EXHIBIT B

CHEMICAL CORPS MEDICAL LABORATORIES

SPECIAL REPORT

MLSR No. 59

THE MEDICAL LABORATORIES OF THE ARMY CHEMICAL CORPS AND THEIR RESEARCH ACTIVITIES

by

Clarence J. Hylander
Chief, Technical Information Office

January 1955

ARMY CHEMICAL CENTER, MARYLAND

CHEMICAL CORPS
MEDICAL LABORATORIES
ARMY CHEMICAL CENTER
MARYLAND

CMLRE-ML-52

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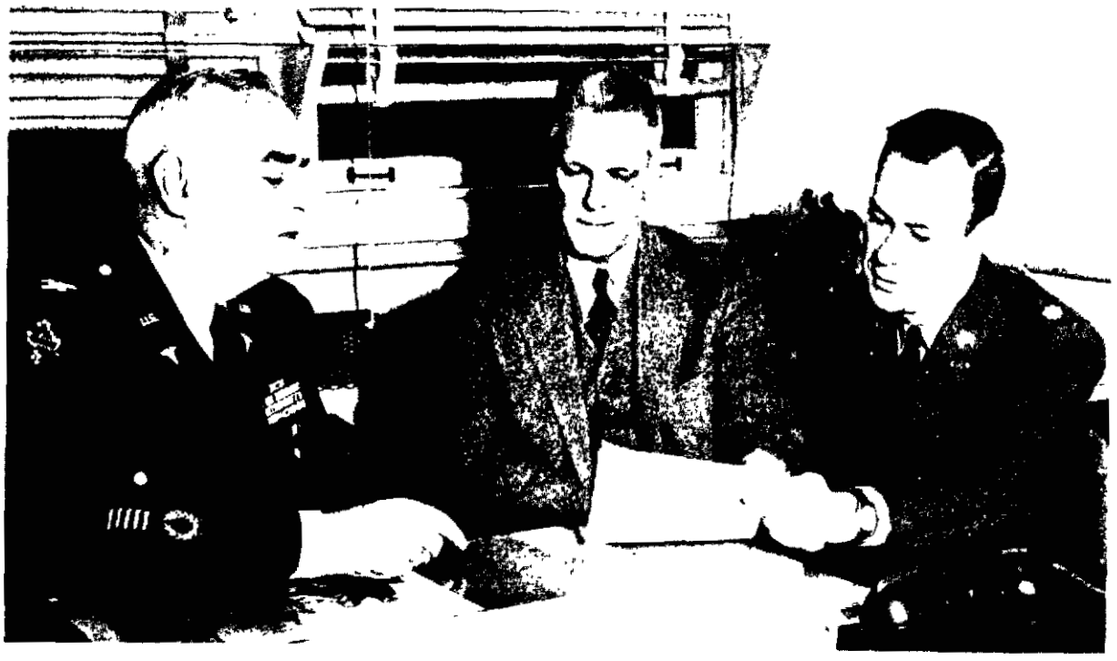

Medical Laboratories is an outstanding example of how civilians and military can cooperate, at all working levels, to achieve a research goal. Here the Commanding Officer, Scientific Director, and Deputy plan a new research project.

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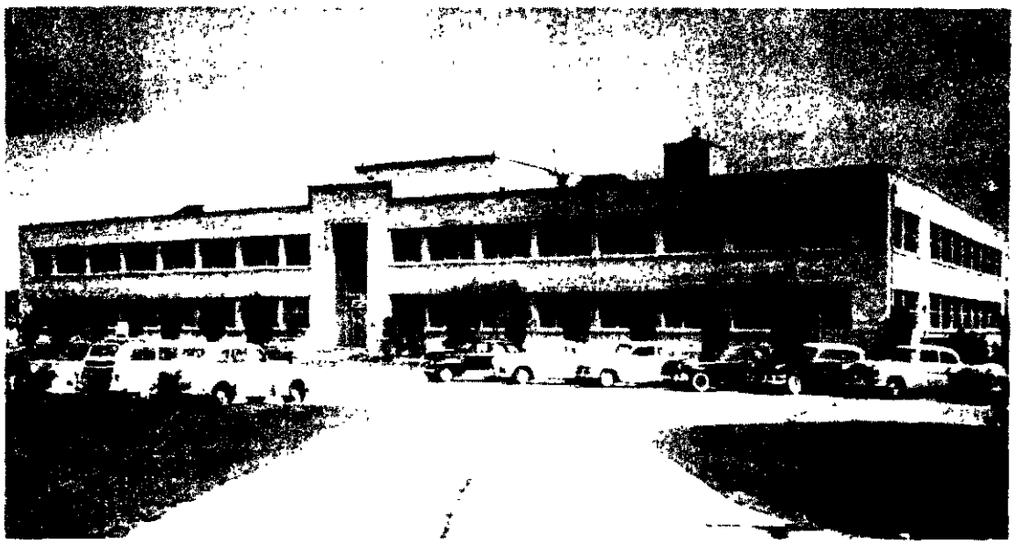
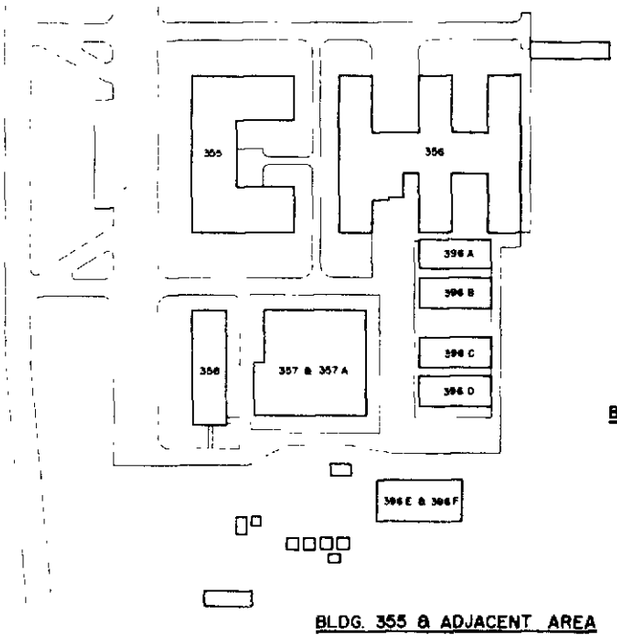
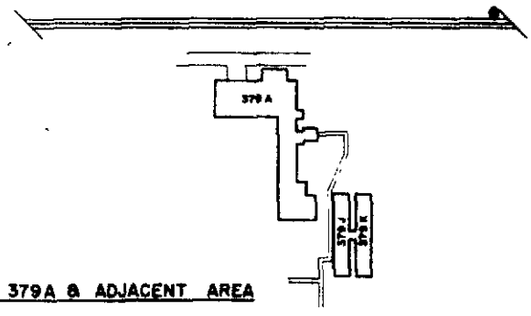


