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CONTRIBUTIONS OF MEDICAL RESEARCH IN CHEMICAL WARFARE TO MEDICINE[1]

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IN the war which has just ended only certain aspects of chemical warfare such as smokes, flame throwers, white phosphorus, incendiaries and fire bombs were employed. The toxic gases remained unused. Yet the potential employment of these substances was a constant threat throughout the entire course of the war. We now have abundant evidence that our enemies were prepared both offensively and defensively for the vigorous use of these agents. Their research institutes investigated the toxic properties of the agents which had been employed in World War I as well as of other agents which were subsequently developed. Our enemies studied in great detail the methods by means of which these agents could best be dispersed, and the relation of their effectiveness to varying conditions of terrain and weather; they developed protective devices, first-aid measures and methods of treatment.

But this country and its allies were at work even more intensively in these various aspects of chemical warfare. England, which was in a particularly vulnerable position because of her proximity to Germany, had maintained an active research group after World War I. When political events indicated the imminence of a second world war, research activities were intensified.

It is not the purpose of the present paper to describe the development of chemical warfare research in this and the Allied countries, but rather to indicate the contributions of such research to medicine. However, it is relevant in this connection to describe briefly the vast array of scientific forces which were marshalled in this country to study the toxic and

[1] Read on October 9, 1945, at the New York Academy of Medicine Graduate Fortnight, Beth Israel Hospital Clinic.

physiological properties of chemical warfare agents, to develop methods of protection against their use and methods of treatment of casualties. Almost all these projects were classified during the war as secret or confidential; the public and indeed many scientific workers were not aware of how thorough and extensive were the preparations for the possible use of chemical warfare.

On June 28, 1941, a Presidential executive order established the Office of Scientific Research and Development under Dr. Vannevar Bush. There were two main subdivisions of this office: the already existent National Defense Research Committee (NDRC) and a new Committee on Medical Research (CMR). In March, 1941, certain sections of the NDRC had been assigned the task of developing and testing new toxic agents, determining the types of injury which they produced and the mechanisms of their actions. In the fall of that year, the Committee on Treatment of Gas Casualties was established under the Committee on Medical Research. In both divisions, contracts to study these problems were given to biochemists, physiologists, pathologists and clinicians at many of our leading medical schools and research institutes.

Simultaneously with the creation of civilian organizations to investigate the medical aspects of chemical warfare, there occurred marked developments in the Army research facilities. In the interval between the two world wars, the medical research group at Edgewood Arsenal was very small and had extremely limited laboratory facilities. It was constantly subjected to the vicissitudes of changing policy. As the European political situation increased in tenseness, the Surgeon General of the Army recognized the need for investigations leading towards definitive treatment of gas casualties, and in 1936 a Medical Department unit was created for this purpose at Edgewood Arsenal. When the possibility arose that we might become involved in the European conflict, activities intensified; the demands for research and for instruction of medical officers increased. Towards the end of 1942 men of known investigative ability were called into the Army for assignment at Edgewood Arsenal and other chemical warfare installations. Plans were made for the building of a large up-to-date, well-equipped laboratory, and in June, 1943, the Medical Division of the Chemical Warfare Service was organized. By an agreement between the Surgeon General of the Army and the Chief, Chemical Warfare Service, one of the ultimate functions of the Medical Division was to recommend methods of protection and treatment of the soldier exposed to chemical warfare agents. In 1944, several months after the new laboratory had been in operation, research activities were at their peak, with about 150 officers and civilians directly engaged in investigation. To supplement its work, especially in those phases where clinical facilities were necessary, the Medical Division contracted directly with research groups in various universities.

Although the prime purpose of the research organizations mentioned above was to study the toxicology and mechanism of action of chemical warfare agents and methods of preventing and treating gas casualties, it was inevitable that there issue from this vast amount of research information both of fundamental and of direct clinical value to medicine. In the present paper it will be shown, in the case of each agent, how this information arose from the necessity of solving certain pressing problems in the therapy of gas casualties. It would not be appropriate at this time to describe in any detail the results of these investigations, since to do so would be to anticipate publication by the various investigators who carried out this work. However, it is possible to indicate the scope of these investigations, to refer to work which has already been published, and to describe in somewhat greater detail that in which the author has participated.

Before beginning the discussion of the studies on the various chemical warfare agents, it is well to emphasize that effective chemical warfare agents appear to possess the common characteristic that their interactions with tissue components are either completely or highly irreversible, at least by the standards of biochemical reactions to which we have been hitherto accustomed. Thus the problem of rational therapy against injury by chemical warfare agents is inherently a very difficult one and involves the general task of investigating more fully the question of the reversibility of cellular biochemical reactions.

