-Hill; 1937: 653.
2. Robinson JP. *The Problem of Chemical and Biological Warfare*. Vol 1. In: *The Rise of CB Weapons*. New York, NY: Humanities Press; 1971.
3. United Nations Security Council, *Report of Specialists Appointed by the Secretary General to Investigate Allegations by the Islamic Republic of Iran Concerning the Use of Chemical Weapons*. New York, NY: United Nations; 1986. *UN Report S/16433*.
4. Wade JV, Gum RM, Dunn MA. Medical chemical defense in Operations Desert Shield and Desert Storm. *J US Army Med Dept*. 1992;PB8-92-1/2:34-36.
5. Sidell FR. The medical management of chemical casualty course in CONUS and Europe during Desert Storm. *J US Army Med Dept*. 1992;PB 8-92-3/4:10-12.
6. Papirmeister B, Feister AJ, Robinson SI, Ford RD. *Medical Defense Against Mustard Gas: Toxic Mechanisms and Pharmacological Implications*. Boca Raton, Fla: CRC Press; 1991.
7. Sidell FR. Clinical considerations in nerve agent intoxication. In: Somani SM, ed. *Chemical Warfare Agents*. San Diego, Calif: Academic Press; 1992: 156-194.
8. Taylor P. Anticholinesterase agents. In: Gilman AG, Rall TW, Nies AS, Taylor P, eds. *The Pharmacological Basis of Therapeutics*. New York, NY: Pergamon Press; 1990: 131-149.
9. Albuquerque EX, Akaike A, Shaw KP, Rickett DL. The interaction of anticholinesterase agents with the acetylcholine receptor-ionic channel complex. *Fundam Appl Toxicol*. 1984;4:S27-S33.
10. O'Neill JJ. Non-cholinesterase effects of anticholinesterases. *Fundam Appl Toxicol*. 1981;1:154-169.
11. Bowers MB, Goodman E, Sim VM. Some behavioral changes in man following anticholinesterase administration. *J Nerv Ment Dis*. 1964;138:383-389.
12. Craig FN, Cummings EG, Sim VM. Environmental temperature and the percutaneous absorption of a cholinesterase inhibitor, VX. *J Invest Dermatol*. 1977;68:357-361.

13. Johns RJ. *The Effects of Low Concentrations of GB on the Human Eye*. Edgewood Arsenal, Md: Medical Research Laboratory; 1952. MRL Report 100.
14. Sidell FR. Soman and sarin: Clinical manifestations and treatment of accidental poisoning by organophosphates. *Clin Toxicol*. 1974;7:1-17.
15. Ward JR. Exposure to a nerve gas. In: Whittenberger JL, ed. *Artificial Respiration: Theory and Applications*. New York, NY: Harper & Row; 1962: 258-265.
16. Program Executive Officer-Program Manager of Chemical Demilitarization. *Chemical Stockpile Disposal Program Final Programmatic Environmental Impact Statement*. Aberdeen Proving Ground, Md: Program Executive Officer-Program Manager of Chemical Demilitarization; 1988: B-23-B-25.
17. Sidell FR, Groff WA. The reactivability of cholinesterase inhibited by VX and sarin in man. *Toxicol Appl Pharmacol*. 1974;27:241-252.
18. Balali-Mood M, Navaeian A. Clinical and paraclinical findings in 233 patients with sulfur mustard poisoning. In: Heyndrickx B, ed. *Proceedings of the 2nd World Congress on New Compounds in Biological and Chemical Warfare: Toxicological Evaluation, Industrial Chemical Disasters, Civil Protection and Treatment, 24-27 August 1986*. Ghent, Belgium, State University of Ghent; 1986: 464-473.
19. Warthin AS, Weller CV. The lesions of the respiratory and gastrointestinal tract produced by mustard gas (dichlorethyl sulphide). *J Lab Clin Med*. 1919;4:229-264.
20. Sohrabpour H. Clinical manifestations of chemical agents on Iranian combatants during the Iran-Iraq conflict. In: Heyndrickx A, ed. *Proceedings of the 1st World Congress on New Compounds in Biological and Chemical Warfare: Toxicological Evaluation, 21-23 May 1984*. Ghent, Belgium: State University of Ghent; 1984: 291-297.
21. Vedder EB. *The Medical Aspects of Chemical Warfare*. Baltimore, Md: Williams & Wilkins; 1925: 125-166.
22. Renshaw B. Mechanisms in production of cutaneous injuries by sulfur and nitrogen mustards. In: *Chemical Warfare Agents and Related Chemical Problems*. Washington, DC: Office of Scientific Research and Development; 1946.
23. Reed CI. The minimum concentration of dichlorethylsulphide (mustard gas) effective for the eyes of man. *J Pharmacol Exp Ther*. 1920;15:77-80.
24. Pechura CM, Rall DP, eds. *Veterans at Risk: The Health Effects of Mustard Gas and Lewisite*. Washington, DC: Institute of Medicine, National Academy Press; 1993.
25. Boskovic B, Kusic R. Long-term effects of acute exposure to nerve gases upon human health. In: *Chemical Weapons: Destruction and Conversion*. New York, NY: Crane, Russak & Co; 1980: 113-116.
26. Fullerton CS, Ursano RJ. Behavioral and psychological responses to chemical and biological warfare. *Milit Med*. 1990;155:54-59.
27. Chew LS, Chee KT, Yeo JM, Jayaratnam FJ. Continuous atropine infusion in the management of organophosphorus insecticide poisoning. *Singapore Med J*. 1971;12:80-85.
28. LeBlanc FN, Benson BE, Gilg AD. A severe organophosphate poisoning requiring the use of an atropine drip. *Clin Toxicol*. 1986;24:69-76.
29. Metcalf RL. Historical perspective of organophosphorus ester-induced delayed neurotoxicity. In: Cranmer JM, Hixson EJ, eds. *Delayed Neurotoxicity*. Little Rock, Ark: Intox Press; 1984: 7-23.
30. Takade DY. Delayed neurotoxicity in perspective: Summary and objectives of the workshop. In:

- Cranmer JM, Hixson EJ, eds. *Delayed Neurotoxicity*. Little Rock, Ark: Intox Press; 1984: 2–6.
31. Johnson MK. Organophosphorus esters causing delayed neurotoxic effects. *Arch Toxicol*. 1975;34:259–288.
 32. Davies DR, Holland P. Effect of oximes and atropine upon the development of delayed neurotoxic signs in chickens following poisoning by DFP and sarin. *Biochem Pharmacol*. 1972;21:3145–3151.
 33. Davies DR, Holland P, Rumens MJ. The relationship between the chemical structure and neurotoxicity of alkyl organophosphorus compounds. *Brit J Pharmacol*. 1960;15:271–278.
 34. Davies, et al. Cited in: Gordon JJ, Inns RH, Johnson MK, et al. The delayed neuropathic effects of nerve agents and some other organophosphorus compounds. *Arch Toxicol*. 1983;52(3):71–81.
 35. Gordon JJ, Inns RH, Johnson MK, et al. The delayed neuropathic effects of nerve agents and some other organophosphorus compounds. *Arch Toxicol*. 1983;52(3):71–81.
 36. Willems JL, Nicaise M, De Bisschop HC. Delayed neuropathy by the organophosphorus nerve agents soman and tabun. *Arch Toxicol*. 1984;55:76–77.
 37. Vranken MA, DeBisschop HC, Willems JL. “In vitro” inhibition of neurotoxic esterase by organophosphorus nerve agents. *Arch Int Pharmacodyn*. 1982;260:316–318.
 38. Willems JL, Palate BM, Vranken MA, DeBisschop HC. Delayed neuropathy by organophosphorus nerve agents. In: *Proceedings of the International Symposium on Protection Against Chemical Warfare Agents*. Umea, Sweden: National Defence Research Institute; 1983.
 39. Hayes WJ Jr. Organic phosphorus pesticides. In: *Pesticides Studied in Man*. Baltimore, Md: Williams & Wilkins; 1982: 294.
 40. DeReuck J, Willems J. Acute parathion poisoning: Myopathic changes in the diaphragm. *J Neurol*. 1975;208:309–314.
 41. Meshul CK, Boyne AF, Deshpande SS, Albuquerque EX. Comparison of the ultrastructural myopathy induced by anticholinesterase agents at the end plates of rat soleus and extensor muscles. *Exp Neurol*. 1985;89:96–114.
 42. Kawabuchi M, Boyne AF, Deshpande SS, Albuquerque EX. The reversible carbamate (–) physostigmine reduced the size of synaptic end plate lesions induced by sarin, an irreversible organophosphate. *Toxicol Appl Pharmacol*. 1989;97:98–106.
 43. Ariens AT, Meeter E, Wolthuis OL, van Benthem RMJ. Reversible necrosis at the end-plate region in striated muscles of the rat poisoned with cholinesterase inhibitors. *Experientia*. 1969;25:57–59.
 44. Dettbarn W. Pesticide induced muscle necrosis: Mechanisms and prevention. *Fundam Appl Toxicol*. 1984;4:S18–S26.
 45. Wadia RS, Sadagopan C, Amin RB, Sardesai HV. Neurological manifestations of organophosphorus insecticide poisoning. *J Neurol Neurosurg Psychiatry*. 1974;37:841–847.
 46. Senanayake N, Karalliedde L. Neurotoxic effects of organophosphorus insecticides. *N Engl J Med*. 1987;316:761–763.
 47. Karademir M, Erturk F, Kocak R. Two cases of organophosphate poisoning with development of intermediate syndrome. *Hum Exp Toxicol*. 1990;9:187–189.
 48. Nadarajah B. Intermediate syndrome of organophosphorus insecticide poisoning: A neurophysiological study. *Neurology*. 1991;41(suppl 1):251.
 49. DeBleecker J, Willems J, Neucker KVD, DeReuck J, Vogelaers D. Prolonged toxicity with intermediate syndrome after combined parathion and methyl parathion poisoning. *Clin Toxicol*. 1992;30:333–345.

