12 RESEARCH NEEDS

Most of the investigations on the effects of ethyl ether on humans concern its use as an anesthetic agent. More information is needed about the effects on humans of industrial exposure to low concentrations of ethyl ether vapor, especially effects on the upper respiratory passages and the CNS. Additional studies on the effects of long-term inhalation of ethyl ether are needed to evaluate chronic toxicity. There is also a need for more studies on possible teratogenic, carcinogenic, and genotoxic effects of ethyl ether exposure. The effects on the kidneys of long-term industrial exposure to ethyl ether in air should be reevaluated. In the older literature, a few case reports describe the development of nephritis but this effect has later been questioned.

13 DISCUSSION AND EVALUATION

The principal exposure routes to ethyl ether in the occupational situation are inhalation and skin contact. Inhalation of ethyl ether vapor causes irritation to the mucous membranes of the nose and respiratory passages. Liquid ethyl ether is a mild skin irritant due to its defatting properties and repeated exposure may cause dermatitis. Inhalation of ethyl ether has effects on the CNS. Acute exposure to high concentrations of ethyl ether vapor produces initial excitement followed by narcosis and respiratory depression. Long-term exposure to low concentrations of ethyl ether vapor in industry has been reported to cause various symptoms from the CNS such as sleepiness, dizziness, excitation, headache, and psychic disturbances. Ethyl ether causes conjunctival irritation in either liquid form or high concentrations in the air. Ethyl ether anesthesia causes an increase in plasma catecholamines which leads to a mobilization of glycogen from the liver and muscle tissue and a rise in blood sugar.

Investigations of possible mutagenic or carcinogenic effects of ethyl ether have shown negative results. The number of these studies is limited, however.

The irritating effects of ethyl ether vapor on the upper respiratory passages is the critical effect which should be taken into consideration in the establishment of an occupational exposure limit for ethyl ether. Complaints of nasal irritation have been reported to start at 200 ppm (616 mg/m^3) of ethyl ether in air. The effects of low concentrations of ethyl ether vapor on the CNS should also be given attention. During the manufacture of smokeless powder, concentrations of 2,000 to 3,000 ppm (6,160 to 9,240 mg/m³) may occur. These concentrations have been reported to cause dizziness in some individuals with increased likelihood of industrial accidents.

The majority of inhaled ethyl ether (87-90%) is excreted unchanged through the lungs. A fraction of ethyl ether is metabolized to ethanol and acetaldehyde by an inducible hepatic microsomal enyme system. Ethanol and acetaldehyde are oxidized to acetate and the acetate then enters the 2-carbon pool of intermediary metabolism.

14 SUMMARY

Björn Arvidson: Ethyl ether. Nordic Expert Group for Documentation of Occupational Exposure Limits, NIOH and NIOSH Basis for an Occupational Health Standard.

A survey of the literature relevant to the discussion of occupational exposure limits for ethyl ether is presented. Ethyl ether has a wide range of uses in the chemical industry. It is used mainly as a solvent and as an extraction medium. Ethyl ether has been used as an inhalation anesthetic for surgery but to a large extent has now been replaced by more modern anesthetics. The acute and chronic toxicity of ethyl ether is low. The principal exposure routes to ethyl ether in the occupational situation are inhalation and skin contact. The critical effect of ethyl ether is irritation of the upper respiratory passages. Long-term exposure to low concentrations of ethyl ether in air may give symptoms from the CNS. Symptoms that have been reported are sleepiness, dizziness, irritability, headache, and psychic disturbances. Ethyl ether is a mild skin irritant, especially after repeated exposures.

Key words: Ethyl ether, occupational exposure limits, solvents, anesthetics.

15 SAMMANFATTNING

Björn Arvidson: Etyleter. Nordiska Expertgruppen för Gränsvärdesdokumentation, NIOH and NIOSH Basis for an Occupational Health Standard.

En litteraturgenomgång har gjorts för att få fram ett underlag till diskussionen kring ett hygieniskt gränsvärde för etyleter. Inom den kemiska industrin används etyleter främst som ett lösningsmedel och ett extraktionsmedel. Etyleter har tidigare använts som narkosmedel i samband med kirurgiska operationer men har nu i stor utsträckning ersatts av modernare medel. Den akuta och kroniska toxiciteten för etyleter är låg. Vid industriell använding är exponeringsvägarna främst inhalation och hudkontakt. Den kritiska effekten för etyleter är irritation av slemhinnor inom de övre luftvägarna. Längre tids exponering för låga halter av etyleter i luft kan ge symtom från det centrala nervsystemet i form av trötthet, yrsel, irritabilitet, huvudvärk, och psykiska störningar. Etyleter i flytande form ger uttorkning av huden, speciellt efter upprepad kontakt.

