More could possibly be said, even in a brief résumé, confining its attention to schemes sponsored by the Ministry of Health, about the development of industry round special sub-standard communities, as exemplified for instance by village settlements; in this connexion it is particularly necessary to keep in view the relationship between diversional therapy and true rehabilitation, with its economic as well as remedial implications.

L. B. Stott.

THE EFFECTS OF ALIPHATIC NITROUS AND NITRIC ACID ESTERS ON THE PHYSIOLOGICAL FUNCTIONS WITH SPECIAL REFERENCE TO THEIR CHEMICAL CONSTITUTION

W. F. Von Oettingen. *National Institute of Health Bulletin*, No. 186. Washington. 1946. Pp. 66. Refs. 228

The pharmacological and toxicological actions of aliphatic nitrous acid esters (alkyl nitrites) are characterized by a fall of the blood pressure due to peripheral vasodilatation, acceleration of the pulse rate, and, if exposure is sufficient, by the formation of methæmoglobin. The fall of the blood pressure is due to peripheral vasodilatation, which is bound to the grouping R-ONO. The properties of ethyl nitrite and amyl nitrite are described in detail.

Aliphatic nitric acid esters are explosive and the properties of methyl nitrate, ethyl nitrate, ethylene glycol mononitrate, ethylene glycol dinitrate, glycerol dinitrate, glycerol trinitrate, erythritol tetranitrate, pentærythritol tetranitrate, mannitol hexanitrate, mannitol pentanitrate, 1, 4, 3, 6-dianhydromannitol-2, 5-dinitrate are reviewed. All cause lowering of the blood pressure and methæmoglobinæmia.

The mechanism of the circulatory changes has only been closely studied for amyl nitrite and glycerol trinitrate. An extensive review of pharmacological literature is given. Both cause an increase in pulse rate and lowering of blood pressure. Small doses which do not affect the blood pressure increase the cardiac output. The pressure on the pulmonary artery increases (and may lead to pulmonary oedema). The coronary arteries are dilated. Little information is available about the effects of continued exposure.

Methæmoglobin resulting from the action of aliphatic nitrous and nitric acid esters is of importance in the acute toxicity of these compounds, especially of those—such as ethylene glycol dihydrate—with which this effect is marked. This methæmoglobinæmia may lead to an anoxic condition in vital organs, especially the brain and the heart muscle.

T. A. Lloyd Davies.

THE TOXICITY AND POTENTIAL DANGERS OF METHYL BROMIDE WITH SPECIAL REFERENCE TO ITS USE IN THE CHEMICAL INDUSTRY, IN FIRE EXTINGUISHERS, AND IN FUMIGATION

W. F. Von Oettingen. *National Institute of Health Bulletin*, No. 185. Washington. 1946. Pp. 37. Refs. 54.

Methyl bromide (monobromomethane CH_3Br) is a colourless gas which solidifies at -93°C . and boils at 4.5°C . On a large scale methyl bromide is made by heating sodium bromide, methanol, and sulphuric acid to 130°C . in a closed process. Methyl bromide-air mixtures are incapable of ignition but at raised temperatures decompose to carbon dioxide and carbon monoxide,

hydrogen bromide and bromine, and in some circumstances to carbon oxybromide. The halide lamp is unreliable for detection of methyl bromide below 50 parts per million. Reliable chemical methods of estimation are described.

Methyl bromide is used as a methylating agent, in fire extinguishers, as a fumigant and insecticide. Absorption is nearly always through the lung but may, if swallowed, be through the gastrointestinal tract. The amount absorbed through the skin is disputed. Methyl bromide is distributed throughout the body and stored in tissues rich in lipid material. Excretion, which is slow, is through the lungs and kidneys. Its toxicity for animals has been widely studied, and in general the symptomatology and pathology are similar to that in man. Deaths from acute poisoning result from its irritant effect on the lungs and from chronic poisoning from changes in the central nervous system. Published reports of experimental findings in dogs, cats, rabbits, mice, rats, guinea pigs, and monkeys are reviewed.

Since 1899, 28 cases of fatal methyl bromide poisoning in the human subject have been reported. Fourteen occurred in chemical or filling operations, 4 from the use of methyl bromide as a fumigant, 10 from the use of fire extinguishers. In addition, 150 cases of non-fatal poisoning, including 6 of systemic poisoning with skin injury, have been recorded. In addition, 32 instances of skin injury have been reported. The literature is reviewed in detail, and a complete list of authors and references given. The fatal cases resulted from exposure to relatively high concentrations (varying from 8,600 to 60,000 parts per million). In general, the onset of toxic symptoms is delayed: the latent period is usually from 4 to 6 hours but may be as short as 2 hours or as long as 48. Early symptoms of fatal poisoning are headache, visual disturbance, nausea, vomiting. Other symptoms, such as smarting of the eyes, skin irritation, listlessness, vertigo, and tremor, may occur first. Tremors and twitching develop into epileptiform convulsions; and, rarely, convulsions or unconsciousness may be the first sign. Cyanosis results from pulmonary oedema; fever is frequent, and heart failure supervenes. In view of the rapid progress clinical studies are rare, but inconsistent signs are met with in the central nervous system. The serum bromide is markedly raised. The most significant changes are found in the respiratory tract: the trachea and bronchi are inflamed with blood-stained or purulent exudate, the lungs are hyperæmic and oedematous. The meninges and brain are hyperæmic, and the latter may show petechial hæmorrhages. The brain is frequently oedematous, with ganglionic changes characterized by fatty degeneration, shrinkage, and pyknosis.