50. DeBleecker J, Neucker KVD, Willems J. The intermediate syndrome in organophosphate poisoning: Presentation of a case and review of the literature. *Clin Toxicol.* 1992;30:321-329.
51. Perron R, Johnson BB. Insecticide poisoning. *N Engl J Med.* 1969;281:274-275.
52. Gadoth N, Fisher A. Late onset of neuromuscular block in organophosphorus poisoning. *Ann Intern Med.* 1978;88:654-655.
53. Benson B. Is the intermediate syndrome in organophosphate poisoning the result of insufficient oxime therapy? *Clin Toxicol.* 1992;30:347-349.
54. Haddad LM. Organophosphate poisoning—intermediate syndrome? *Clin Toxicol.* 1992;30:331-332.
55. Gershon S, Shaw FH. Psychiatric sequelae of chronic exposure to organophosphorus insecticides. *Lancet.* 1961;1:1371-1374.
56. Bidstrup PL. Psychiatric sequelae of chronic exposure to organophosphorus insecticides. *Lancet.* 1961;2:103. Letter.
57. Biskind MS. Psychiatric manifestations from insecticide exposure. *JAMA.* 1972;220:1248. Letter.
58. Levin HS, Rodnitzky RL, Mick DL. Anxiety associated with exposure to organophosphate compounds. *Arch Gen Psychiatry.* 1976;33:225-228.
59. Metcalf DR, Holmes JH. EEG, psychological, and neurological alterations in humans with organophosphorus exposure. *Ann N Y Acad Sci.* 1969;160:357-365.
60. Rowntree DW, Nevin S, Wilson A. The effects of diisopropylfluorophosphate in schizophrenic and manic-depressive psychosis. *J Neurol Neurosurg Psychiatry.* 1950;13:47-62.
61. Durham WF, Wolfe HR, Quinby GE. Organophosphorus insecticides and mental alertness. *Arch Environ Health.* 1965;10:55-66.
62. Namba T, Nolte CT, Jackrel J, Grob D. Poisoning due to organophosphate insecticides. *Am J Med.* 1971;50:475.
63. Dille JR, Smith PW. Central nervous system effects of chronic exposure to organophosphate insecticides. *Aerospace Med.* 1964;35:475-478.
64. Tabershaw IR, Cooper WC. Sequelae of acute organic phosphate poisoning. *J Occup Med.* 1966;8:5-20.
65. Rosenstock L, Keifer M, Daniell WE, McConnell R, Claypoole K. Chronic central nervous system effects of acute organophosphate pesticide intoxication. *Lancet.* 1991;338:223-227.
66. Grob D. The manifestations and treatment of poisoning due to nerve gas and other organic phosphate anticholinesterase compounds. *Arch Intern Med.* 1956;98:221-239.
67. Gaon MD, Werne J. *Report of a Study of Mild Exposures to GB at Rocky Mountain Arsenal.* Rocky Mountain Arsenal, Colo: US Army Medical Department; n.d.
68. Grob D, Harvey AM, Langworthy OR, Lillienthal JL. The administration of di-isopropyl fluorophosphate (DFP) to man. *Bull Johns Hopkins Hosp.* 1947;31:257.
69. Duffy FH, Burchfiel JL. Long term effects of the organophosphate sarin on EEGs in monkeys and humans. *Neurotoxicol.* 1980;1:667-689.
70. Duffy FH, Burchfiel JL, Bartels PH, Gaon M, Sim VM. Long-term effects of an organophosphate upon the human electroencephalogram. *Toxicol Appl Pharmacol.* 1979;47:161-176.