Building 355



BLDG. 355 & ADJACENT AREA



BLDG. 379A & ADJACENT AREA

Medical Laboratories Building 355 houses the offices of the Commanding Officer, Scientific Director, and various administrative offices, as well as some laboratories. Additional laboratories, animal quarters, climatic facility and other special activities are housed in surrounding buildings.

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The medical aspects of the effects of toxic chemicals are of vital interest to the Chemical Corps since, from both the offensive and defensive viewpoints, the reactions of the human body play an important part in determining policies and procedures in the field of chemical warfare. As a result, a medical laboratory is essential to our technological "know-how" in use of new weapon systems, and a safeguard to our population in determining therapy and protection in the event of use of chemical warfare against the United States.

In order to study the mechanism of action of those toxic chemicals considered chemical warfare agents, as well as methods of protection and treatment, a staff of specialists is required. These include toxicologists, biochemists, chemists, pharmacologists, physiologists, neurologists, entomologists and pathologists. Their work requires special equipment, particularly a large animal colony, because of the obvious limitations on the use of man for experimental purposes.

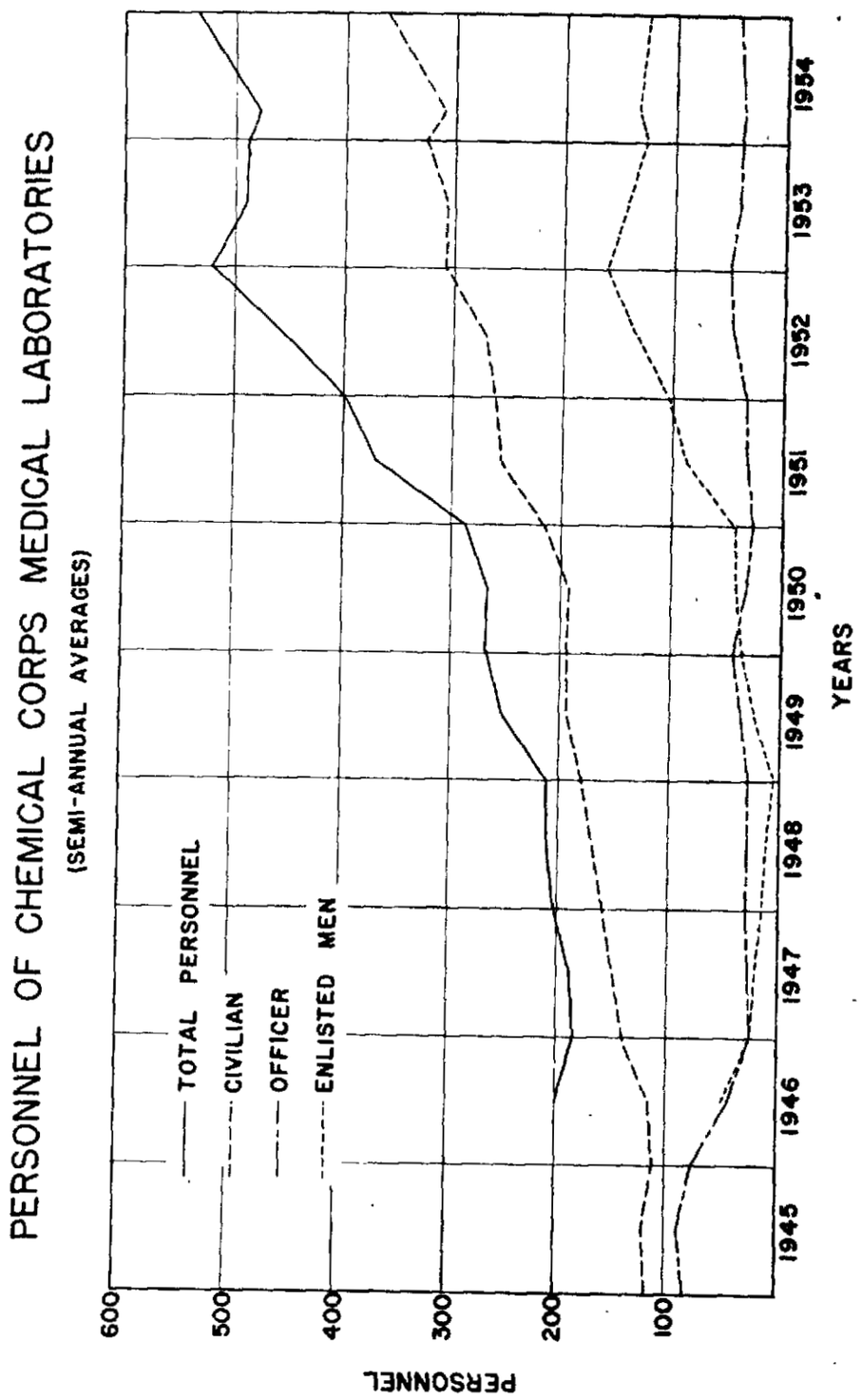
As the outstanding toxicological laboratory within the military establishment, Medical Laboratories was found to be valuable in studying harmful effects of other chemicals than CW agents. Thus the specialized staff and equipment have been utilized in solving medical-toxicological problems for the other services in the Army, notably Ordnance and Quartermaster Corps, and for the Navy and Air Force. An outstanding example is the Medical Laboratories study of such military chemicals as fuels and oxidizers for jet planes and rockets, hydraulic fluids, and lubricants.

