bladder and bile ducts in the liver may both be infected. In this case cholecystectomy does not cure the carrier condition. Cultures of duodenal contents are still positive. We have no way of determining in which of these two classes a given case falls except actual trial, but it is known that gallbladder carriers are more common than bile duct carriers. There is a third possibility (*c*), namely, the gallbladder might be normal and the bile passages alone might be infected. In this case also cholecystectomy would not be curative; but, from the evidence at hand, such cases must be very rare, if indeed they occur at all.

We are not competent to discuss the strictly surgical aspects of these cases, but are, of course, interested in the outcome from an operative as well as from a bacteriologic point of view. In operations such as these, which are done more for the good of the group than of the individual, it is necessary to insist on excellent surgical technic and judgment, in order to avoid a fateful tragedy such as that which befell a medical officer who had been taking care of meningitis cases and who expected to go home on leave to visit his wife and baby. Although his throat cultures were negative for meningococci, in order to be doubly sure that he was not a carrier he had his tonsils removed and died of hemorrhage.

In the cases mentioned, the operative results were good, although in one case there was what is called a stormy convalescence. The gallbladder was removed from below in some cases and from above in others. The cystic duct was found normal in all. It is obvious that these cases should be worked out with full cooperation between the pathologist and the surgeon. Whether a new specialty of "carrier surgery" should be established to handle this growing field need not be discussed here, but there should be a full understanding about the situation. The laboratory man has taken the initiative in this field and has asked for assistance from the surgeon. The surgeon should be in sympathy with and familiar with the problem. Most surgeons do not refuse an indicated operation, but apparently some surgeons do not agree that a person should be operated on for the good of the group in the absence of personal symptoms. Such surgeons can hardly be expected to do good carrier surgery. But, even with the personal point of view uppermost, these operations come under personal prophylactic surgery, as the organs are always chronically inflamed and the gallbladders usually contain stones.

In cholera the pathology of carriers is apparently identical with that in typhoid carriers, with the exception that there is some question as to the mechanism of gallbladder infection, whether it is through the portal circulation and bile or whether it is an ascending or lymphatic infection. The same principles in surgical treatment should hold in case of cholera, and the surgical treatment of carriers can be expected to be of even more value than in typhoid, as the disease has a more definite seasonal occurrence. In dysentery the evidence is not sufficient to warrant definite statements, but by analogy the same situation may also obtain.

SUMMARY AND CONCLUSIONS

1. So-called "urinary" typhoid carriers are really kidney carriers and can be cured by nephrectomy. An additional argument for operation is present if the infected kidney is functionless. One such case is recorded.

2. "Intestinal" carriers are really bile passage carriers of two kinds:

(*a*) Cases in which the gallbladder alone is infected. These can be cured by cholecystectomy. Four such cases are recorded.

(*b*) Cases in which the gallbladder and bile passages are both infected. In these cases cholecystetcomy does not cure the carrier condition and the condition is incurable at present. Two such cases are recorded.

3. The surgical treatment of typhoid carriers, while not perfect, is the best available.

MUSTARD GAS*

E. K. MARSHALL, JR., PH.D., M.D.
Associate Professor of Pharmacology, Johns Hopkins Medical School
BALTIMORE

One of the best known of all the war gases[1] and perhaps the most interesting is the so-called "mustard gas" or dichlorethylsulphid. This gas was first used by the Germans in July, 1917, and received its name from its smell, which resembles the odor of garlic or mustard. It is not a gas at all, but a high boiling, oily liquid, which vaporizes slowly in the air. It is a very poisonous substance and exerts a local action on the respiratory tract, eyes and skin, and a general systemic action when absorbed in sufficient concentration into the blood stream. In the concentrations of this "gas" which are present in the field, probably very little systemic action is generally noticed. The systemic action of the substance is of importance, however, as it leads us to a better understanding of the mechanism of action of the poison, and hence to an intelligent pursuit for a rational method of treatment.