71. Burchfiel JL, Duffy FH. Organophosphate neurotoxicity: Chronic effects of sarin on the electroencephalogram of monkey and man. *Neurobehav Toxicol Teratol*. 1982;4:767-778.
72. Burchfiel JL, Duffy FH, Sim V. Persistent effect of sarin and dieldrin upon the primate electroencephalogram. *Toxicol Appl Pharmacol*. 1976;35:365-379.
73. Bucci TJ, Parker RM, Crowell JA, Thurman JD, Gosnell PA. *Toxicity Studies on Agent GA (Phase II): 90 Day Subchronic Study of GA (Tabun) in CD Rats*. Jefferson, Ark: National Center for Toxicological Research; 1992.
74. Bucci TJ, Parker RM, Gosnell PA. *Toxicity Studies on Agents GB and GD (Phase II): 90-Day Subchronic Study of GD (Soman) in CD-Rats*. Jefferson, Ark: National Center for Toxicological Research; 1992.
75. Jacobson KH, Christensen MK, DeArmon IA, Oberst FW. Studies of chronic exposures of dogs to GB (isopropyl methylphosphono-fluoridate) vapor. *Arch Indust Health*. 1959;19:5-10.
76. Bucci TJ, Parker RM, Cosnell PA. *Toxicity Studies on Agents GB and GD (Phase II): Delayed Neuropathy Study of Sarin, Type I, in SPF White Leghorn Chickens*. Jefferson, Ark: National Center for Toxicological Research; 1992.
77. Bucci TJ, Parker RM, Gosnell PA. *Delayed Neuropathy Study of Sarin, Type II, in SPF White Leghorn Chickens*. Jefferson, Ark: National Center for Toxicological Research; 1992.
78. Henderson JD, Higgins RJ, Rosenblatt L, Wilson BW. *Toxicity Studies on Agent GA: Delayed Neurotoxicity—Acute and Repeated Exposures of GA (Tabun)*. Davis, Calif: University of California Davis Lab for Energy; 1989.
79. Bucci TJ, Parker RM, Gosnell PA. *Toxicity Studies on Agents GB and GD*. Jefferson, Ark: National Center for Toxicological Research; 1992.
80. Goldman M, Klein AK, Kawakami TG, Rosenblatt LS. *Toxicity Studies on Agents GB and GD*. Davis, Calif: University of California Davis Laboratory for Energy; 1987.
81. Kawakami TG, Goldman M, Rosenblatt L, Wilson BW. *Toxicity Studies in Agent GA: Mutagenicity of Agent GA (Tabun) in the Mouse Lymphoma Assay*. Davis, Calif: University of California Davis Laboratory for Energy; 1989.
82. Nasr M, Cone N, Kawakami TG, Goldman M, Rosenblatt L. *Toxicity Studies on Agent GA: Mutagenicity of Agent GA (Tabun) in the In Vitro Cytogenetic Sister Chromatid Exchange Test Phase I*. Davis, Calif: University of California Davis Laboratory for Energy; 1988.
83. Goldman M, Nasr M, Cone N, Rosenblatt LS, Wilson BW. *Toxicity Studies on Agent GA: Mutagenicity of Tabun (GA) in the Ames Mutagenicity Assay*. Davis, Calif: University of California Davis Laboratory for Energy; 1989.
84. Morgenstern P, Koss FR, Alexander WW. Residual mustard gas bronchitis: Effects of prolonged exposure to low concentrations of mustard gas. *Ann Intern Med*. 1947;26:27-40.
85. Buscher H; Conway N, trans. *Green and Yellow Cross*. Cincinnati, Oh: Kettering Laboratory of Applied Physiology, University of Cincinnati, Oh; 1944.
86. Prokes J, Svovoda V, Hynie I, Proksova M, Keel K. The influence of X-radiation and mustard gas on methionin-35-S incorporation in erythrocytes. *Neoplasma*. 1968;15:393-398.
87. Manning KP, Skegg DCG, Stell PM, Doll R. Cancer of the larynx and other occupational hazards of mustard gas workers. *Clin Otolaryngol*. 1981;6:165-170.
88. Heston WE. Induction of pulmonary tumors in strain A mice with methyl-bis (beta-chloroethyl)amine hydrochloride. *J Natl Cancer Inst*. 1949;10:125-130.