Mustard had proven a very effective agent during World War I, being definitely responsible for almost 40 per cent. of the total gas casualties. The prevention or treatment of casualties due to this agent and to related substances, the nitrogen mustards, which had been developed since World War I, became a problem of prime importance when war threatened. There were two aspects of the action of these agents which demanded consideration, the vesicant and systemic effects.

It will be readily realized that the problem of vesication is one of considerable interest to dermatologists, and indeed to clinicians generally. Here was a group of chemical compounds which in very small amounts reacted with some constituent of the skin and set in motion an apparently irreversible train of events resulting in the progressive development of liquefaction necrosis in the cells of the lower layers

of the epidermis, the exudation of tissue fluid and the final formation of intraepidermal vesicles which might be of considerable size. The approach to this problem was fundamental. The kinetics of the interaction of the mustards with various amino acids and proteins, the action of the mustards on various enzyme systems both *in vitro* and *in vivo,* the mechanism of skin penetration and the effect on cell structures were all studied in considerable detail. Although in the treatment of vesication due to the mustards, success was limited, similar studies, as we shall presently see, provided a basis for the rational treatment of vesication due to lewisite. But in both instances, the studies referred to have produced a considerable amount of basic biochemical knowledge which will undoubtedly find its application in the future.

Although the systemic effects of the mustards had not been neglected, the Bari incident focussed considerable attention on this aspect. On December 2, 1943, German planes raided the harbor of Bari and several ships were sunk. One ship containing a considerable load of mustard bombs exploded; the floating mustard and the oil from a broken pipe line formed a mixture through which survivors were forced to swim. In addition to the skin, eye and respiratory tract injuries usually noted, systemic effects appeared to be especially marked. Many of the individuals appeared to be in shock, but did not respond to the usual shock therapy. The question arose as to whether the systemic effects noted were specific or were basically the same as those produced by thermal or traumatic injury. Considerable animal experimentation was initiated to study electrolyte and water equilibria, electrophoretic serum protein patterns, and tissue phosphorylation reactions not only in mustard poisoning but in thermal and traumatic injury as well.

The eye is especially vulnerable to the action of mustard vapor; the injuries range from a mild conjunctivitis to severe corneal involvement, depending upon the concentration of the vapor and duration of exposure. The earliest attempts at therapy were concerned with finding some drug which might neutralize the combination of mustard with components of the eye tissues. These attempts entailed the laborious and painstaking collection of new data on the effect of different compounds instilled into the normal eye. When penicillin was not yet available to the general medical profession, its effect in preventing secondary infections in mustard-gassed eyes was already being established. As will be noted later, in the eye as in the case of the skin, fundamental studies provided a basis for the rational treatment of injuries due to lewisite.

One of the most marked actions of the mustards is the production of leukopenia. In experimental animals, the administration of these compounds causes involution of the lymph nodes and aplasia of the bone marrow. These observations stimulated the use of some of the mustard compounds in the treatment of malignant lymphomatous diseases. Work along these lines is now in progress at several universities. It is, of course, too early to make any statements concerning the efficacy of any procedures so far carried out.

Phosgene also proved its worth as an effective chemical warfare agent during World War I. The lethal action of this gas is due to increased permeability of alveolar membranes and the production of pulmonary edema, a process which, once set into motion, is difficultly, if at all, reversible. The mechanism of this production claimed considerable attention, therefore, at the outset of the present war. The value of oxygen administration during the phase of the development of pulmonary edema was explored. As a consequence of experimental work indicating that oxygen inhalation was of value in decreasing mortality, apparatus was developed which incorporated the full-face Army gas mask facepiece and expiratory valve and an oxygen hose line which permitted twenty men to inhale oxygen simultaneously through a demand system. This apparatus enabled investigators to employ large numbers of subjects in order to answer a question which has been the subject of considerable debate, namely, whether 100 per cent. oxygen administered for 24 to 48 hours is toxic.

This work which has recently been published[2] showed that 100 per cent. oxygen administered continuously for 24 hours produced substernal distress in 82 per cent. of the cases. Signs of nose and throat irritation were common, and vital capacity was decreased. Inhalation of 100 per cent. oxygen at high altitudes (low oxygen tension) or inhalation of 50 per cent. oxygen at ordinary atmospheric pressures did not result in any symptoms. It was concluded that administration of 100 per cent. oxygen for short periods of time probably is safe in all patients, but that if it is necessary to give oxygen for longer than 12 hours, the oxygen content should be reduced to 60 per cent. unless this is insufficient to saturate the arterial blood. If 100 per cent. oxygen must be given, careful attention should be paid to the appearance of symptoms due to the toxicity of oxygen.