Nyckelord: Etyleter, hygieniskt gränsvärde, anestesimedel, lösningsmedel.

16 REFERENCES

- 1. Abt JP, Essman WB, Jarvik ME. Ether-induced retrograde amnesia for one-trial conditioning in mice. Science 133 (1961) 1477-1478.
- 2. ACGIH. Documentation of the threshold limit values. American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio (1971) 106.

- 3. Adriani J. The chemistry and physics of anesthesia. Charles C. Thomas, Springfield, Illinois, USA (1962) 287-294.
- 4. Alpern HP, Kimble DP. Retrograde amnesic effects of diethyl ether and bis (trifluoroethyl) ether. J Comp Physiol Psychol 63 (1967) 168-171.
- 5. Amor AA. The toxicity of solvents. Paint Manufacture 20 (1950) 53-58.
- 6. Andrews E, Potter RM, Friedemann TE, Livingstone HM. Determination of ethyl ether in blood. J Lab Clin Med 25 (1940) 966-970.
- 7. Anonymous. Chemical safety data sheet SD-29, ethyl ether. Manufacturing Chemists Association, Inc. Washington, DC (1965).
- 8. Anonymous. Ethyl ether. Hygienic Guide Series, American Industrial Hygiene Association (1978).
- 9. Aune H, Olsen H, Morland J. Diethyl ether influence on the metabolism of antipyrine, paracetamol and sulphanilamide in isolated rat hepatocytes. Br J Anaesth 53 (1981) 621-626.
- Aune H, Hals P-A, Hansen BI, Aarbakke J. Effect of diethyl ether on the formation of paracetamol sulphate and glucuronide in isolated rat hepatocytes. Pharmacology 28 (1984) 67-73.
- Aviado DM. Regulation of bronchomotor tone during anesthesia. Anesthesiology 42 (1975) 68-80.
- 12. Baden JM, Simmon VF. Mutagenic effects of inhalational anesthetics. Mutat Res 75 (1980) 169-189.
- 13. Baekeland F, Greene NM. Effect of diethyl ether on tissue distribution and metabolism of pentobarbital in rats. Anesthesiology 19 (1958) 724-732.
- Bajaj P, Agarwal M, Vora YC. Effect of diethyl ether, halothane and trichloroethylene on coagulation power of blood. Asian Arch Anaesthesiol Resusc 24 (1986) 7-13.
- 15. Barrett JD, Eggena P, Krall JF. Independent change of plasma and tissue renin in response to anesthetics. Clin Exp Hypertens A10 (1988) 757-765.
- 16. Bartholomew AA. Two cases of ether addiction/habituation. Med J Austr 49 (1962) 550-553.

- 17. Baselt RC. Biological monitoring methods for industrial chemicals. Biomedical Publications, Davis, California (1980) 134-136.
- 18. Bean BP, Shrager P, Goldstein DA. Modification of sodium and potassium channel gating kinetics by ether and halothane. J Gen Physiol 77 (1981) 233-253.
- 19. Bessesen A, Smith-Kielland A, Gadeholt G, Mörland J. Reduced synthesis of hepatic and plasma proteins in rats during diethyl ether anaesthesia. Acta Pharmacol Toxicol 54 (1984) 241-246.
- 20. Bessesen A, Mörland J. Effects of anaesthetics on protein synthesis in isolated rat hepatocytes: Inhibition by diethyl ether in contrast to no influence by pentobarbital and fentanyl. Acta Pharmacol Toxicol 57 (1985) 23-29.
- 21. Black GW, McArdle L, McCullough H, Unni VKN. Circulatory catecholamines and some cardiovascular, respiratory, metabolic and pupillary responses during diethyl ether anesthesia. Anesthesia 24 (1969) 168-176.
- 22. Boissier JR, Gindicelli JF, Advemier C, et al. Sur le mechanisme de línteraction ether-propranolol au niveau des bronches. Therapie 25 (1970) 523-538.
- 23. Bourne W. On the effects of acetaldehyde, ether peroxide, ethyl mercaptan, ethyl sulphide and several ketones, when added to anaesthetic ether. J Pharmacol Exp Ther 28 (1926) 409-432.
- 24. Brady JF, Lee MJ, Li M, Ishizaki H, Yang CS. Diethyl ether as a substrate for acetone/ethanol-inducible cytochrome P-450 and as an inducer for cytochrome P-450. Molecular Pharmacol 33 (1988) 148-154.
- 25. Brandom BW. Pain control with general and local anesthetics. In: Wingard LB, Brody TM, Larner J, Schwartz A (eds). Human Pharmacology. Molecular to Clinical. Wolfe Publishing Ltd, London (1991) 413-433.
- 26. Brewster WR, Isaacs JP, Wainö-Andersen T. Depressant effects of ether on myocardium of the dog and its modification by reflex release of epinephrine and norepinephrine. Amer J Physiol 75 (1953) 399-406.
- 27. Brown BR, Sagalyn AM. Hepatic microsomal enzyme induction by inhalation anesthetics: mechanism in the rat. Anesthesiology 40 (1974) 152-161.
- 28. Browning E. Toxicity and metabolism of industrial solvents. Elsevier, New York (1965) 493-521.
- 29. Burnett HW, Levine B, Smyth D. An unfortunate complication of self-therapy for seborrheic dermatitis. Cutis 41 (1988) 284.

