34

Clinical Toxicology

CLINTON H. THIENES, M.D., Ph.D.

Emeritus Director, Huntington Institute of Applied Medical Research, Huntington Memorial Hospital, Pasadena; Emeritus Adjunct Professor of Pharmacology and Toxicology, School of Medicine, University of Southern California, Los Angeles; Emeritus Attending Pathologist (Toxicology), Los Angeles County Hospital; Consulting Member of Staffs of Huntington Memorial Hospital, Glendale Adventist Hospital, Memorial Hospital of Glendale, Mission Hospital, Huntington Park, and Temple Hospital, Los Angeles.

THOMAS J. HALEY, Ph.D.

Adjunct Professor of Pharmacology, Schools of Medicine and Pharmacy, University of North Carolina; Consultant, Department of Health, Education and Welfare; Food and Drug Administration, Washington, D.C.; Research Triangle Institute, Research Triangle Park, North Carolina.

FIFTH EDITION

ILLUSTRATED

LEA & FEBIGER • *Philadelphia* • 1972

First Edition, 1940
Second Edition, 1948
Third Edition, 1955
Fourth Edition, 1964
Fifth Edition, 1972

ISBN 0-8121-0237-1

Library of Congress Catalog Card Number: 73-152032

Published in Great Britain by Henry Kimpton Publishers, London

PRINTED IN THE UNITED STATES OF AMERICA

myocardium to catecholamines. It also produces some degree of myocardial depression but as great as the other anesthetics. Myocardial arrhythmias have also been reported. Halothane has been shown to inhibit uterine contractility and depress gastrointestinal motility. Transient fatty changes in the liver but not the kidney have been reported but this subject is highly controversial.

Methoxyflurane, 1,1,-difluoro-2,2-dichloroethylmethyl ether (Penthrane), is similar in its effects to halothane and in addition it causes profound muscle relaxation. There is a high degree of accumulation of the drug in body fat which causes a slow recovery. Blood sugar is also increased. This agent has a profound depressant effect on pulmonary ventilation.

Fluoroxene, 2,2,2-trifluorethylvinyl ether, has the drawback of being flammable. It is similar in most respects to the other two agents.

Fate and Excretion. Halothane is converted into bromide, chloride, trifluoroacetic acid and trifluoroethanol glucuronide by the liver and excreted in the urine. Fluoroxene is metabolized similarly to halothane; methoxyflurane is metabolized to fluoride, chloride, CO_2, formaldehyde, 1,1-difluoro-2,2-dichloroethanol, 2,2-dichloroethanol, 2-hydroxy-1,1-difluoroethylmethyl ether, and perhaps methoxydifluoroacetic acid, hydroxyfluoroacetic acid and oxalic acid, and excreted into the urine, partly as glucuronides. In two patients recently reported by Taves *et al.*, the fluoride in blood and tissues reached toxic concentrations, with degeneration of liver and kidneys, and eventual death.

IMPURITIES IN ANESTHETIC DRUGS

Chloroform. Oxidation of chloroform yields phosgene, a gas highly irritating to pulmonary structures. For this reason only freshly opened bottles should be employed for anesthesia. Chloroform oxidizes less rapidly when protected by a small amount of ethyl alcohol. For this reason, chloroform for anesthesia contains 1% ethanol.

Divinyl Ether. On exposure to light and air, divinyl oxide polymerizes, and also decomposes to aldehydes. Such altered samples of the drug are quite irritating to the nose and throat and have a "stinging odor," according to Chen and Leake.

Ether. Aldehydes, acetic acid and peroxides are found in ether which has been exposed to air and sunlight. It is doubtful whether these substances are of sufficient toxicity to warrant the waste of ether now obtaining in hospitals where small cans instead of drums of ether are purchased and where ether that has stood in an opened can more than 24 hours is considered unfit for anesthetic purposes. (See papers by Gold and Dooley and their collaborators.) However, Mendenhall and Connolly reported ether containing aldehydes and peroxides to be more toxic to cilia than pure ether, and Knoefel found such impure ether to produce anesthesia in mice more slowly than high purity ether.

The fact that the U.S.P. recognizes Ether, intended for anesthesia, and the National Formulary recognizes Ethyl Oxide or solvent ether, may lead to a mistake.

Ethylene. Carbon monoxide was an occasional contaminant of ethylene in the early years of its use, but more refined methods of manufacture have eliminated this hazard.