89. Heston WE. Carcinogenic action of the mustards. *J Natl Cancer Inst.* 1950;11:415-423.
90. Heston WE. Occurrence of tumors in mice injected subcutaneously with sulfur mustard and nitrogen mustard. *J Natl Cancer Inst.* 1953;14:131-140.
91. McNamara BP, Owens EJ, Christensen MK, Vocci FJ. *Toxicological Basis for Controlling Levels of Mustard in the Environment.* Aberdeen Proving Ground, Md: Biomedical Laboratory; 1975. EB-SP-74030.
92. Case RAM, Lea AJ. Mustard gas poisoning, chronic bronchitis, and lung cancer: An investigation into the possibility that poisoning by mustard gas in the 1914-1918 war might be a factor in the production of neoplasia. *Br J Prev Soc Med.* 1955;9:62-72.
93. Norman JR, Jr. Lung cancer mortality in World War I veterans with mustard-gas injury: 1919-1965. *J Natl Cancer Inst.* 1975;54:311-317.
94. Fletcher C, Peto R, Tinker C, Speizer FE. *The Natural History of Chronic Bronchitis and Emphysema.* Oxford, England: Oxford University Press; 1976.
95. Wada S, Miyanishi M, Nashimoto Y, Kambe S, Miller RW. Mustard gas as a cause of respiratory neoplasia in man. *Lancet.* 1968;1:1161-1163.
96. Easton DF, Peto J, Doll R. Cancers of the respiratory tract in mustard gas workers. *Br J Ind Med.* 1988;45:652-659.
97. Minoue R, Shizushiri S. Occupationally-related lung cancer—Cancer of the respiratory tract as sequentia from poison gas plants. *Jpn J Thorac Dis.* 1980;18:845-859.
98. Albro PW, Fishbein L. Gas chromatography of sulfur mustard and its analogs. *J Chromatogr.* 1970;46:202-203.
99. Yanagida J, Hozawa S, Ishioka S, et al. Somatic mutation in peripheral lymphocytes of former workers at the Okunojima poison gas factory. *Jpn J Cancer Res.* 1988;79:1276-1283.
100. Watson AP, Jones TD, Grinnin GD. Sulfur mustard as a carcinogen: Application of relative potency analysis to the chemical warfare agents H, HD, and HT. *Regul Toxicol Pharmacol.* 1989;10:1-25.
101. Willems JL. Clinical management of mustard gas casualties. *Ann Med Milit Belg.* 1989;3(suppl):1-61.
102. Urbanetti JS. Battlefield chemical inhalation injury. In: Loke J, ed. *Pathophysiology and Treatment of Inhalation Injuries.* New York, NY: Marcel Dekker; 1988.
103. Balali M. Clinical and laboratory findings in Iranian fighters with chemical gas poisoning. In: Heyndrickx B, ed. *Proceedings of the 1st World Congress on New Compounds in Biological and Chemical Warfare: Toxicological Evaluation, 21-23 May 1984.* Ghent, Belgium: State University of Ghent; 1984: 254-259.
104. Balali-Mood M. First report of delayed toxic effects of yperite poisoning in Iranian fighters. In: Heyndrickx B, ed. *Proceedings of the 2nd World Congress on New Compounds in Biological and Chemical Warfare: Toxicological Evaluation, Industrial Chemical Disasters, Civil Protection and Treatment, 24-27 August 1986.* Ghent, Belgium, State University of Ghent; 1986: 489-496.
105. Freitag L, Firusian N, Stamatis G, Greschuchna D. The role of bronchoscopy in pulmonary complications due to mustard gas inhalation. *Chest.* 1991;100:1436-1441.
106. Gilchrist HL. *A Comparative Study of World War Casualties From Gas and Other Weapons.* Washington, DC: Government Printing Office; 1928.
107. Beebe GW. Lung cancer in World War I veterans: Possible relation to mustard-gas injury and 1918 influenza epidemic. *J Natl Cancer Inst.* 1960;25:1231-1252.

108. Winternitz MC. Anatomical changes in the respiratory tract initiated by irritating gases. *Milit Surg.* 1919;44:476-493.
109. Rimm WR, Bahn CF. Vesicant injury to the eye. In: *Proceedings of the Vesicant Workshop.* Aberdeen Proving Ground, Md: US Army Medical Research Institute of Chemical Defense; 1987.
110. Hughes WF Jr. Mustard gas injuries to the eyes. *Arch Ophthalmol.* 1942;27:582-601.
111. Blodi FC. Mustard gas keratopathy. *Int Ophthalmol Clin.* 1971;2:1-13.
112. Duke-Elder WS, MacFaul PA. Chemical injuries. In: Duke-Elder WS, MacFaul PA, eds. *System of Ophthalmology.* St. Louis, Mo: CV Mosby; 1994.
113. Duke-Elder WS, MacFaul PA. *System of Ophthalmology.* St. Louis, Mo: CV Mosby; 1972.
114. Otto CE. *A Preliminary Report on the Ocular Action of Dichlorethyl Sulfide (Mustard Gas) in Man as Seen at Edgewood Arsenal, Edgewood, Maryland.* Edgewood Arsenal, Md: Chemical Warfare Service; 1946. EAL 539.
115. Novick M, Gard DH, Hardy SB, Spira M. Burn scar carcinoma: A review and analysis of 46 cases. *J Trauma.* 1977;17:809-817.
116. Treves N, Pack GT. Development of cancer in burn scars: analysis and report of 34 cases. *Surg Gynecol Obstet.* 1930;51:749-782.
117. Inada S, Hiragun K, Seo K, Yamura T. Multiple Bowen's disease observed in former workers of a poison gas factory in Japan with special reference to mustard gas exposure. *J Dermatol.* 1978;5:49-60.
118. US Army, US Navy, and US Air Force. Vesicants (blister agents). Section I—Mustard and nitrogen mustard. In: *NATO Handbook on the Medical Aspects of NBC Defensive Operations.* Washington, DC: US Army, US Navy, US Air Force; 1973. AMedP-6.
119. Anslow WP, Houch CR. Systemic pharmacology and pathology of sulfur and nitrogen mustards. In: *Chemical Warfare Agents and Related Chemical Problems.* Washington, DC: Office of Scientific Research and Development; 1946.
120. Lohs K. *Delayed Toxic Effects of Chemical Warfare Agents.* Stockholm, Sweden: Almqvist & Wiksell; 1979. SIPRI monograph.
121. Lawley PD, Lethbridge JH, Edwards PA, Shooter KV. Inactivation of bacteriophage T7 by mono- and difunctional sulphur mustards in relation to crosslinking and depurination of bacteriophage DNA. *J Mol Biol.* 1969;39:181-198.
122. Flamm WG, Bernheim NJ, Fishbein L. On the existence of intrastrand crosslinks in DNA alkylated with sulfur mustard. *Biochim Biophys Acta.* 1970;224:657-659.
123. Fox M, Scott D. The genetic toxicology of nitrogen and sulphur mustard. *Mutat Res.* 1980;75:131-168.
124. Scott D, Fox M, Fox BW. The relationship between chromosomal aberrations, survival and DNA repair in tumor cell lines of differential sensitivity to X-rays and sulphur mustard. *Mutat Res.* 1974;22:207-221.
125. Wulf HC, Aasted A, Darre E, Neibuhr E. Sister chromatid exchanges in fishermen exposed to leaking mustard gas shells. *Lancet.* 1985;1:690-691.
126. Sasser LB, Miller RA, Kalkwarf DR, Buschbom RL, Cushing JA. *Toxicology Studies on Lewisite and Sulfur Mustard Agents: Two-Generation Reproduction Study of Sulfur Mustard (HD) in Rats.* Richland, Wash: Pacific Northwest Laboratory; 1989.