- 30. Campbell JE. Deaths associated with anesthesia. J For Sci 5 (1960) 501-549.
- 31. Carroll J, Kirwin JR, Sandmeyer E. Ethers. In: Clayton GD, Clayton FE (eds). Patty's industrial hygiene and toxicology, Vol. 2. John C. Wiley and Sons, New York, USA (1982) 2491-2565.
- 32. Chengelis CP, Neal RA. Microsomal metabolism of diethyl ether. Biochem Pharmacol 29 (1980) 247-248.
- Chenoweth MB, Robertson DN, Erley DS, Golhke R. Blood and tissue levels of ether, chloroform, halothane and methoxyflurane in dogs. Anesthesiology 23 (1962) 101-106.
- 34. Cohen EN, Hood N. Application of low-temperature autoradiography to studies of the uptake and metabolism of volatile anesthetics in the mouse: II. diethyl ether. Anesthesiology 31 (1969) 61-68.
- 35. Coleman AJ. Inhalation anaesthetic agents. In: Churchill-Davidson HC (ed). A practice of anaesthesia. Lloyd-Luke Medical Books Ltd, London (1984) 167-222.
- 36. Cook WA. Maximum allowable concentrations of industrial atmospheric contaminants. Ind Med 14 (1945) 936-945.
- 37. Dawson B, Adson MA, Dockerty MB, Fleisher GA, Jones RR, Hartridge VB, Schnelle N, McGuckin WF, Summerskill WHJ. Hepatic function tests: postoperative changes with halothane or diethyl ether anesthesia. Mayo Clin Proc 41 (1966) 599-607.
- 38. De Flora S, Zanacchi P, Camoirano A, Bennicelli C, Badolati G. Genotoxic activity and potency of 135 compounds in the Ames reversion test and in a bacterial DNA-repair test. Mutat Res 133 (1984) 161-198.
- 39. Dills RL, Klaassen CD. Decreased glucuronidation of bilirubin by diethyl ether anesthesia. Biochem Pharmacol 33 (1984) 2813-2814.
- 40. Dundee JW, McCaughey W. Drugs in anesthetic practice. In: Avery GS (ed). Drug Treatment. Principles and Practice of Clinical Pharmacology and Therapeutics. Adis Press, Sydney and New York (1980) 282-334.
- 41. Dybing F, Dybing O. Ether concentration in blood and brain in the early stages of ether narcosis. Acta Pharmacol Toxicol 1 (1945) 270-279.
- 42. Dybing F, Dybing O. Ether concentration in brain, blood and muscles during ether elimination. Acta Pharmacol Toxicol 4 (1948) 164-168.