I. Historical Background

The present Medical Laboratories of the Army Chemical Corps represents the consolidation of the Medical Research Laboratory and the Toxicological Research Laboratory which existed at the Army Chemical Center (then known as Edgewood Arsenal) prior to 1945. At that time these activities were combined to form a consolidated Medical Division; this was re-designated the present Medical Laboratories in 1951. Growth has been steady since that time; new buildings, new equipment, and highly-trained personnel have been added as the responsibilities of Medical Laboratories to the Department of Defense have increased.

II. Mission

The chief mission of the Chemical Corps Medical Laboratories is to conduct basic and applied research essential to maximum offensive and defensive effectiveness in chemical warfare. This necessitates a coordination of research in the physiological, biochemical, toxicological, pharmacological, neurological and pathological fields, as well as clinical investigation of chemical casualties. Other objectives of the research program include development of methods and equipment for treating chemical casualties, for detecting toxic chemicals in food and water, for purifying contaminated food and water, for studies of the mechanism of action of insecticides and rodenticides, and for physiological and toxicological research on the health hazards of military chemicals such as propellant fuels and fire-extinguishants. In collaboration with the Army Ordnance Corps and the



During the past ten year period, Medical Laboratories has more than doubled its research staff and supporting services.

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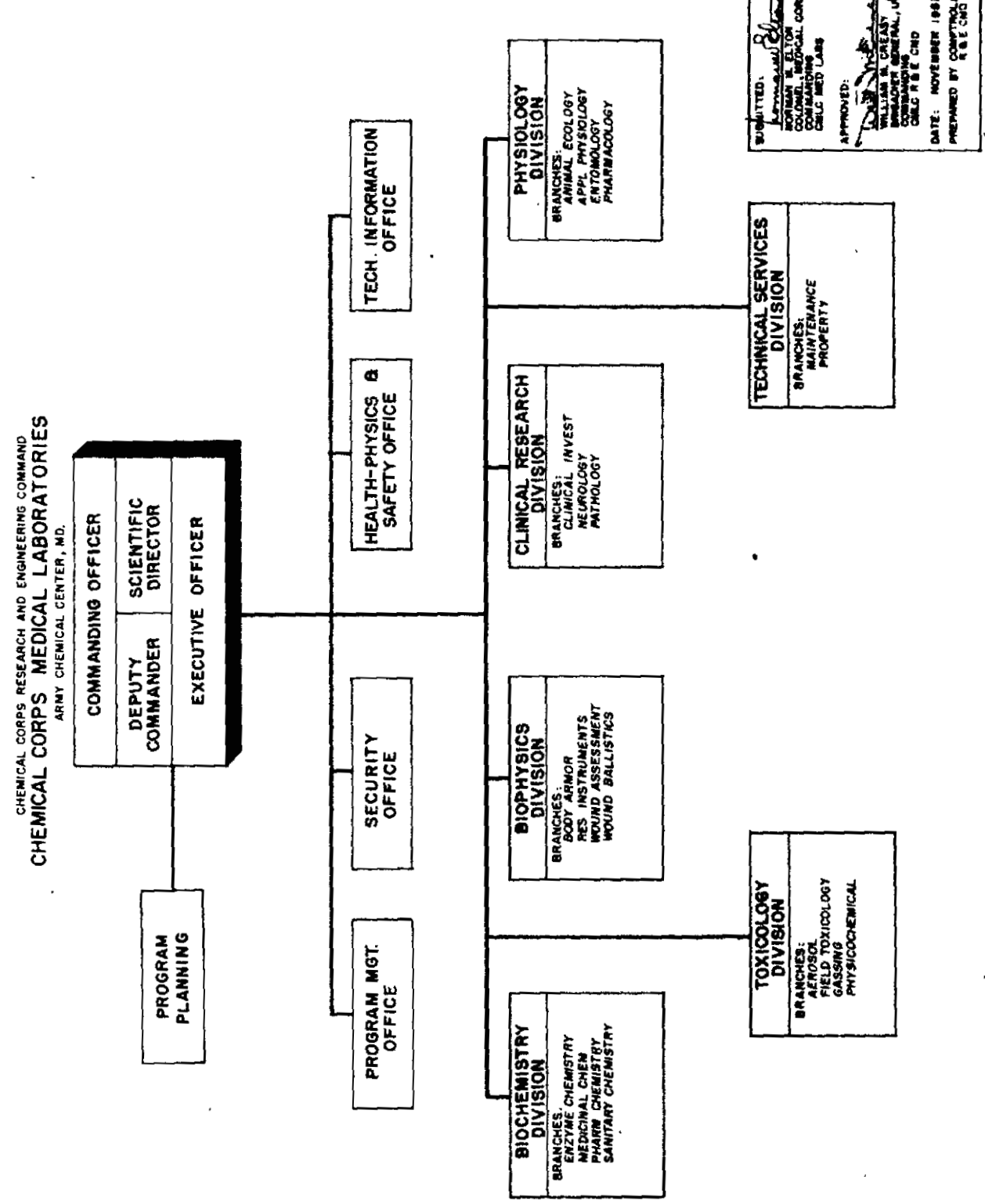

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three medical services, research of wound ballistics is carried on to achieve greater effectiveness of armor and weapons. Basic studies in this field have made great contributions to our knowledge of military surgery and shock.