One of the dramatic accomplishments in chemical warfare therapy was the British development of a compound which specifically counteracted the injurious effects of lewisite, both systemically and in local lesions of the eye and skin. We may not at present

[2] Comroe *et al., Jour. Am. Med. Asn.,* 128: 710, 1945.

reveal the formula of this compound, which has been designated as BAL, or "British anti-lewisite."

The mechanism of the action of BAL was based on a reversal of the interaction of the arsenic in lewisite with certain tissue components. Several investigators readily appreciated at this point that the action of BAL might be directly applicable to the treatment of heavy metal poisoning in general, and active study along these lines was inaugurated in several institutions.

The most immediate and gratifying results were obtained in the treatment of toxic reactions resulting from the administration of arsenic-containing compounds, particularly mapharsen, in the course of antisyphilitic treatment. Details concerning the use of BAL in this connection may be given here, since this information has been published in an open War Department Technical Bulletin (No. 104, 12 October, 1944). BAL is used as a solution in oil, packaged in sterile ampoules containing 500 mg BAL in 5 cc and is for intramuscular injection only. The recommended dose is 0.025 cc per kg of body weight, repeated 4 times at 4 hourly intervals during the first day, and once daily for the following 6 days. Minor toxic reactions at this dosage of BAL occur in about 1 per cent. of injections and may consist of nausea, generalized aches and pains and a burning sensation in the mouth and eyes. The symptoms are transitory and disappear in 30 to 60 minutes. This treatment has given highly satisfactory results in patients with arsenical dermatitis and toxic arsenical encephalitis. Work in selected institutions is continuing, and negotiations are under way with the British for the release of BAL for general use by the medical profession.

At the beginning of this war, the British chemical warfare investigators began to study the physiological properties of a group of compounds which had been described by German chemists in the open literature in 1932. The British investigators found that these agents possessed an anticholinesterase action. In 1943, the Medical Division at Edgewood Arsenal became interested in this group of compounds, and comprehensive programs were initiated to study fully their toxicity and the mechanism of action and, if possible, to devise therapy against their injurious effects. One of these compounds appeared at first to be promising as a chemical warfare agent and, although it did not finally qualify in this respect, studies on the mechanism of its action revealed very interesting anticholinesterase properties.

In contrast to the action of such substances as prostigmine and physostigmine, this compound decreased the activity of cholinesterases in tissues and in blood in an apparently irreversible manner. It was also found that when animals or men were exposed to or injected with this substance, the cholinesterase activity of the blood and of tissues was decreased for a considerable length of time. For example, a number of men were exposed to very low concentrations of this compound. Except for a marked miosis which occurred in all these individuals, symptoms were minimal. There was a feeling of tightness and constriction in the chest in most of the men which persisted till the next day. Rhinorrhea, salivation, diarrhea each occurred in a few of the men. However, the most striking change observed was biochemical in nature; there was a marked decrease in the serum cholinesterase activity to about only 1 to 5 per cent. of the pre-exposure value. This degree of inhibition of the activity of a body enzyme is, so far as the author is aware, unprecedented. The rate of return to normal serum cholinesterase activity was very slow, being about 30 per cent. of normal in 4 days, 50 per cent. of normal in 8 days and about 70 per cent. of normal in 15 days.

Because of this prolonged anticholinesterase effect, it was decided to investigate the extent to which this compound could be used in clinical conditions in which there may be a disturbance in acetylcholine-cholinesterase relationship. It has been postulated that in myasthenia gravis there is a deficiency of acetylcholine at the myoneural junctions. Prostigmine is used in this condition on the basis that it inhibits cholinesterase activity at the myoneural junctions and thereby permits the accumulation of acetylcholine with a resultant improvement in muscle strength. However, it is necessary to give prostigmine at rather frequent intervals. It was believed that the compound to which we have referred might produce a more prolonged inhibition of the enzyme at the myoneural junctions and therefore simplify therapy considerably. Programs to investigate the efficacy of this chemical warfare agent in the therapy of myasthenia gravis have been inaugurated in several institutions. The use in glaucoma has also been investigated and is under further consideration.