- 43. Dybing O, Skovlund K. Ether in fatty tissue during ether absorption and elimination. Acta Pharmacol Toxicol 13 (1957) 252-255.
- 44. Eger EI, Shargel R, Merkel G. Solubility of diethyl ether in water, blood and oil. Anesthesiology 24 (1963) 676-684.
- 45. Eriksson G, Stråth D. Decreased UDP-glucuronic acid in rat liver after ether narcosis. FEBS Lett 124 (1981) 39-42.
- 46. Fluck ER, Poirier LA, Ruelius HW. Evaluation of a DNA polymerase-deficient mutant of E. coli for the rapid detection of carcinogens. Chem-Biol Interact 15 (1976) 219-231.
- 47. Flury F, Klimmer O. Ethers. In: Lehmann KB, Flury F (eds). Toxicology and Hygiene of Industrial Solvents. Williams and Wilkins, Baltimore USA (1943) 248-253.
- 48. Franks NP, Lieb WR. Molecular mechanisms of general anaesthesia. Nature 300 (1982) 487-493.
- Gamo S, Megumi T, Satoh Y, Nakashima-Tanaka E. Opposing effects between 60 Co gamma-irradiation damage and ether anesthesia in anesthetic-resistant strain of Drosophila melanogaster: Evidences in chromosomal analysis. Jpn J Genet 61 (1986) 315-328.
- 50. Gamo S, Megumi T, Nakashima-Tanaka E. Sensitivity to ether anesthesia and to gamma-rays in mutagen-sensitive strains of Drosophila melanogaster. Mutat Res 235 (1990) 9-13.
- 51. Gattegno B, Michel F, Thibault P. A serious complication of vesical ether instillation: ether cystitis. J Urol 139 (1988) 357-358.
- 52. Geldmacher-v Mallinckrodt, M. Forensische Toxikologie. In: Mueller, B (ed). Gerichtliche Medizin. Springer, Berlin, Heidelberg, New York (1975) 1037-1038.
- 53. Gordon AJ, Ford RA. Detection of peroxides and their removal. In: The chemists companion, Wiley-Interscience, New York (1972) p. 437.
- 54. Grant WM. Toxicology of the eye. Charles C. Thomas Publisher, Springfield, Illinois USA (1974) 464-465.
- 55. Gréen K, Cohen EN. On the metabolism of ¹⁴C-diethyl ether in the mouse. Biochem Pharmacol 20 (1971) 393-399.
- 56. Grigoriew I. Gigiena Truda 11 (1924) 86-90.

30

- 57. Gross EG, Cullen SC. The effect of anesthetic agents on muscular contraction. J Pharmacol Exp Ther 78 (1943) 358-366.
- 58. Grossman Y, Kendig JJ. General anesthetic block of a bifurcating axon. Brain Res 245 (1982) 148-153.
- 59. Guedel AE. Inhalation anesthesia. A fundamental guide. The Macmillan Company, New York USA 1952.
- 60. Guinan ME, MacCalman J, Kern ER, Overall JC, Spruance, SL. Topical ether and herpes simplex labialis. JAMA 243 (1980) 1059-1061.
- 61. Haggard HW. The absorption, distribution and elimination of ethyl ether. J Biol Chem 59 (1924) 737-751.
- 62. Haleem S, Ansari MM, Shakoor A, Bano S. Prospective study of changes in serum calcium after diethyl-ether anaesthesia. Indian J Med Res (B) 92 (1990) 192-194.
- 63. Halsey MJ. Molecular mechanisms of anaesthesia. In: Nunn JF, Utting JE, Brown BR (eds). General Anaesthesia, Butterworths, London (1989) 19-29.
- 64. Hamilton A. Industrial poisons in the U.S. Macmillan, New York, USA 1925.
- 65. Hamilton A, Minot GR. Ether poisoning in the manufacture of smokeless powder. J Ind Hyg 2 (1920) 41-49.
- 66. Hammond WG, Vandam LD, Davis JM, Carter RD, Ball MR, Moore FD. Studies in surgical endocrinology. IV. Anesthetic agents as stimuli to change in corticosteroids and metabolism. Ann Surg 148 (1958) 199-208.
- 67. Hashimoto K, Murakami K, Takao T, Makino S, Sugawara M, Ota Z. Effect of acute ether or restraint stress on plasma corticotropin-releasing hormone, vasopressin and oxytocin levels in the rat. Acta Med Okayama 43 (1989) 161-167.
- 68. Hayhursth, EK. Ether. In: Occupation and health. Encyclopedia of hygiene, pathology and social welfare. International Labour Office, Geneva Switzerland (1930) 684-691.
- 69. Henderson Y, Haggard HW. Noxious gases. Rheinhold Publishing Corporation, New York, USA (1943) 194-195.
- 70. Hirsch J, Kappus AL. On the quantities of anesthetic ether in the air of operating rooms. Z Hyg 110 (1929) 391-398 (Ger).