DIFFICULTY OF DETERMINING TOXICITY

One of the first points which must be carefully determined in investigating a substance of this kind is its toxicity. It is important that this be determined very carefully for numerous reasons: (1) to learn what concentrations are dangerous in the field; (2) to ascertain how effective protective devices have to be to remove the "gas," and (3) to furnish a basis for accurate experimental work on treatment. This necessitates the determination of the toxicity of the substance in the form of vapor, and not by the ordinary method of administration by mouth, subcutaneously or intravenously. The simplest method of determining its toxicity in the form of vapor would appear to be to place animals in a gas-tight box and introduce a known amount of the substance in the form of vapor. But difficulties arise. The concentration is not accurately known unless chemical analyses of the air are made, and then it is found to be much less than that calculated from the amount of substance introduced, mainly because of condensation on the walls of the chamber, of absorption of the substance by the skin and the hair of the animals and, probably, in some cases, of decomposition of the substance by moisture in the air. Moreover, it is found that the concentration decreases markedly with time. Because

* Read before the Section on Pathology and Physiology at the Seventieth Annual Session of the American Medical Association, Atlantic City, N. J., June, 1919.

* The experimental investigations on which this paper is based were conducted by the Pharmacological Research Section, Medical Division, Chemical Warfare Service, at the American University Experiment Station, Washington, D. C.

1. For description of gases used by the Germans, see Auld: J. Washington Acad. Sc. **8**: 45, 1918.

of these factors, the figure used for the concentration is more or less guesswork. To overcome these difficulties, a chamber is used through which a continuous current of air, containing a known and constant amount of the poisonous vapor, is passed. In fact, the air in the chamber is changed once or twice a minute.[2]

Another point of difficulty is the great individual variation in the susceptibility of animals. This is probably greater than when the poison is administered subcutaneously or intravenously. It necessitates the use of a large number of animals in making a determination of the toxicity of a gas. Again, the toxicity for different species may vary, and as our ultimate aim is a knowledge of the toxicity for man, a great many different species must be used. If the toxicity is widely different for different animal species, it is hard to arrive at a conclusion as to the toxicity on man. In the case of mustard gas, determinations on dogs, rabbits, guinea-pigs, rats, mice, goats and monkeys have shown that there is no wide species variation as with some other gases. Hence, the figures obtained on animals will probably apply to man.

EXTREME TOXIC EFFECT

Without giving detailed figures, it may be said that this gas is an extremely toxic one. Five-tenths mg. per liter of air (or one part in 14,000) will kill an animal on an exposure of less than five minutes, while less than 0.01 mg. per liter (or about one part in 1,000,000) will prove fatal on eight hours' exposure. Death will not be immediate, of course, but will take place some days later. Concentrations smaller than the lethal ones will produce toxic effects.

For instance 0.0005 mg. per liter (or about one part in 14,000,000) will cause conjunctivitis on a prolonged exposure, and may incapacitate a man. About 0.002 mg. per liter (or about one part in 3,000,000) will cause a skin burn in a sensitive person on prolonged exposure. The reason why mustard gas has proved to be more an incapacitating gas than a lethal gas, under warfare conditions, is undoubtedly its very low vapor pressure. Very low concentrations are obtained in the field with this substance for any length of time.

SYMPTOMS AND SYSTEMIC EFFECTS

The symptoms which arise from exposure to mustard gas are now too well known to need detailed description.[3] They consist essentially of local irritation of the upper respiratory tract, eyes and skin, giving rise to conjunctivitis and superficial necrosis of the cornea, hyperemia, edema, vesication, and later necrosis of the skin, leading to a skin lesion of great chronicity, and congestion and necrosis of the epithelial lining of the pharynx, trachea and bronchi. In animals exposed to high concentrations of this gas, vomiting and diarrhea, hyperexcitability and convulsions, and effects on the heart suggest an absorption into the blood stream and a systemic action.

Experiments demonstrate clearly that there is an absorption through the lungs of dichlorethylsulphid. When this substance is injected either subcutaneously or intravenously into a dog, the following symptoms make their appearance after a latent period: salivation; hyperexcitability and convulsions; vomiting and bloody diarrhea; a slow and irregular heart, which becomes rapid before death; muscular weakness, and finally, coma and death. Necropsy reveals a more or less intense congestion of the intestinal mucosa, which is frequently accompanied by hemorrhage into the lumen of the intestine. These effects on the heart, the gastro-intestinal tract and the central nervous system can practically all be observed in dogs poisoned by inhalation of high concentrations of mustard gas. This leaves little room for doubt that in high concentrations this gas is absorbed through the lungs and produces systemic effects in the body. Further proof of the absorption through the lungs is furnished by the detection of one of the decomposition products of mustard gas in the urine of gassed animals. On contact with water, mustard gas hydrolyzes very readily and gives rise to hydrochloric acid and dihydroxyethylsulphid:[4]

$$\begin{matrix}\mathrm{ClCH_2CH_2}\\ \mathrm{ClCH_2CH_2}\end{matrix}\!\!>\!\mathrm{S} + 2\mathrm{H_2O} = \begin{matrix}\mathrm{OH.CH_2CH}\\ \mathrm{OH.CH_2CH_2}\end{matrix}\!\!>\!\mathrm{S} + 2\mathrm{HCl}$$