III. Organization

The Commanding Officer, Cml C Medical Laboratories, has administrative supervision of the entire staff, and is responsible for the planning and direction of the research program. By mutual agreement between the Medical Service and the Chemical Corps, support for the Medical Laboratories comes from the Chemical Corps, but administrative responsibility is in the hands of a medical officer selected by the Medical Department. Commanding Officers, since 1945, have been:

1945-1950. Col. John R. Wood, M.D., Med. Coll. Va., 1928
1950-1953. Col. M. W. Bayliss, M.D., Univ. of Chicago, 1941
1953- Col. N. W. Elton, M.D., Boston University, 1926

Assisting the Commanding Officer, and having responsibility for technical supervision of the research program is the Scientific Director, Dr. D. B. Dill (Ph.D., Stanford University, 1925). The Assistant Scientific Director is Dr. W. H. Chambers (Ph.D., Washington University, 1920). Attached to the office of the Commanding Officer are the necessary offices which take care of administrative and supervisory duties inherent in necessary supporting activities.

The research staff is organized into five divisions, each made up of a number of branches. The divisional organization is intended to group together, for research planning purposes as well as for administration, related research groups whose individual functions constitute portions of the mission of the division. Each branch is a combination of specialists (pharmacologists, physiologists, biochemists, physicians, etc.) essential for the function of the branch. These work together as a research team, aimed at achieving a balanced and well-rounded approach to their research mission.

1. The BIOCHEMISTRY DIVISION includes four branches. The Enzyme Chemistry Branch carries on research dealing with the effect of toxic chemicals on biochemical mechanisms, both in the whole organism and in isolated tissues; with the effect of toxic chemicals on the action of enzymes, in vivo and vitro; with their effect on carbohydrate, protein, fat and mineral metabolism; and with the mechanisms of their detoxication. The Medicinal Chemistry Branch investigates the application of organic chemistry to the problems of prophylaxis and therapy against toxic agents; the relation between chemical structure and drug action; the chemical reactivity of toxic agents as a factor in personnel decontamination; and the relation between chemical structure of organic molecules and their biological activity. The Pharmaceutical Chemistry Branch applies the results of research to the development of pharmaceutical preparations and equipment for the prevention and treatment of chemical casualties. This branch also conducts surveillance tests, develops methods

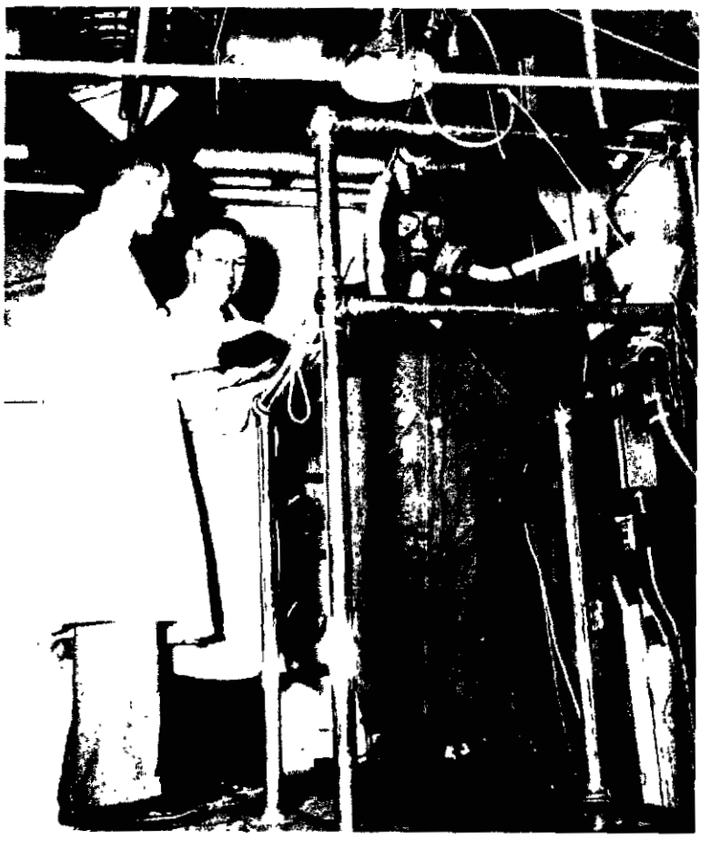
for quantitative estimation of active ingredients of therapeutic items for application to such studies, and conducts research and development on protective ointments. The Sanitary Chemistry Branch devises tests and field procedures to detect contamination of food and water by toxic chemicals, develops methods and field expedients for gas-proofing food and water supplies, and devises procedures for food and water decontamination.

2. The BIOPHYSICS DIVISION includes four branches. The Body Armor Branch conducts research in the mechanisms by which body armor offers protection against missiles, and on the wounding picture occurring when body armor is penetrated. This branch also advises other agencies on design problems in body armor, introduced by wound ballistics studies. The Research Instruments Branch furnishes the special instrumentation required in wound ballistics studies, and also maintains the electronic and mechanical instruments used in the division's research. The Wound Assessment Branch investigates the pathology of wounds and the associated anatomical and histological changes; assesses the significance of wounds to the military value of personnel, and with their relation to the resulting pathology; and also investigates the vulnerability of the animal body to missiles. The Wound Ballistics Branch correlates the physical and ballistic characteristics of missiles encountered on the battlefield with the resultant effect on the physiology of the injured animal body; investigates effect of projectile parameters on wounding and on the factors required to establish sound rationale for the treatment of resulting wounds; and investigates both anti-personnel effect of incendiary agents and necessary protective measures against them.