- 71. Hobara N, Watanabe A, Nagashima H. Effect of various central nervous systemacting drugs on ethanol and acetaldehyde metabolism in rats. Pharmacology 30 (1985) 333-338.
- 72. Industrial Solvents Handbook. Flick E (ed). Noyes Data Corporation, Park Ridge, NJ, USA (1991) 514.
- 73. Johannessen W, Gadeholt G, Aarbakke J. Effects of diethyl ether anaesthesia on the pharmacokinetics of antipyrine and paracetamol in the rat. J Pharm Pharmacol 33 (1981) 365-368.
- 74. Jubert AV, Lee ET, Hersh EM, McBride CM. Effects of surgery, anesthesia and intraoperative blood loss on immunocompetence. J Surg Res 15 (1973) 399-403.
- 75. Kang YG, Nemotot EM, Bleyaert AL, Winter PM, Eidelman BH, Taylor FH. Mechanisms of cerebrovascular dilation by ether in monkeys. J Cerebral Blood Flow Metab 7 (1987) 230-236.
- 76. Kaplan AS, Vatter AE. A comparison of herpes simplex and pseudorabies virus. Virology 7 (1959) 394-407.
- 77. Karis JH, Gissen AJ, Nastuk WL. Mode of action of diethyl ether in blocking neuromuscular transmission. Anesthesiology 27 (1966) 42-51.
- 78. Karteszi M, Makara GB, Stark E. The rise of plasma ACTH induced by ether is mediated through neural pathways entering the medial basal hypothalamus. Acta Endocrinol 93 (1980) 129-133.
- 79. Keefer LK, Garland WA, Oldfield NF, Swagzdis JE, Mico BA. Inhibition of N-nitrosodimethylamine metabolism in rats by ether anesthesia. Cancer Res 45 (1985) 5457-5460.
- 80. Keeley DE. Ethers. In: Kirk-Ohmer (ed). Encyclopedia of chemical technology, 3rd ed, Vol 9. Wiley-Interscience, New York, USA (1980) 381-393.
- 81. Kendig JJ, Courtney KR, Cohen EN. Anesthetics: molecular correlates of voltage and frequency dependent sodium channel block in nerve. J Pharmacol Exp Ther 210 (1979) 446-452.
- 82. Kidd P, Scales D, Inesi G. Structural and functional lability induced by diethyl ether on the sarcoplasmic reticulum membrane. Biochim Biophys Acta 645 (1981) 124-131.
- 83. Kimura ET, Ebert DM, Dodge PW. Acute toxicity and limits of solvent residue for sixteen organic solvents. Toxicol Appl Pharmacol 19 (1971) 699-704.

- 84. Knoefel PK, Murrell FC. The rate of production of anesthesia in mice by ether containing aldehyde and peroxide. J Pharmacol Exp Therap 55 (1935) 235-245.
- Kobayashi K. Strain differences of ether susceptiblity in mice. Exp Anim 54 (1985) 379-386
- 86. Kärber G, Lendle L. Untersuchungen uber kombinierte Narkosen. IV. Mitteliung: Die Narkosbreite der kombinierten Avertin-Äthernarkose im Tierversuch. Arch Exp Pathol Pharmakol 142 (1929) 1-16.
- 87. Lam C-W, Galen TJ, Boyd JF, Pierson DL. Mechanism of transport and distribution of organic solvents in blood. Toxicol Appl Pharmacol 104 (1990) 117-129.
- Land PC, Owen EL, Linde HW. Morphologic changes in mouse spermatozoa after exposure to inhalational anesthetics during early spermatogenesis. Anesthesiology 54 (1981) 53-56.
- 89. Langer P, Földes O, Brozmanová H, Geschwendtová K. Studies on the effect of pentobarbiturate, ether and heparin on plasma thyroxine level in rats. Endokrinologie 76 (1980) 309-314.
- 90. Larrabee MG, Posternak JM. Selective action of anesthetics on synapses and axons in mammalian sympathetic ganglia. J Neurophysiol 15 (1952) 91-114.
- 91. Lebowitz RL, Effman EL. Ether cystitis. Urology 12 (1978) 427-428.
- 92. Leichnitz K. Detector tube handbook. Air investigations and technical gas analysis with Dräger tubes. Drägerwerk Aktiengesellschaft, Lubeck Germany (1989) 76.
- 93. Leung LS. Differential effects of pentobarbital and ether on the synaptic transmission of the hippocampal CA1 region in the rat. Electroenc Clin Neurophysiol 51 (1981) 291-305.
- 94. Lieber CS. Mechanism of ethanol induced hepatic injury. Pharmac Ther 46 (1990) 1-41.
- 95. Markovic SN, Murasko DM. Anesthesia inhibits Poly I:C induced stimulation of natural killer cell cytotoxicity in mice. Clin Immunol Immunopathol 56 (1990) 202-209.
- 96. Martinez JL, Jensen RA, McGaugh JL. Attenuation of experimentally-induced amnesia. Prog Neurobiol 16 (1980) 155-186.
- 97. Matsuki A, Oyama T. The thyroid and anesthesia. In: Oyama T (ed). Endocrinology and the anesthetist. Elsevier, Amsterdam (1983) 65-79.