Dihydroxyethylsulphid was injected into a dog, and the urine was collected and examined for this substance. A positive test was obtained. This proves that the substance is excreted, in part at least, unchanged. The injection of dichlorethylsulphid was next tried and the urine found to contain the dihydroxyethylsulphid. The latter substance was then detected in the urine of animals which had been poisoned by inhalation of mustard gas.

MECHANISM OF ACTION

The latent period in the development of the effects of mustard gas either when inhaled or injected, suggests that the substance may be altered chemically in the body before exhibiting its characteristic effects. The simplest chemical change which the substance undergoes in the test tube is a hydrolysis into hydrochloric acid and dihydroxyethylsulphid. That this change also takes place, in part at least, in the animal organism is evidenced by the excretion of dihydroxyethylsulphid in the urine. The injection, however, of a completely hydrolyzed solution of mustard gas is followed by absolutely no symptoms. The dihydroxyethylsulphid has no irritating effect on the skin and is comparatively a nontoxic substance when injected intravenously. This decomposition product is, therefore, not responsible for the effects of mustard gas. Hydrochloric acid, the other product of hydrolysis, is not a very toxic substance. It can be injected in small doses without very much effect. The buffer system of the blood immediately neutralizes the acid, and the tissues are really never exposed to it. When the body is flooded with large doses of acid, however, death results. An acid reaction is incompatible with life. Both products of hydrolysis of mustard gas are readily soluble in water and sparingly soluble in organic solvents, while mustard gas is very sparingly soluble in water and freely soluble in organic solvents. The hydrolytic products have a low lipoid solubility and would not be expected to penetrate cells easily, while mustard gas has a high lipoid solubility and would probably penetrate cells readily.[5] Its effects on the skin prove its power of penetration. Having penetrated into the cell, it would undoubtedly hydrolyze in

2. Marshall and Kolls: J. Pharmacol. & Exper. Therap. **12**: 385 (March) 1919.
3. Lynch, Smith and Marshall: J. Pharmacol. & Exper. Therap. **12**: 291 (Dec.) 1918. Warthin et al.: J. Lab. & Clin. M. **3**: 447 (May) 1918; **4**: 785 (Oct.) 1918; **4**: 833 (Oct.) 1918; **4**: 229 (Feb.) 1919; **4**: 265 (Feb.) 1919.
4. Hopkins: J. Pharmacol. & Exper. Therap. **12**: 393, 1919.
5. Harvey: Publication 212, Carnegie Inst. of Washington, 1915, p. 143.

the aqueous phase of the cell. The liberation of free hydrochloric acid within the cell would produce serious results and might explain the effects of dichlorethylsulphid. To summarize, then, the mechanism of the action of dichlorethylsulphid appears to be:

1. Rapid penetration of the substance into the cell by virtue of its high liquid solubility.
2. Hydrolysis by the water within the cell, to form hydrochloric acid and dihydroxyethylsulphid.
3. Destruction by hydrochloric acid of some part or mechanism of the cell.

Accumulated knowledge of various other facts tends to substantiate this theory of the intracellular liberation of hydrochloric acid as the mechanism of the action of mustard gas.[6] The ideal treatment for mustard gas poisoning would be to employ some nontoxic substance which would penetrate the cell and neutralize the effects of the hydrochloric acid. Efforts made in this direction have not been entirely successful.

It is interesting to note that all the war gases contain a halogen and can give rise to hydrochloric or hydrobromic acid on decomposition. One might, therefore, speculate on the possibility of the action of all war gases being due to the liberation of acid. At present, however, this is merely speculation.