Chapter 11

INCAPACITATING AGENTS

JAMES S. KETCHUM, M.D., ABPN*[†]; AND FREDERICK R. SIDELL, M.D.[†]

INTRODUCTION

USE OF INCAPACITATING AGENTS

Historical Precedents

Contemporary Use

POSSIBLE APPROACHES TO INCAPACITATION

Nonchemical Agents

Chemical and Biological Warfare Agents

Psychochemical Agents

THE ANTICHOLINERGICS AS CANDIDATE INCAPACITATING AGENTS

General Characteristics of Anticholinergics

The Most Likely Candidate: BZ or a Related Glycolate

Clinical Pharmacology of BZ

Anticholinergic Delirium Produced by BZ

DIAGNOSIS OF INCAPACITATING AGENT SYNDROMES

MEDICAL MANAGEMENT

BZ and Other Anticholinergics

LSD, Other Indoles, and Phenethylamine Derivatives

Opioids

SUMMARY

* Colonel, Medical Corps, U.S. Army (Ret); Assistant Clinical Professor, Department of Psychiatry, University of California at Los Angeles, Los Angeles, California 90024

[†]Formerly, Chief, Chemical Casualty Care Office, and Director, Medical Management of Chemical Casualties Course, U.S. Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, Maryland 21010-5425; currently, Chemical Casualty Consultant, 14 Brooks Road, Bel Air, Maryland 21014

INTRODUCTION

As defined in *The American Heritage Dictionary of the English Language*, to “incapacitate” means “to deprive of strength or ability.” The word is not synonymous with paralysis, confusion, or any other specific affliction. It is a general term, implying neither global inability to act nor any particular type of disability. For example, blurred near vision might be incapacitating for a computer programmer or air traffic controller but probably