- 98. Millar RA, Morris ME. Sympatho-adrenal responses during general anesthesia in the dog and man. Can Anaesth Soc J 8 (1961) 356-386.
- 99. Moeschlin S. Klinik und Therapie der Vergiftungen. Georg Thieme Verlag. Stuttgart, New York (1986) 337.
- 100. Molitor H J. Some pharmacological and toxicological properties of vinyl ether. Pharmacol Exp Ther 57 (1936) 274-288.
- Moody EJ, Suzdak PD, Paul SM, Skolnick P. Modulation of the benzodiazepine/GABA receptor chloride channel complex by inhalation anesthetics. J Neurochem 51 (1988) 1386-1393.
- 102. Morgan TH. The failure of ether to produce mutations in Drosophila. Am Nat 48 (1914) 705-711.
- 103. Mörch ET, Aycrigg JB, Berger MS. The anaesthetic effects of ethyl vinyl ether, divinyl ether and diethyl ether on mice. J Pharmacol Exp Ther 117 (1956) 184-189.
- 104. Neill P, Sleigh JW. Ether does not antagonize bronchoconstriction caused by acetylcholine, histamine or phenylephrine. Anesth Analg 69 (1989) 226-228.
- 105. Nellans RE, Ellis LR, Kenny GM. Ether cystitis. JAMA 254 (1985) 530.
- 106. Nelson KW, Egwe JF, Ross M, Woodman LE, Silverman L. Sensory response to certain industrial solvent vapors. J Ind Hyg Toxicol 25 (1943) 282-285.
- 107. Ngai SH, Hanks EC, Farhie SE. Effects of anesthetics on neuromuscular transmission and somatic reflexes. Anesthesiology 26 (1965) 162-167.
- 108. Nico B, Ribatti D, Bertossi M, Mancini L, Roncali L. Ethyl-oxide effects on a newly formed blood-brain barrier. J Submicroscop Cutol Pathol 21 (1989) 535-541.
- 109. NIOSH. NIOSH manual of analytical methods, 3rd ed. DHHS (NIOSH) Publication No. 84-100. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, Ohio 1984.
- Normann PT, Ripel Å, Mörland J. Diethyl ether inhibits ethanol metabolism in vivo by interaction with alcohol dehydrogenase. Alcohol Clin Exp Res 11 (1987) 163-166.
- 111. Ogaki M, Nakashima-Tanaka E, Murakami S. Inheritance of ether resistance in Drosophila melanogaster. Jpn J Genet 42 (1967) 387-394.

- 112. Onchi Y, Asao Y. Absorption, distribution and elimination of diethyl ether in man. Br J Anesth 33 (1961) 544-548.
- 113. Oyama T. Endocrine responses to anaesthetic agents. Brit J Anaesth 45 (1973) 276-281.
- 114. Oyama T, Wakayama S. The endocrine responses to general anesthesia. International Anesthesiol Clin 26 (1988) 176-181.
- 115. Oyama T. Influence of anesthesia on the endocrine system. In: Stoeckel H, Oyama T (eds). Endocrinology in anaesthesia and surgery. Springer Verlag, Berlin (1980) 39-51.
- 116. Pasricha JS, Nayyasr KC, Pasricha A. A new method for treatment of herpes simplex. Arch Dermatol 107 (1973) 775-778.
- 117. Price HL, Price ML. Determination of diethyl ether in blood. Anesthesiology 17 (1956) 293-296.
- 118. Price HL. Circulatory actions of general anesthetic agents. Clin Pharmacol Ther 2 (1961) 163-168.
- 119. Price HL, Helrich M. The effect of cyclopropane, diethyl ether, nitrous oxide, thiopental, and hydrogen ion concentration on the myocardial function of the dog heart-lung preparation. J Pharmacol Exp Ther 115 (1955) 206-212.
- 120. Price ML. Sympatho-adrenal responses to general anesthesia in man and their relation to hemodynamics. Anesthesiology 20 (1959) 563-567.
- 121. Ramirez-Gonzalez MD, Barna I, Wiegant VM, de Jong W. Effect of anaesthetics on the release of beta-endorphin-immunoreactivity in rat plasma. Life Sci 48 (1991) 1371-1377.
- 122. Richards CD, White AE. The actions of volatile anesthetics on synaptic transmission in the dentate gyrus. J Physiol 252 (1975) 241-257.
- 123. Rittner C, Goebel K-J, Goenechea S. Tod eines Kleinkindes infölge Etherintoxikation. Arch Kriminal 173 (1984) 103-105 (Ger.).
- 124. Robbins BJ. Ether anesthesia-concentrations in inspired air and in blood required for anesthesia, loss of reflexes and death. J Pharmacol Exptl Therap 53 (1935) 251-263.
- 125. Robertson CE, Steedman D, Sinclair CJ, Brown D, Smith N. Use of ether in life threatening acute severe asthma. Lancet 1 (1985) 187-188.