In regard to the action of mustard gas on the skin, it is well known that some persons are more readily affected than others. We have been able to devise simple tests for determining the susceptibility of the skin of an individual to mustard gas. Without going into detail as to the methods used, I may summarize certain interesting facts which have been discovered. One man may be 600 times as susceptible to the action of mustard gas as another. Negroes, as a race, are far more resistant than white men. About 2 to 3 per cent. of white men are hypersensitive, while 20 to 40 per cent. are resistant. If a hypersensitive and resistant man are exposed to mustard gas, the former will undoubtedly receive severe skin burns, while the latter may entirely escape them.[7]

6. Lynch, Smith and Marshall: J. Pharmacol. & Exper. Therap. **12**: 265 (Dec.) 1918. Lillie, Clowes and Chambers: Science **48**: 382, 1919.
7. Smith, Clowes and Marshall: J. Pharmacol. & Exper. Therap. **13**: 1, (Jan.) 1919. Marshall, Lynch and Smith (Footnote 3).

Birth Rate of Whites During War Normal.—To ascertain whether the war affected the birth rate of Maryland and Baltimore, because of agitation regarding this subject abroad and elsewhere in the United States, Dr. Frederick V. Beitler, Halethorp, Md., of the bureau of vital statistics, has compiled statistics covering the period from 1915 to July 1, 1919, inclusive, and the conclusions which the study of the figures presented revealed that the birth rate, whatever has happened abroad, has not been affected appreciably in Maryland. On the contrary, births in 1918 and thus far in 1919 have been normal. The only doubt which might exist that they may perhaps make the rate appear a shade less than normal lies in the inability to estimate properly the growth of population in the state during those months of the war period — that is, the growth from outside sources — from migration here from other sections of the country. Just what this has been no one seems to know with any certainty, but that it has not been sufficient to weigh heavily on the side of diminution of birth rate is a generally accepted fact among those who have given the matter serious attention. In 1918 the death rate exceeded the birth rate, a condition which had not been noted before since the health wardens have been tabulating the returns. This was caused by the influenza epidemic and ailments incident thereto and it is reflected in the early returns of 1919, but the present year, unless there is a recurrence of the malady, will about measure up to other years in proportion to the population.

POISONING WITH THE LETHAL WAR GASES *

PHYSIOLOGY AND EXPERIMENTAL TREATMENT *

FRANK P. UNDERHILL, PH.D.
Professor of Experimental Medicine, Yale University School of Medicine
NEW HAVEN, CONN.

The most important members of the group of lethal gases are chlorin, phosgen and chlorpicrin. These substances are alike in that they act on the respiratory tract, producing edema and congestion. Chlorin acts with extreme rapidity. The toxic action of phosgen is slower, probably because, to produce its effects, it must undergo chemical change. This fact has earned for phosgen the name of having a delayed action. Chlorpicrin appears to stand somewhere between chlorin and phosgen, both in regard to the type of influence provoked and in the rate of production of intensive edema.

From an extensive investigation, on dogs and goats, of the acute effects of gassing, it is quite evident that the detrimental influence of these gases is confined to the respiratory tract and that all other effects must be regarded as secondary, since it has been impossible to determine the absorption of these gases into the blood stream. Exposure to them results in a variety of changes in the organism, in addition to the development of pulmonary edema. Thus, gassing has a definite influence on the respiration, heart beat, temperature, concentration of the blood, the water content of the lungs and other tissues, the chlorid content of the blood and tissues (with resulting changes in chlorid excretion by way of the kidney), the number of red and white cells of the blood and the respiratory function of the blood, leading to dyspnea and partial asphyxia. Acidosis is present at times, and there is a distinct influence on protein metabolism.

When one attempts to correlate these various effects, the task at first seems well nigh impossible. Closer inspection, however, brings to light one significant feature, namely, changes in the concentration of the blood. Viewed from this standpoint, the picture presented by a typical lethal gas, namely, phosgen, shows that acute gas poisoning may be divided into three stages.

STAGES IN PHOSGEN POISONING

In the first stage, which lasts from five to eight hours, there is usually a very significant dilution of the blood. In this period, pulmonary edema is developing. In the first part of this period the temperature may fall markedly; in the latter part of the period there is a greatly accelerated pulse, accompanied by a rise in temperature considerably above the normal.

The second stage, which reaches its maximum between the fifth and twenty-fourth hours, is characterized by a very marked concentration of the blood. In this period the temperature may be well maintained, or there may be a distinct drop below normal. If the temperature is well maintained, the condition of the individual is considered good. On the other hand, if the temperature suddenly falls, the outcome is usually fatal.

* Read before the Section on Pathology and Physiology at the Seventieth Annual Session of the American Medical Association, Atlantic City, N. J., June, 1919.