Nitrous Oxide. Rarely are there irritating oxides present in nitrous oxide now marketed for anesthesia. However, atmospheric nitrogen is present in excessive amounts more frequently than is generally appreciated (Chaney and Lombard). Because of the greater volatility of nitrogen, it escapes from the liquefied gases in the cylinders more rapidly than nitrous oxide. Therefore the first patients anesthetized from such cylinders require a dangerous degree of asphyxia to produce anesthesia. It is quite probable that the delayed toxic effect of nitrous oxide anesthesia occasionally seen in large hospitals can be attributed to the pro-

Chapter 15

Cardiac Poisons

The cardiac actions of chloroform (Chapter S), of cocaine and other local anesthetics (Chapter 1), of aconite and veratrum (Chapter **2),** nicotine (Chapters **1, 2, 3)** and of epinephrine, ephedrine, amphetamine and similar compounds (Chapter **13)** have been discussed. Benzene is included in this chapter because of its ability to produce fatal cardiac arrhythmia, Toluene and xylene are included because of the chemical but not toxicological similarity.

BENZENE

Toxic Dose. Two ml by mouth may produce symptoms, and 10 ml may be fatal. The TLV in air is **25** ppm (80 mg per cu M).

Inhalation of **100** ppm for several hours causes headache and a sense of fatigue; **1500** ppm for an hour causes marked depression, **3000** ppm is irritating to the eyes and nose on but a few minutes' exposure and **7,500** ppm for half an hour or **20,000** ppm for **a** few minutes may cause death. Daily inhalation of 100 ppm may cause bone marrow injury with pancytopenia of the blood. The odor is detectable at **1.5** to **5** ppm.

Absorption. Benzene is absorbed from the alimentary tract, through the skin and, as the vapor, from the lungs.

Etiology of Poisoning. Benzene is widely used as a commercial solvent. Some motor fuels contain **20** to **50%** or more of benzene. Benzene may be a contaminant (0.5–7%) of commercial xylene, toluene, cyclohexane and light and heavy naphthas which are largely xylene, toluene and cumene. Many cases of poisoning are due to inhalation **of** the vapor in improperly ventilated rooms, or from contact with the skin. Several deaths have occurred among workmen cleaning out tank cars.

Symptoms and ***Actions.*** The symptoms are due to gastric irritation and to depression of the central nervous system, myocardium and bone marrow. There is vomiting if the drug is taken orally; giddiness, vertigo, muscular incoordination and unconsciousness may follow one another quickly, following either ingestion or inhalation of toxic amounts. Fever often develops in acute **and** subacute poisoning. Muscle twitchings **and** convulsions may precede acute death. The heart beat becomes weak and irregular. Injection of epinephrine into benzene poisoned animals readily produces ventricular fibrillation. Many acute deaths are due **to** ventricular fibrillation due to effort and release of epinephrine. This was probably the mechanism involved in the death of workers in tank cars which had contained benzene. Frequently, the man who went into the tank car to carry out an unconscious worker died during the effort of lifting the unconscious man up the ladder. There is prolonged

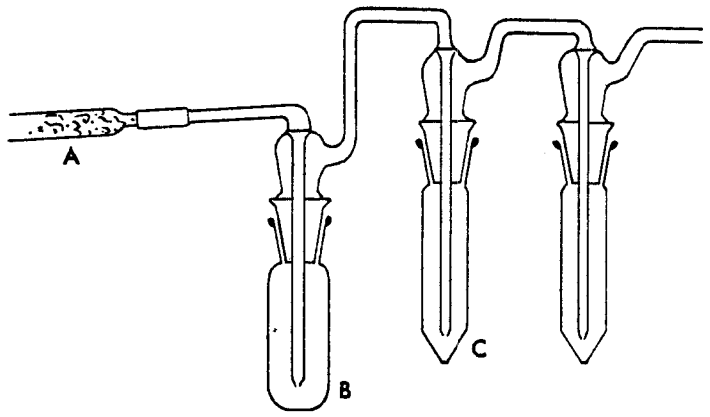


FIG. 10. Blood CS_2 Apparatus. *(A)* Sulfide trap containing lead acetate cotton. *(B)* Blood sample tube. *(C)* Reaction mixture tubes.

Table 33. calibration Data for *Determination of Aromatics in Blood*

Compound	*Absorption* Band nm	*Base Line nm*	*Conc. Range*	*Abe. Range*
Benzene	255	240-275	0.023-0.210	0.060-0.550
n-Butyl Benzene	268	230-275	0.034-0.269	0.038-0.349
Sec. Butyl Benzene	267	235-275	0.039-0.308	0.045-0.363
Ethyl Benzene	268	230-276	0.039-0.310	0.062-0.541
Kerosene	272	245-310	0.025-0.388	0.017-0.431
n-Propyl Benzene	268	230-275	0.016-0.340	0.015-0.490
Toluene	269	240-275	0.046-0.184	0.107-0.442
m-Xylene	273	235-280	0.036-0.284	0.083-0.712
p-Xylene	274	235-285	0.016-0.124	0.090-0.752

*

3 drops of octyl alcohol. Place 1.25 ml of reaction mixture in tubes C and connect the apparatus to a vacuum pump. Pass air through the apparatus for 30 minutes. After 15 more minutes mix together the contents of the tubes C and determine the absorbence in a photoelectric colorimeter using a green filter. Compare with a similarly derived standard curve.