- 126. Rosenthal S, Bourne W. The effect of anesthetics on hepatic function. JAMA 90 (1928) 377-379.
- 127. Ross WT Jr, Cardell RR Jr. Proliferation of smooth endoplasmic reticulum and induction of microsomal drug-metabolizing enzymes after ether or halothane. Anesthesiology 48 (1978) 325-331.
- 128. Roth SH. Physical mechanisms of anesthesia. Ann Rev Pharmacol Toxicol 19 (1979) 159-178.
- 129. Salama G, Scarpa A. Enhanced Ca²⁺ uptake and ATPase activity of sarcoplasmic reticulum in the presence of diethyl ether. J Biol Chem 255 (1980) 6525-6528.
- 130. Salo M. Effect of anaesthesia and surgery on the number of and mitogen-induced transformation of T- and B-lymphocytes. Ann Clin Res 10 (1978) 1-13.
- Sampson DA, Masor M, Jansen GR. Protein synthesis in rat tissues during lactation.
 No effect of diethyl ether anesthesia. Biochem J 224 (1984) 681-683.
- 132. Schwetz BA, Becker BA. Comparison of the lethality of inhaled diethyl ether in neonatal and adult rats. Toxicol Appl Pharmacol 18 (1971) 703-706.
- 133. Silverman L. Industrial air sampling and analysis. Industrial Hygiene Foundation, Pittsburgh USA 1947.
- 134. Skovsted P, Price HL. Central sympathetic excitation caused by diethyl ether. Anesthesiology 32 (1970) 202-209.
- 135. Smith BE, Gaub ML, Lehrer SB. Teratogenic effects of diethyl ether in the chick embryo. In: Fink BR (ed). Toxicity of anesthetics. Williams & Wilkins (1968) 269-278.
- 136. Smith BS, Zenz C. In: Zenz C (ed). Occupational medicine. Principles and practical applications. Year Book Medical Publishers, Inc., Chicago, USA (1988) 729-730.
- 137. Smith DC, Oster RH, Snyder L, Proutt LM. Immediate effects of ether and nembutal upon some of the blood components in the cat. Am J Physiol 152 (1949) 6-10.
- 138. Smyth HF, Carpenter CP, Carrol S, Weil MA, Pozzani UC, Striegel JA. Rangefinding toxicity data. List VI. Amer Ind Hyg Assoc J 23 (1962) 95-107.

- 139. Spector WS. Handbook of toxicology, Vol. I, Saunders, Philadelphia. 1956.
- 140. Stahl WH. ASTM data series DS48, American Society for Testing and Materials, Philadelphia, USA 1973.
- 141. Stanek KA, Davis MH, Coleman TG. Residual effects of ether anesthesia on whole-body hemodynamics and organ blood flows in the rat. J Pharmacol Methods 20 (1988) 95-102.
- 142. Stefanovic J, Starsia Z, Murgasova I, Absolonova O. In vitro effects of organic solvents on immunity indicators in serum. J Hyg Epidem Microbiol Immunol 31 (1987) 1-7.
- 143. Stevens WC, Eger EI, White A, Halsey MJ, Munger W, Gibbons RD, Dolan W, Shargel R. Comparative toxicities of halothane, isoflurane and diethyl ether at subanesthetic concentrations in laboratory animals. Anesthesiology 42 (1975) 408-419.
- 144. Stewart RD, Erley DS, Torkelson TR, Hake CL. Post-exposure analysis of organic compounds in the blood by a rapid infra-red technique. Nature 184 (1959) 192-193.
- 145. Stowell A, Aune H, Mörland J. Production of acetaldehyde and ethanol by isolated rat liver parenchymal cells in the presence of diethyl ether. Biochem Pharmacol 30 (1981) 1967-1972.
- 146. Subgroup for evacuation of anesthesia gases, hospital engineering cooperative group: Recommendations for arrangements against pollution by anesthesia gases in operating rooms, recovery rooms, and similarly equipped rooms. Anesthesia division II, KAS Gentofte, Copenhagen, October 1974 (unpublished material).
- 147. Suzuki SS, Smith GK. Spontaneous EEG spikes in the normal hippocampus. V. Effects of ether, urethane, pentobarbital, atropine, diazepam and bicuculline. Electroenc Clin Neurophysiol 70 (1988) 84-95.
- 148. Swann HE, Kwon BK, Hogan GK, Snellings WM. Acute inhalation toxicology of volatile hydrocarbons. Am Ind Hyg Assoc J 35 (1974) 511-518.
- 149. Takagaki K, Jidoi J. Topical application of ethyl ether to recurrent herpes simplex.
 J Dermatol 8 (1981) 109-11.
- 150. Tan Y, Keefer LK, Yang CS. Inhibition of microsomal N-nitrosodimethyl-amine demethylase by diethyl ether and other anaesthetics. Biochem Pharmacol 36 (1987) 1973-1978.