The immediate cause of death is the pulmonary injury associated with circulatory failure; whereas the cerebral changes, though significant for the clinical picture, are less extensive.

The clinical picture of non-fatal poisoning shows great variation. Symptoms have followed exposure to between 100 and 500 of methyl bromide parts per million. Fatigue, blurred or double vision, nausea, and vomiting, are frequent. Inco-ordination with tremors and convulsions are common; the patellar reflexes are exaggerated, clonus is present, and Babinski's sign is positive. Nearly every type of nervous disturbance has been reported. In contrast with fatal cases, the pulmonary symptoms are comparatively slight. Even moderate poisoning may lead to prolonged illness or permanent injury, commonly characterized by sensory disturbances, weakness, paresthesia and blurred vision. Occasionally

the liver may be enlarged, but more frequently damage to the kidneys is shown by albuminuria. Blood changes give little help in diagnosis. Blood bromide is raised. The greatest reliance must be placed on the neurological examination. With one exception the cerebrospinal fluid has been reported to be of normal constitution and pressure. Exposure to high concentrations (about 8,000 parts per million) of vapour may cause pricking of the skin, erythema, and vesication. These injuries occur most frequently where the body is irritated by close-fitting garments. More severe injuries result from splashes, and methyl bromide will penetrate clothes, gloves, and boots. Skin changes result from the toxic effect of methyl bromide on the skin.

Moderate symptoms will disappear on stopping exposure and transferring the patient to fresh air. All contaminated clothing should be removed. The patient should be kept under observation and at rest for 48 hours. Oxygen should be given for cyanosis, and venesection may be indicated if pulmonary oedema develops. Convulsions may be controlled by the barbiturates, but for severe convulsions the inhalation of chloroform and oxygen may be required. Glucose may be administered intravenously if there is enlargement of the liver, but such injections should not be given if there is a risk of pulmonary oedema. Sodium bicarbonate solution has been recommended for cleansing the skin; blisters should be aspirated. The use of tanning agents has been disputed.

The mode of action of methyl bromide has been the subject of much speculation. In cases of acute and fatal poisoning it is open to question whether the pulmonary injury is primary or secondary to the circulatory changes, and whether methyl bromide acts directly on the vascular system. In less acute poisoning, circulatory and respiratory changes may be insignificant, but severe and irreparable damage to the central nervous system is produced. It is generally accepted that the narcotic action of aliphatic narcotics such as chloroform is due to the entire molecule and depends on their lipoid solubility. Whilst the narcotic action of methyl bromide is in accordance with its relatively low solubility, toxic manifestations not shown either by ethyl bromide or chloroform must be due to a different mechanism. Rabbits exposed to methanol vapour or fed with sodium bromide do not show the same changes. Ethyl bromide is relatively non-toxic to rabbits compared with methyl bromide, and the few cases of ethyl bromide poisoning reported have nothing in common with the clinical picture of methyl bromide poisoning. It seems established that alkyl halides such as methyl bromide penetrate the cells and dissolve in the intracellular fluid. If hydrolysis

takes place within the cells, bromide ions are liberated and trapped intracellularly. The assumption has been made that under these conditions bromide ions have an unusual action, but at present there is no experimental evidence that this is so. The toxic action of methyl bromide and methyl iodide on the one hand, and the difference between the toxic effect of methyl bromide and ethyl bromide on the other hand, point to the importance of the methyl group in producing the characteristic action of methyl bromide. It may be possible that methyl bromide as well as methyl iodide forms a quaternary ammonium compound with nitrogen enzymes and other biologically important amines. Methyl bromide differs from other aliphatic chlorinated hydrocarbons in having a very weak narcotic action, but after a latent period it produces functional and pathological changes in the brain and basal ganglia. In this it resembles manganese and carbon monoxide, both of which affect the oxygen metabolism in parts of the brain. It is possible that methyl bromide may affect iron-containing pigments and interfere with the catalytic action of haemoglobin.

Accidents from methyl bromide most frequently result from leaking pipe lines and containers or the bursting of these due to sudden changes in temperature. Joints should be lubricated with soap, and gaskets should be made from soft copper, leather, sheet lead, or hard felt.

Workers must be instructed in the hazards of methyl bromide and told of the need of immediate removal of soiled garments and shoes. An adequate supply of gas masks should be available, and it should be emphasized that rubber and leather gloves offer no protection and may increase the hazard.

As a fire extinguisher, methyl bromide is so dangerous that it should not be used by persons uninstructed in its hazards. Its use in domestic fire extinguishers is unwarrantable, and if fire extinguishers filled with methyl bromide are used the operator should stand to the windward side. The use of methyl bromide fire-extinguishing equipment as on board ship presents many dangers. All containers filled with methyl bromide should be weighed regularly to make sure a leak has not occurred.

The use of methyl bromide as an insecticide for the fumigation of foodstuffs has caused a number of accidents. Unauthorized entrance into freight cars and other places where methyl bromide is being used must be vigorously avoided. If fumigation has been properly performed, no residues which may have deleterious effects if such foods are eaten will remain. Containers of methyl bromide should be stored in cool, well-ventilated places away from inhabited rooms.

T. A. Lloyd Davies.