BENZENE

If benzene is suspected place the tissue into a flask, add 400 ml of distilled water and a few ml of concentrated sulfuric acid. Steam distill using a long condenser fitted with an adapter projecting below a layer of carbon tetrachloride in a small receiving flask. Allow the distillate to separate and draw off the tetrachloride layer, which will contain the benzene. To the benzene-carbon tetrachloride mixture add 10 ml of 2:1 nitric-sulfuric acid mixture and shake. Evaporate off the carbon tetrachloride on a water bath and allow to cool. Add 50 ml of water, and shake out with three portions of ether in a separatory funnel. Collect the three ether fractions and evaporate over a water bath. Nitrobenzene remains as a yellow residue. This may be identified by tests already described (p. 300).

Quantitative Estimation of Benzene, Alkylbenzenes and Kerosene in Blood (Guertin and Gerarde, Arch. Ind. Health, *20*, 262, 1959).

REAGENTS. Cyclohexane spectrophotometric grade. Hydrochloric acid 0.1 N.

DETERMINATION IN BLOOD. Deliver 5 ml of blood into a 60-ml wide mouth bottle con-

Chapter 24
Bone Marrow Poisoning

There is a list of drugs and chemicals reputed to cause anemia and leukopenia through bone marrow suppression or injury. Those drugs known to or strongly suspected of having occasionally affected the blood-forming cells are included in Table 22. Evidence for involvement of most of these chemicals is insufficient for proof.

Chronic administration or exposure is necessary for bone marrow injury by most of the effective substances, although aminopyrine is reported to have caused granulopenia in sensitive patients after a single dose, and a single dose of benzene may cause anemia.

Various drugs, vitamins and tissue extracts have been reputed of value in treating patients with bone marrow damage. Most of these are probably ineffective; transfusions of whole blood or of red or white blood cells where specifically indicated are often lifesaving.

Most of the bone marrow poisons are discussed in detail under other headings. For example, benzene is described among the cardiac poisons, because of its acute effects on the heart. A few, however, need additional discussion here.

Of 1676 cases of drug-associated blood dyscrasias reported in 1959 to 1961, inclusive, there were 438 cases of pancytopenia, 183 of thrombocytopenia, 449 of leukopenia, 112 of anemia and 13 of miscellaneous effects. Table 23 lists the 11 drugs or drug groups with the highest number of cases. The frequency of dosage is not known. In many instances, other drugs were being used at the same time, hence, cause and effect are not certain.

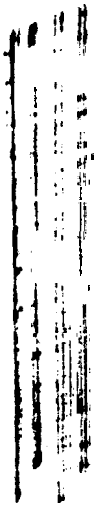
ANTINEOPLASTIC DRUGS

Antineoplastic drugs which injure the blood-forming organs and produce anemia, leukopenia or both, are the alkylating agents and the antimetabolites. These drugs in therapeutically effective doses usually produce unpleasant side reactions. Larger doses can be fatal.

Alkylating Agents. These drugs belong to the group of compounds known as nitrogen mustards and sulfur mustards, so named because in World War I the sulfur mustards, particulary, had somewhat the odor of mustard oil and were used militarily as cutaneous vesicants. They are employed therapeutically against a wide variety of malignant tumors. Since they are highly reactive substances, they must be administered intravenously or intra-arterially. The principal side reactions are nausea, vomiting, diarrhea, erosions of lips and oral mucosa, glossitis, amenorrhea, anhidrosis, skin pigmentation, alopecia, pulmonary fibrosis and interference with blood cell maturation.

cases have lived for as long as 4 days before succumbing to acute poisoning. Chronic poisoning persists for an indefinite period before death or recovery.

Pathology. Hematoporphyrinuria and hepatic and renal degeneration and often degenerative lesions of the central and peripheral nervous system are found at death.



Diagnosis. Hematoporphyrinuria may be due to a constitutional or idiopathic disorder. In such cases, close relatives often exhibit the same dysfunction. Identification of the drug in urine or tissues and a history of taking the drug will establish the toxic etiology of the condition.

Cause of Death. Respiratory failure results from acute poisoning; in chronic poisoning, death may be due to anemia, renal or hepatic degeneration or depression of the central nervous system.