- 151. Budavari S (ed). The Merck Index. 11th ed. Merck & Co Inc, Rahway, NJ, USA (1989) 600.
- 152. To ECA, Wells PG. Biochemical changes associated with the potentiation of acetaminophen hepatotoxicity by brief anesthesia with diethyl ether. Biochem Pharmacol 35 (1986) 4139-4152.
- 153. Umeda T, Inaba T. Effects of anesthetics on diphenylhydantoin metabolism in the rat: Possible inhibition of diethyl ether. Can J Physiol Pharmacol 56 (1978) 241-244.
- 154. NIOSH. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, Ohio. Health Hazard Evaluation Determination Report No. HHE 76-107-373, 1977.
- 155. NIOSH. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, Ohio. Health Hazard Evaluation and Technical Assistance Report No. HETA 89-199-2033, 1990.
- 156. NIOSH. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, Ohio. Hazard Evaluation and Technical Assistance Report No. HETA 77-33, 1977.
- 157. NIOSH. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, Ohio. Health Hazard Evaluation Determination Report No. HHE 79-19-740, 1980.
- 158. Vaisman AI. Working conditions in surgery and their effects on the health of anesthesiologists. Eksp Khir Anesteziol 12 (1967) 44-49.
- 159. Van Buskirk R, McGaugh JL. Retrograde amnesia and brain seizure activity in mice: strain differences. Exp Neurol 51 (1976) 150-159.
- 160. Van Dyke RA, Chenoweth MB, Van Poznak A. Metabolism of volatile anesthetics-I. Conversion in vivo of several anesthetics to ¹⁴CO₂ and chloride. Biochem Pharmacol 13 (1964) 1239-1247.
- 161. Vermeulen NPE, Danhof M, Setiawan I, Breimer DD. Disposition of hexobarbital in the rat. Estimation of "first-pass" elimination and influence of ether anesthesia. J Pharmacol Exp Ther 226 (1983) 201-205.

- 162. Vickers MD, Morgan M, Spencer PSJ (eds). Drugs in anaesthetic practice. Butterworth-Heinemann Ltd, Oxford (1991) 157-159.
- Virtue RW, Helmreich ML, Gainza E. The adrenal-cortical response to surgery. I. The effect of anesthesia on plasma 17-hydroxycorticosteroid levels. Surgery 41 (1957) 549-557.
- 164. Walton B. Effects of anesthesia and surgery on immune status. Br J Anaesth 51 (1979) 37-43.
- 165. Waskell L. A study of the mutagenicity of anesthetics and their metabolites. Mutation Research 57 (1978) 141-153.
- 166. Watkins JB, Klaassen CD. Chemically-induced alteration of UDP-glucuronic acid concentraion in rat liver. Drug Metab Dis 11 (1983) 37-40.
- 167. Weissman A. Drugs and retrograde amnesia. Int Rev Neurobiol 10 (1967) 167-198.
- 168. Werthmann H. Beitrag zur chronishen Ätherintoxikation der Chirurgen. Beitr Klin Chir 178 (1949) 149-156 (Ger.).
- 169. White AE, Takehisa S, Eger EI, Wolff S, Stevens WC. Sister chromatid exchanges induced by inhaled anesthetics. Anesthesiology 50 (1979) 426-430.
- 170. Wimer RE. Bases of a facilitative effect upon retention resulting from post-trial etherization. J Comp Physiol Psychol 65 (1968) 310-312.
- 171. Wimer RE, Huston C. Facilitation of learning performance by post-trial etherization. Behav Biol 10 (1974) 385-389.
- 172. Wollman H, Smith AL, Alexander SC. Effects of general anesthetics in man on the ratio of cerebral blood flow to cerebral oxygen consumption. In: Brock M, Fieschi C, Ingvar D, Lassen NA, Schurmann K (eds). Cerebral blood flow. Springer-Verlag, New York (1969) 242-243.
- 173. Zarembka FR, Koller DE, Plotka ED. Effect of ether or ketamine anesthesia on rat uterine estrogen and progesterone receptors. Clin Chem 35 (1989) 143-145.