REFERENCES

1. Goodman E. *The Descriptive Toxicology of Atropine*. Edgewood Arsenal, Md. Unpublished manuscript, 1961.
2. Frontinus SJ; Bennet CH, trans. *The Strategems*. London, England: William Heinemann; 1925. Quoted in: Goodman E. *The Descriptive Toxicology of Atropine*. Edgewood Arsenal, Md. Unpublished manuscript, 1961.
3. Buchanan G; Watkins J, trans. *The History of Scotland*. London, England: Henry Fisher, Son, and P. Jackson; 1831. Cited in: Goodman E. *The Descriptive Toxicology of Atropine*. Edgewood Arsenal, Md. Unpublished manuscript, 1961.
4. Lewin L. *Die Gifte in der Weltgeschichte*. Berlin, Germany: Julius Springer; 1920: 537–538. Cited in: Goodman E. *The Descriptive Toxicology of Atropine*. Edgewood Arsenal, Md. Unpublished manuscript, 1961.
5. Mitchel TD. *Materia Medica and Therapeutics*. 2nd ed. Philadelphia, Pa: JB Lippincott; 1857: 233. Cited in: Goodman E. *The Descriptive Toxicology of Atropine*. Edgewood Arsenal, Md. Unpublished manuscript, 1961.
6. Gaultier M, trans. Narrative of the poisoning of one hundred and eighty persons by the berries of belladonna. *Medical and Physical Journal* (London). 1814;32:390–393. Cited in: Goodman E. *The Descriptive Toxicology of Atropine*. Edgewood Arsenal, Md. Unpublished manuscript, 1961.
7. Leder R. *Sahara*. Garden City, NY: Hanover House; 1954: pp 151 ff. Cited in: Goodman E. *The Descriptive Toxicology of Atropine*. Edgewood Arsenal, Md. Unpublished manuscript, 1961.
8. Skolle J. *Azalei*. New York, NY: Harper and Brother; 1956: pp 22 ff. Cited in: Goodman E. *The Descriptive Toxicology of Atropine*. Edgewood Arsenal, Md. Unpublished manuscript, 1961.
9. Cornewin C. *Des Plantes Veneneuses*. Paris, France: Librairie de Firmin-Didot et Cit; 1893: 473. Cited in: Goodman E. *The Descriptive Toxicology of Atropine*. Edgewood Arsenal, Md. Unpublished manuscript, 1961.
10. Lewin L. *Gifte und Vergiftungen*. Berlin, Germany: Georg Stilke; 1929: 809. Cited in: Goodman E. *The Descriptive Toxicology of Atropine*. Edgewood Arsenal, Md. Unpublished manuscript, 1961.
11. *The Times*. London, England: 3 July 1908:8; 9 July 1908:7. Cited in: Goodman E. *The Descriptive Toxicology of Atropine*. Edgewood Arsenal, Md. Unpublished manuscript, 1961.
12. *Newsweek*. 28 Dec 1959;54(26):27. Cited in: Goodman E. *The Descriptive Toxicology of Atropine*. Edgewood Arsenal, Md. Unpublished manuscript, 1961.
13. *US News and World Report*. 28 Dec 1959;47(26):10. Cited in: Goodman E. *The Descriptive Toxicology of Atropine*. Edgewood Arsenal, Md. Unpublished manuscript, 1961.
14. Ketchum JS. Effects of secobarbital on time estimation performance. Edgewood Arsenal, Md; 1962. Unpublished study.
15. Simon EJ, Hiller JM, Edelman I. Stereospecific binding of the potent narcotic analgesic (3H) etorphine to rat-brain homogenate. *Proc Natl Acad Sci USA*. 1973;70:1947–1949.
16. Sim VM. *Clinical Investigation of EA 1729*. Edgewood Arsenal, Md: Chemical Research and Development Laboratory; 1961. CRDL Technical Report 3074.
17. Ketchum JS, Aghajanian GK, Bing O. *The Human Assessment of EA 1729 and EA 3528 by the Inhalation Route*. Edgewood Arsenal, Md: Chemical Research and Development Laboratory; 1964. CRDL Technical Report 3226.

18. West LJ, Pierce CM, Thomas WD. Lysergic acid diethylamide: Its effects on a male Asiatic elephant. *Science*. 1962;138(3545):1100-1103.
19. Buckman J. Senior Medical Officer, Marlborough Day Hospital, St. John's Wood, London, England. Personal communication, July 1965.
20. Leib G. Captain, Medical Corps, US Army. Clinical Research Department, Medical Research Laboratory, Edgewood Arsenal, Md. Personal communication, 1968.
21. Shulgin A, Shulgin A. *PIHKAL: A Chemical Love Story*. Berkeley, Calif: Transform Press; 1991.
22. Sircar R, Zukin SR. Characterization of specific sigma opiate/phencyclidine (PCP)-binding sites in the human brain. *Life Sci*. 1983;33(suppl 1):259-262.
23. Wolff HG, Curran D. Nature of delirium and allied states: Dysergastic reaction. *Arch Neurol Psychiatr*. 1935;33:1175-1215.
24. Ketchum JS, Kitzes D, Mershon M, et al. *The Human Assessment of EA 3443*. Edgewood Arsenal, Md: 1967. Edgewood Arsenal Technical Report 4066.
25. Waelbroeck M, Tasknoy M, Camus J, Christophe J. Binding kinetics of quinuclidinyl benzilate and methyl quinuclidinyl benzilate enantiomers at neuronal (M1), cardiac (M2), and pancreatic (M3) muscarinic receptors. *Mol Pharmacol*. 1991;40:413-420.
26. Ketchum JS. Incapacitating compounds. In: *Proceedings of the 1st Meeting of the Quadripartite Standing Working Group on Chemical Warfare*. Edgewood Arsenal, Md: Chemical Research and Development Laboratory; 1965.
27. Innes IR, Nickerson M. Drugs inhibiting the action of acetylcholine on structures innervated by postganglionic parasympathetic nerves (antimuscarinic or atropinic drugs). In: Goodman LS, Gilman A, eds. *The Pharmacological Basis of Therapeutics*. 3rd ed. New York, NY: Macmillan; 1965: 521-545.
28. Bliss CI. *The Statistics of Bioassay*. New York, NY: Academic Press; 1952.
29. Yamamura HI, Kuhar MJ, Snyder SH. In vivo identification of muscarinic cholinergic receptor binding in rat brain. *Brain Res*. 1974;80:170-176.
30. Yamamura HI, Snyder SH. Muscarinic cholinergic receptor binding in the longitudinal muscle of the guinea pig ileum with [3H] quinuclidinyl benzilate. *Mol Pharmacol*. 1974;10:861-867.
31. Ketchum JS. *The Human Assessment of BZ*. Edgewood Arsenal, Md: Chemical Research and Development Laboratory; 1963. Technical Memorandum 20-29.
32. Moran LJ, Mefferd RB. Repetitive psychometric measures. *Psychol Rep*. 1959;3:209-275.
33. Kitzes DL, Vancil ME. *Estimate of Minimal Effective Doses of BZ by the Intramuscular Route in Man*. Edgewood Arsenal, Md: Chemical Research and Development Laboratory; 1965. Technical Memorandum 2-30.
34. Aghajanian GK, Bing OH. Persistence of lysergic acid diethylamide in the plasma of human subjects. *Clin Pharmacol Ther*. 1964;5:611-614.
35. Kleinwachter I. Observations concerning the effectiveness of extract of Calabar against atropine poisoning. *Berl klin Wschr*. 1864;1:369-377.
36. Forrer GR, Miller JJ. Atropine coma: A somatic therapy in psychiatry. *Am J Psychiatry*. 1958;115:455-458.
37. Forrer GR. Atropine toxicity in the treatment of schizophrenia. *Journal of the Michigan State Medical Society*. 1950;49:184-185.