The extremely toxic properties of hydrocyanic acid have been known for centuries. During the last war there was considerable difference of opinion as to whether hydrocyanic acid would constitute an efficient war gas. The French used this gas on one occasion with what they believed to be a high degree of success. With changes in types of munition and dispersal since the last war, hydrocyanic acid came to the fore again as a chemical warfare agent.

The problem of therapy therefore became an important one. In 1888 Pedigo first showed that amyl nitrite inhalation was effective in the treatment of dogs subcutaneously injected with cyanide. About 1930, several groups of investigators, notably Chen

and his collaborators, showed that the immediate intravenous injection of a combination of sodium nitrite and sodium thiosulphate was effective in saving animals subcutaneously injected with sodium cyanide. Consideration of Chen's experiments shows that his advocated therapy would be more effective in oral poisoning where the poison is absorbed gradually than in that due to inhalation of cyanide where absorption occurs instantaneously and the maximal effect on the tissue oxidative systems has occurred by the time therapy is instituted. It was necessary for us to determine the extent to which such therapy was effective in inhalation poisoning.

The mechanism underlying the use of nitrites in cyanide poisoning is the formation of methemoglobin. There is considerable *in vitro* evidence to indicate that this pigment competes with the respiratory pigment, ferricytochromeoxidase, for cyanide ion. The question arose as to whether the deliberate production of methemoglobin in the blood might not constitute an effective prophylactic measure against cyanide and thus be employed, in addition to the gas mask, to safeguard the soldier. In this connection, it was necessary to investigate substances which could readily produce methemoglobinemia without any physiological effects other than that due to the methemoglobinemia itself. A compound which had previously been reported in the literature appeared to fulfil these requirements. Methemoglobinemia was induced in animals as well as in a considerable number of men. Various aspects of the induced methemoglobinemia were then studied: the blood chemistry, the oxygen dissociation characteristics of the blood, the work capacity, effect on dark adaptation and the effects on hematopoietic, renal and liver functions. Embarrassing and lethal levels of methemoglobinemia were ascertained in animals. Methods of treatment of various degrees of methemoglobinemia were investigated.

The application of these studies to clinical medicine is apparent. Methemoglobinemia may result from the administration of certain drugs or from the absorption of toxic materials used in industry. Cases of familial idiopathic methemoglobinemia have also been reported in the literature. The information which has been obtained in the course of the studies referred to above will be of considerable aid in the diagnosis, prognosis and treatment of such conditions.

The studies on cyanides have had other interesting implications. In 1918, Loevenhart, in the course of studying the property of sodium cyanide as a respiratory stimulant, observed that the administration of cyanide to a schizophrenic patient resulted in a brief return towards normal mental processes. So far as the author is aware, this observation did not find any subsequent application. For a number of years physiologists and biochemists have been studying the effect of cyanide on tissue metabolic reactions. It has been possible for us at the Medical Division to extend and elaborate these studies. Since the lethal action of cyanide depends upon a central nervous system effect, the metabolic reactions in brain tissue have claimed special attention. With these and studies on toxicity of cyanides as a background, attention was redirected to the possible use of cyanides in the treatment of certain types of schizophrenia. A program is now in progress at one of the neuropsychiatric centers in this country to study, by means of encephalographic and other newer techniques, the effect of cyanide on brain activity and, if feasible, to apply these results to the treatment of certain selected cases of schizophrenia.

In this paper it has been possible to sketch only briefly the contributions which research in chemical warfare has made to medicine. There have been other contributions which, for lack of time, it has not been possible to describe or mention. It is interesting to note that the story of these contributions is the story of fundamental research everywhere. The prime purpose of the research workers in chemical warfare was to determine the toxicity of certain chemical warfare agents and to devise therapy against their use. But, wherever possible, the approach used was fundamental, not empirical. It did not consist of haphazard, disconnected attempts to find substances which somehow might prove useful in therapy. Its methods were to initiate systematic investigations into the mechanisms of action of the chemical warfare agents, and to build therapeutic procedures upon the results of such investigations. It was this type of approach which, in spite of the urgencies of war, yielded practical returns in our treatment of gas casualties and contributed substantially to fundamental and clinical progress in medicine.

OBITUARY

ROBERT H. GODDARD

IN the passing on August 10, 1945, of Dr. Robert H. Goddard, American science and engineering lost one of its greatest pioneers—the creator of the modern science of jet propulsion and rocketry.

His investigations had covered almost every essential principle involved in both the theory and practice of jet propulsion, particularly as applied to high-power rockets. His work was mainly responsible for the immense progress of the subject in the last three