Treatment. In acute poisoning, empty the stomach; for respiratory depression give caffeine and sodium benzoate (1 Gm) or pentylenetetrazol (0.1 Gm) intravenously, or if necessary, artificial respiration, with oxygen.

The liver and kidneys should be protected by carbohydrates and alkalies. For excessive hematoporphyrin formation, bleeding, with subsequent blood transfusion may be indicated.

loids, snake bite, stingray, tribromoethanol, veratrum.

7. *Vasoconstriction, Gangrene.* Amphetamine, chloroquine (retina), ephedrine, epinephrine, ergot, lead, nicotine, posterior pituitary extract, tobacco.

8. *Hemorrhage, Petechiae, Purpura.* Arsenic, benzene, chlorthiazides, corrosives, dicumarol, digitalis, ethacrynic acid, heparin, parathyroid, quinidine, Sedorniid, sulfonamides, thiouracil.

9. *Changes in Blood Cells. (a) Anemia:* alcohol (chronic), arsenic, barbital (chronic), benzene (chronic), favism, lead, morphine addiction, nitrofurantoin, nitrogen mustards, perchlorate, phenylhydrazine, radium, sulfonamides, trinitrotoluene. *(b) Brown Blood:* acetanilid, aniline derivatives, nitrites, sulfanilamide, sulfites. *(c) Hemolysis:* Arsine, castor bean, chlorates, copper sulfate, dimethyl sulfate, dinitrophenol, favism, mephenesin, naphthalene, nitrofurantoin, phenylhydrazine, quinine substitutes, snake venom, sulfonamides. *(d) Leukocytosis:* pilocarpine, titanium tetrachloride. *(e) Leukopenia:* Aminopyrine, aniline derivatives, antimonials, arsenicals, benzene, chloramphenicol, lead, perchlorate, radium, sulfonamides, thiouracil. *(j) Polycythemia:* acetanilid (chronic), aniline derivatives (chronic), arsenical dysentery, carbon monoxide (chronic), cathartics, cobalt. *(g) Stippling:* antimony, bismuth, lead, phenobarbital (chronic).

COMA OR DROWSINESS

Alcohol, amphetamine withdrawal, anesthetics, anticonvulsants, antihistamines, aromatic hydrocarbons, arsenic, barbiturates, bromides, cannabis, carbon disulfide, carbon monoxide, carbon tetrachloride, chloral hydrate, chloroquine, cyanide, diabetic coma, diazepam, herbicides, hydrocarbons, glutethimide, insulin, iodine, lithium, mercurial nephritis, metaldehyde, methyl bromide, methyl chloride, naphazoline, naphthalene, opium derivatives, pentachlorophenol, phenol, salicylates, somnifacients, sulfanilamide, sulfides, tetrahydrozoline, tricyclic antidepressants, vitamin D.

CONSTIPATION

Adrenergic blocking agents, calcium salts, cathartics (chronic use), dihydromorphinone (Dilaudid), ergot, ganglionic blocking agents, lead, morphine, opium.

CONVULSIONS

1. *Tonic or Tetanic Convulsions.* Antibiotics, asphyxia, camphor, carbon monoxide, cocaine, cyanide, fluoride, fluoroacetate, insulin, metaldehyde, Metrazol, naphthalene, nicotine, nitrogen mustard (children), prochlorperazine, rotenone, strychnine, tetanus, tricyclic antidepressants, uremia, zinc phosphide.

2. *Clonic Convulsions.* Absinthe, antihistamines, asphyxia, atropine, caffeine, camphor, carbon disulfide (chronic), chlorinated hydrocarbon insecticides (DDT, lindane, etc.), chromium, cocaine, codeine, coriamyrtin, ergot, insulin, mushrooms (children), phenol, picrotoxin, rotenone, strychnine (early), theophylline.

3. *Tremor.* Alcohol, amphetanline, arsenic, barbiturates, barium, chlorinated hydrocarbon insecticides (DDT, lindane, etc.), chloroquine, ergot, ephedrine, epinephrine, insulin, lathyrism, lead, manganese (chronic), mercury (chronic, by inhalation or as methylmercury orally), methylphenidate, milk-sick, neostigmine, nicotine, physostigmine, reserpine, thyroid, tranquilizers, uremia.

COUGH

Acid fumes, beryllium, cadmium, castor bean meal, chlorine, chromium, dimethyl sulfate, formaldehyde, hydrazine, metal fumes, nickel carbonyl, nitrogen oxides, organic phosphate insecticides, silica, sulfur dioxide, tellurium, titanium tetrachloride, toluene diisocyanate, vanadium oxide.

EXCITEMENT, DELIRIUM AND INSANITY

Alcohol, amphetamine, anti-adrenergics, arsenic, atropine, barbiturates, bromide,