3. The CLINICAL RESEARCH DIVISION includes three branches. The Clinical Investigation Branch has general responsibility for all aspects of human exposures to toxic chemicals. This includes search for improved therapeutic measures, tests for efficacy of available methods of treatment of casualties, and investigation of all casualties resulting from handling toxic chemicals. The branch also advises and participates in all tests involving human volunteers in order to minimize possible hazards. The Neurology Branch carries on research dealing with the neurological and psychological effects of toxic chemicals and therapeutic agents, and with the mechanism and site of action in the nervous system of such compounds. The branch also has the responsibility for neurophysiological and neuropharmacological research designed to explain the fundamental processes whose toxic alterations cause neurological disturbances. The Pathology Branch has an important service function in conducting pathological examinations of animals used in the Medical Laboratories program. The branch also plans, in collaboration with other branches, toxicologic studies designed to elucidate pathologic mechanism of action of toxic chemicals; it also conducts research on effects of CW agents on animals, emphasizing gross and microscopic anatomic changes and on infectious aspects.

4. The PHYSIOLOGY DIVISION includes four branches. The Applied Physiology Branch conducts research on the physiological action of toxic chemicals of military interest, with emphasis on environmental influences;

The chief of the Biophysics Division (center) participates in a test of missiles, at a station in the wound ballistics range.



The chief of the Physiology Division (center) is informed of progress on physiological testing of protective clothing.

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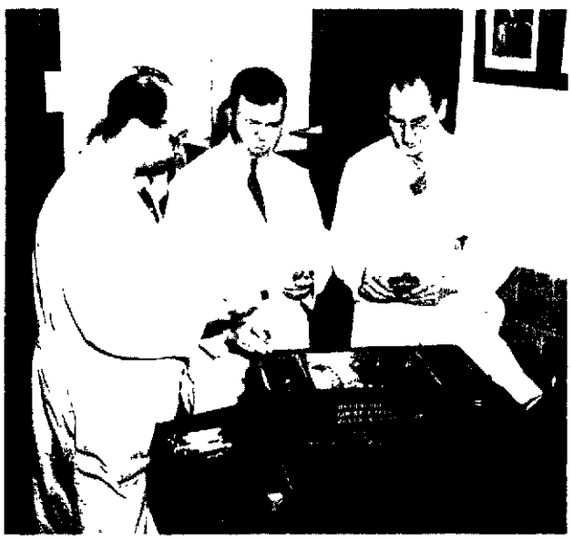
The chief of the Clinical Research Division (left foreground) demonstrates use of a brain wave recording apparatus to a visiting group of veterinary officers.



The chief of the Biochemistry Division (center) consults with two of his branch chiefs on items in the gas casualty treatment kit.

A technician in the Toxicology Division reads the pressure gauge of a high vacuum apparatus.

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investigates the defensive capabilities of CW personal protective equipment; and determines the limitations imposed by protective equipment on the functional efficiency of military personnel under various conditions of work, climate, and exposure to chemical warfare agents. The Animal Ecology Branch maintains adequate facilities and supplies of various species of animals required for Medical Laboratories research. It also carries on research on environmental conditions essential to the proper care, selection, and use of animals for laboratory experiments and field trials; and on pertinent problems in veterinary medicine. The Entomology Branch conducts research on the mechanism of action of insecticides, insect repellents and attractants; and on the detection of chemical warfare agents by means of insects. It also investigates the potential use of chemical warfare agents as insecticides. The Pharmacology Branch investigates the action of toxic chemicals on the physiological mechanisms of animals, and studies the actions of possible new drugs on the animal's physiological processes. In collaboration with the Clinical Investigation Branch and other branches, it also devises appropriate therapy for poisoning by toxic chemicals, and tests them experimentally on animals and man.

5. The TOXICOLOGY DIVISION includes four branches. The Aerosol Branch as its name implies, conducts toxicological research on materials dispersed as aerosols, and studies related problems such as physical characterization of disseminated aerosols, factors governing deposition on surface, locus of impaction, etc. The staff, in cooperation with other branches, investigates therapeutic measures using drugs dispersed as aerosols. The Field Toxicology Branch conducts toxicological studies in connection with field tests of CW agents and other toxic chemicals, determines toxicity of CW agents by screening methods; and undertakes comparative toxicological studies of CW agents using all routes of administration except inhalation. The Gassing Branch studies the mechanism of action of vapors of toxic chemicals, and investigates the value of selected drugs for therapy after exposure to such chemicals. The branch also screens new agents by inhalation and percutaneous exposure to vapors, and tests the effectiveness of various protective items against toxic vapors. The Physicochemical Branch carries out research on the physical and chemical changes of toxic chemicals caused by surface interfaces, and on the modifications of toxicological and biochemical reactions at surfaces and interfaces. The branch is also responsible for the development of new or improved instrumentation for use by Medical Laboratories staff.

A research organization the size of Medical Laboratories depends for its success to a great extent on numerous "service" branches which take care of the housekeeping details. A Technical Services Division assumes responsibility for transportation; requisitions of equipment, storage and issue of property; preparing drawings for and constructing special equipment; maintenance of buildings, grounds, services, and utilities; assisting in preparing specifications for modification of existing buildings and construction of new ones.