38. Crowell EB, Ketchum JS. The treatment of scopolamine induced delirium with physostigmine. *Clin Pharmacol Ther.* 1967;8:409-414.
39. Ketchum JS, Sidell FR, Crowell EB, Aghajanian GK, Hayes AH. Atropine, scopolamine, and Ditrán: Comparative pharmacology and antagonists in man. *Psychopharmacologia.* 1973;28:121-145.
40. Bell C, Gershon S, Carroll B, Holan G. Behavioural antagonism to a new psychotomimetic: JB-329. *Arch Intern Pharmacodyn Ther.* 1964;147:9-25.
41. Kitzes DL, Ketchum JS, Weimer JT, Farrand RL. *The Human Assessment of EA 3580 by the Aerosol Route.* Edgewood Arsenal, Md; 1967. Edgewood Arsenal Technical Report 4041.
42. Ketchum JS, Kitzes D, Copelan H. *Effects of EA 3167 in Man.* Edgewood Arsenal, Md; 1973. Edgewood Arsenal Technical Report 4713.
43. McCarroll E, Markis J, Ketchum JS, Houff W, Sim VM. Effects on Performance of the Administration of EA 3834 to Members of a Small Infantry Element Under Simulated Combat Conditions. Edgewood Arsenal, Md; 1971. Edgewood Arsenal Technical Report 4633.
44. Duvoisin RC, Katz R. Reversal of central anticholinergic syndrome. *JAMA.* 1968;206:1963.
45. Heiser JF, Gillin JC. The reversal of anticholinergic drug-induced delirium and coma with physostigmine. *Amer J Psychiatry.* 1971;127:1050.
46. Sidell FR. *Use of Physostigmine by the Intravenous, Intramuscular, and Oral Routes in the Therapy of Anticholinergic Drug Intoxication.* Biomedical Laboratory, Edgewood Arsenal, Md; 1976. EB-TR-76-12.
47. Ghoneim MM. Antagonism of diazepam by physostigmine. *Anesthesiology.* 1980;54:372.
48. Rumack BH. Anticholinergic poisoning: Treatment with physostigmine. *Pediatrics.* 1973;52:449-451.
49. Daunderer M. Physostigmine salicylate as an antidote. *Int J Clin Pharmacol Ther Toxicol.* 1980;18:523-535.
50. Directorate of Medical Research. *Guide to the Management of BZ Casualties, I.* Edgewood Arsenal, Md; 1965.
51. Ketchum JS, Tharp B, Crowell E, Sawhill D, Vancil M. *The Human Assessment of BZ Disseminated Under Field Conditions.* Edgewood Arsenal, Md; 1967. Edgewood Arsenal Technical Report 4140.
52. Sidell FR, Aghajanian GK, Groff WA. The reversal of anticholinergic intoxication in man with the cholinesterase inhibitor VX. *Proc Soc Exp Biol Med.* 1973;144:725-730.
53. Lipka LJ, Lathera CM. Psychoactive agents, seizure production, and sudden death in epilepsy. *J Clin Pharmacol.* 1987;27:169-183.
54. Aghajanian GK, Bing O. 1963. Unpublished report. Cited in: Ketchum JS. Incapacitating compounds. In: *Proceedings of 1st Meeting of the Quadripartite Standing Working Group on Chemical Warfare.* Edgewood Arsenal, Md; 1965.
55. Freedman DX. Chairman and Professor of Psychiatry and Pharmacology, University of Chicago Medical School, Chicago, Ill. Personal communication, 1973.
56. Wikler A. Characteristics of opioid addiction. In: Jarvik ME, ed. *Psychopharmacology in the Practice of Medicine.* New York, NY: Appleton-Century-Crofts; 1977: 419-432.