Scientific information based on Medical Laboratories research represents the end-items of an agency which deals mainly in ideas. The Technical Information Office is responsible for publication of all the research;

it also assists the research program by expediting the acquisition of scientific information from other agencies, and making these reports available through the Library and Documents Sections.

IV. Personnel

In 1954 Medical Laboratories included a total of some 520 personnel; of these approximately 190 were officers and enlisted men, and 330, civilians. Medical Laboratories is an excellent example of how civilians and military can cooperate, at all working levels, to achieve a research goal. Enlisted men and officers are assigned duties commensurate with their training and experience, working side by side with the civilian scientists.

The civilian research staff is made up of approximately 117 specialists in civil service grades GS-7 to GS-17. Their distribution according to the scientific categories established by civil service is illustrated in Figure 3. In addition, the research program requires 70 employees in the categories of animal caretakers, medical biological technicians, physical science aids, research technicians, pharmaceutical technicians, histopathology technicians, and first aid attendants.

The military personnel assigned to Medical Laboratories form an important portion of the research staff.* They are integrated into the branches where their specialities and training make them valuable. Out of a total of 32 officers participating in the research program as scientists, 12 are M.D.'s, 3 have Ph.D. degrees and 1 has both an M.D. and a Ph.D. Five have M.S. degrees in pathology, biology or chemistry, and 5 have D.V.M. degrees. Many of the Medical Laboratories publications are authored or co-authored by these scientists in uniform.

Enlisted military personnel as of this date include 130 men in the category ESPP (Enlisted Scientific and Professional Personnel). The utilization of ESPP's has resulted in marked acceleration of the research program, by providing an additional source of scientifically trained men and women. Of the 130 ESPP's, all but two have either A.B. or B.S. degrees; 55 have M.S. degrees, and 11 Ph.D. degrees. They are distributed through the various scientific fields as follows: chemists 55, biologists 35, engineers 11, physicists 5, biochemists 3, zoologists 3, psychologists 3, entomologists 2, mathematicians and statisticians 3, bacteriologists 2, and miscellaneous 3.

V. Facilities and Equipment

Laboratories, workshops, animal colony, and offices are housed in over twenty buildings, suitably constructed for experimental work in applied physiology, biochemistry, pharmacology, entomology, pathology, neurology and toxicology.

* See Appendix I: Senior Military Personnel as of December 1954.

BRANCH AND DIVISION CHIEFS OF RESEACH DIVISIONS, MEDICAL LABORATORIES, AS OF DECEMBER 1954

BIOCHEMISTRY DIVISION

Chief, William H. Summerson - Ph.D., Cornell, 1937

Enzyme Chemistry Branch	-	Chief, Bernard J. Jandorf Ph.D., Harvard, 1942
Medicinal Chemistry Branch	-	Chief, Theodor Wagner-Jauregg Ph.D., University of Munich, 1926
Pharmaceutical Chemistry Branch	-	Chief, Albert A. Kondritzer Ph.D., Cincinnati, 1938
Sanitary Chemistry Branch	-	Chief, Joseph E. Epstein M.S., University of Pennsylvania, 1940

BIOPHYSICS DIVISION

Chief, Carl M. Herget - Ph.D., Johns Hopkins, 1940

Body Armor Branch	-	Acting Chief, Floyd A. Odell Ph.D., Yale, 1940
Research Instruments Branch	-	Chief, David Grossman Electronics Engineer, Rensselaer Polytechnic
Wound Assessment Branch	-	Chief, Frederick W. Light Ph.D., Johns Hopkins, 1948 and M.D., Johns Hopkins, 1930
Wound Ballistics Branch	-	Chief, Arthur J. Dziemian Ph.D., Princeton, 1939

CLINICAL RESEARCH DIVISION

Chief, Amedeo S. Marrazzi - M.D., N.Y.U. College of Medicine, 1928

Clinical Investigation Branch	-	Chief, Gustave Freeman M.D., Duke University, 1934
Neurology Branch	-	Chief, E. Ross Hart Ph.D., University of California, 1940
Pathology Branch	-	Chief, J. R. M. Innes Ph.D., Cambridge University, 1931

PHYSIOLOGY DIVISION

Chief, William H. Chambers - Ph.D., Washington University, 1920

Applied Physiology Branch	-	Chief, Francis N. Craig Ph.D., Harvard, 1937
Entomology Branch	-	Chief, Leigh E. Chadwick Ph.D., Harvard, 1939
Pharmacology Branch	-	Chief, J. Henry Wills Ph.D., University of Rochester, 1940
Animal Ecology Branch	-	Chief, Charles G. Wilber Ph.D., Johns Hopkins, 1942

TOXICOLOGY DIVISION

Chief, Eugene H. Krackow - B.A., Johns Hopkins, 1934

Aerosol Branch	-	Chief, Bernard P. McNamara Ph.D., University of Maryland, 1942
Field Toxicology Branch	-	Chief, Francis N. Marzulli Ph.D., Johns Hopkins, 1941
Gassing Branch	-	Chief, Fred W. Oberst Ph.D., State University of Iowa, 1930
Physicochemical Branch	-	Chief, Hans J. Trurnit M.D., Berlin University, 1931

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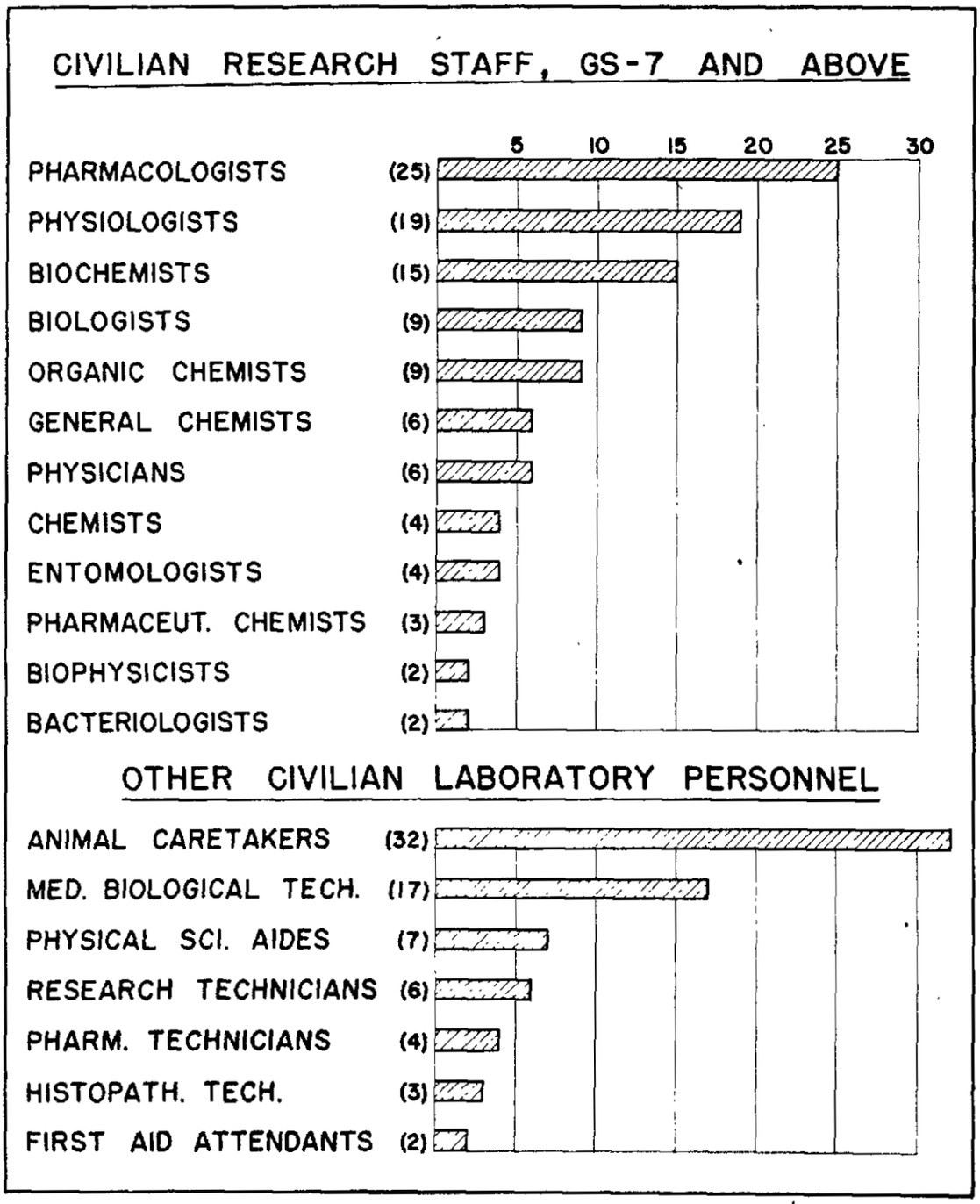

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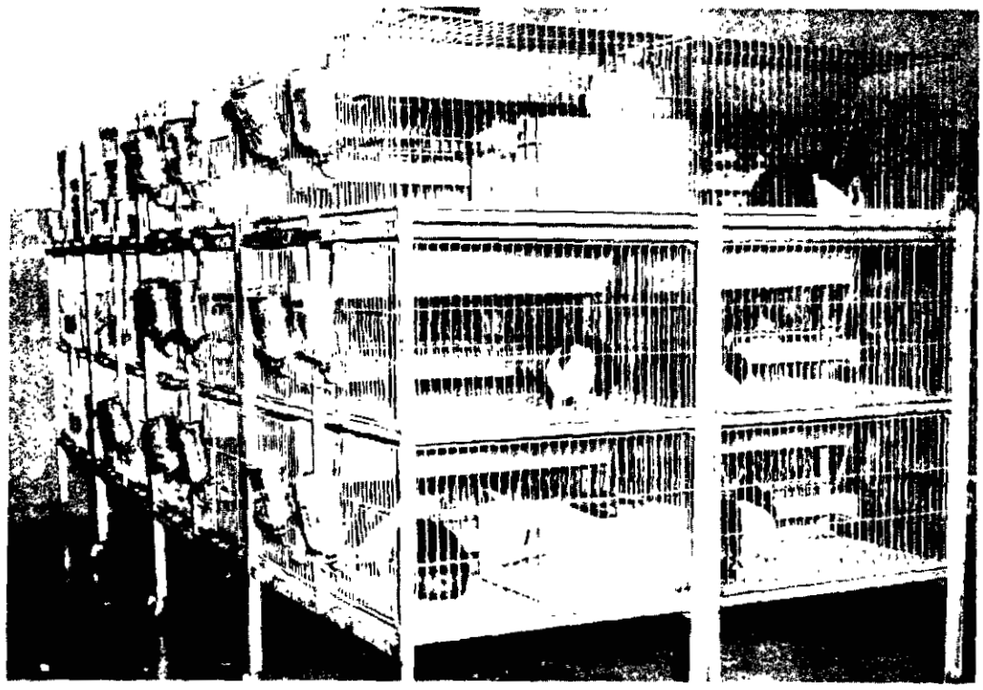
Goat Corral



Rabbit Breeding Cages

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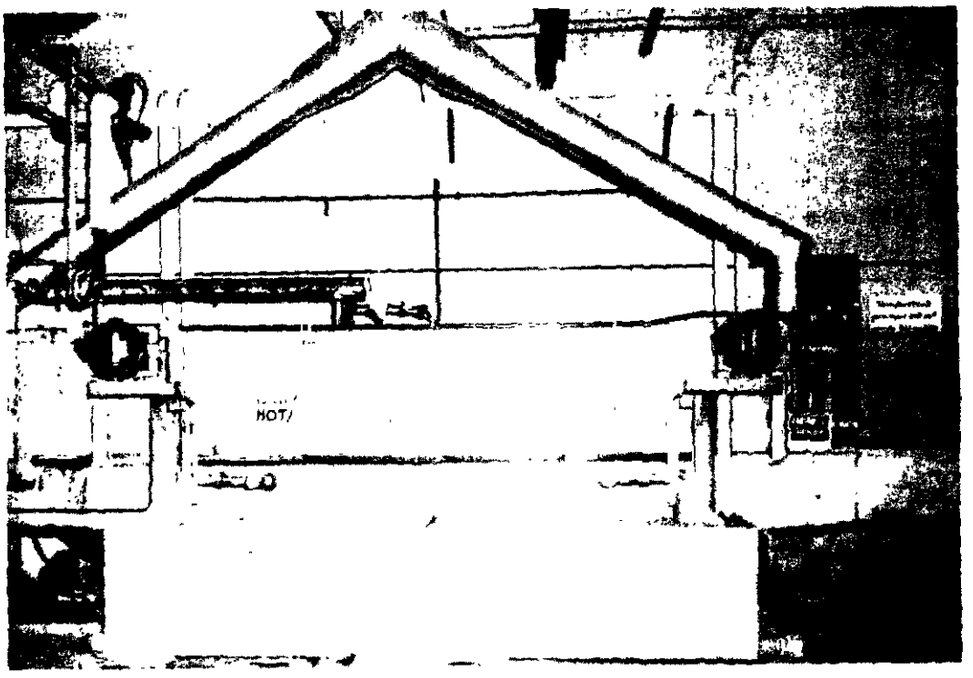
Rabbit Hutches



Cage Sterilizer: cages are passed through the washing chamber by a conveyer, entering at right, and after 11 minutes emerge at left completely sterilized (200° water, detergent).

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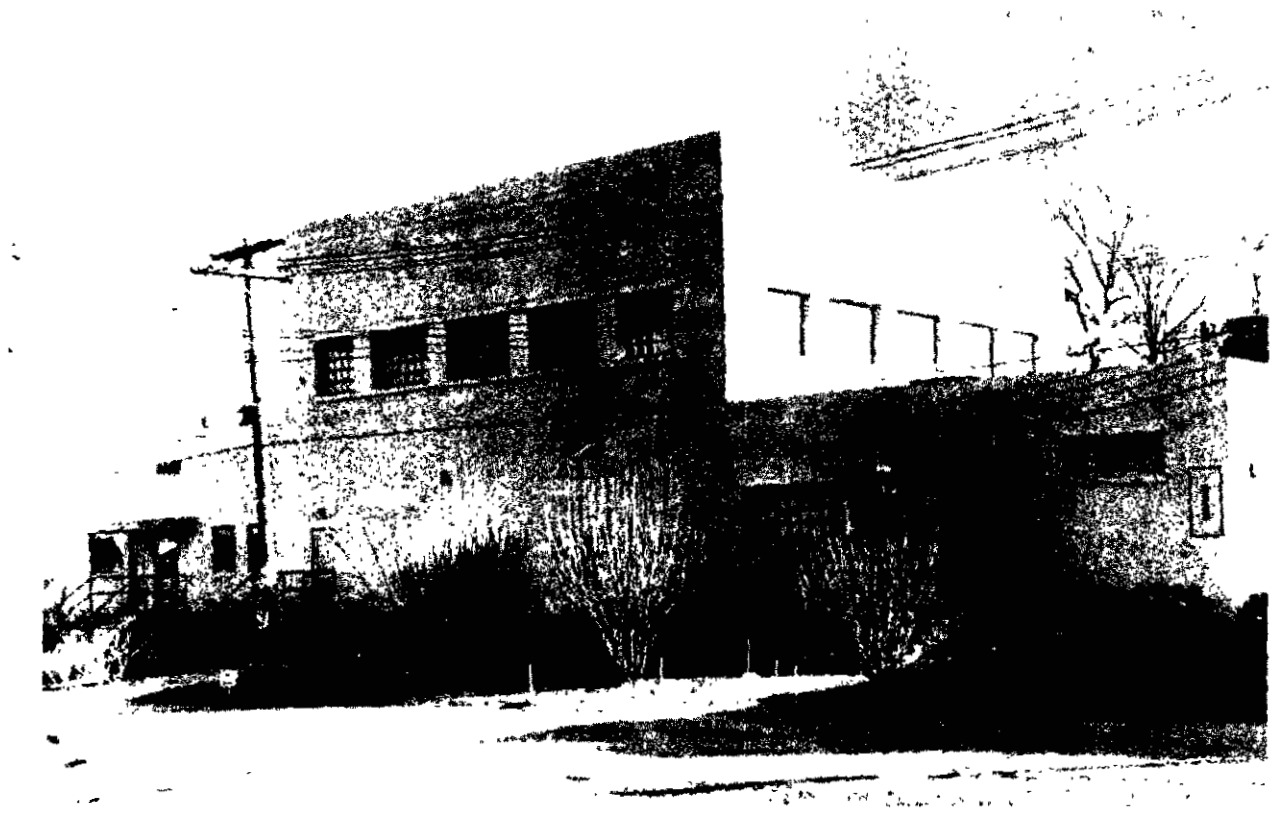
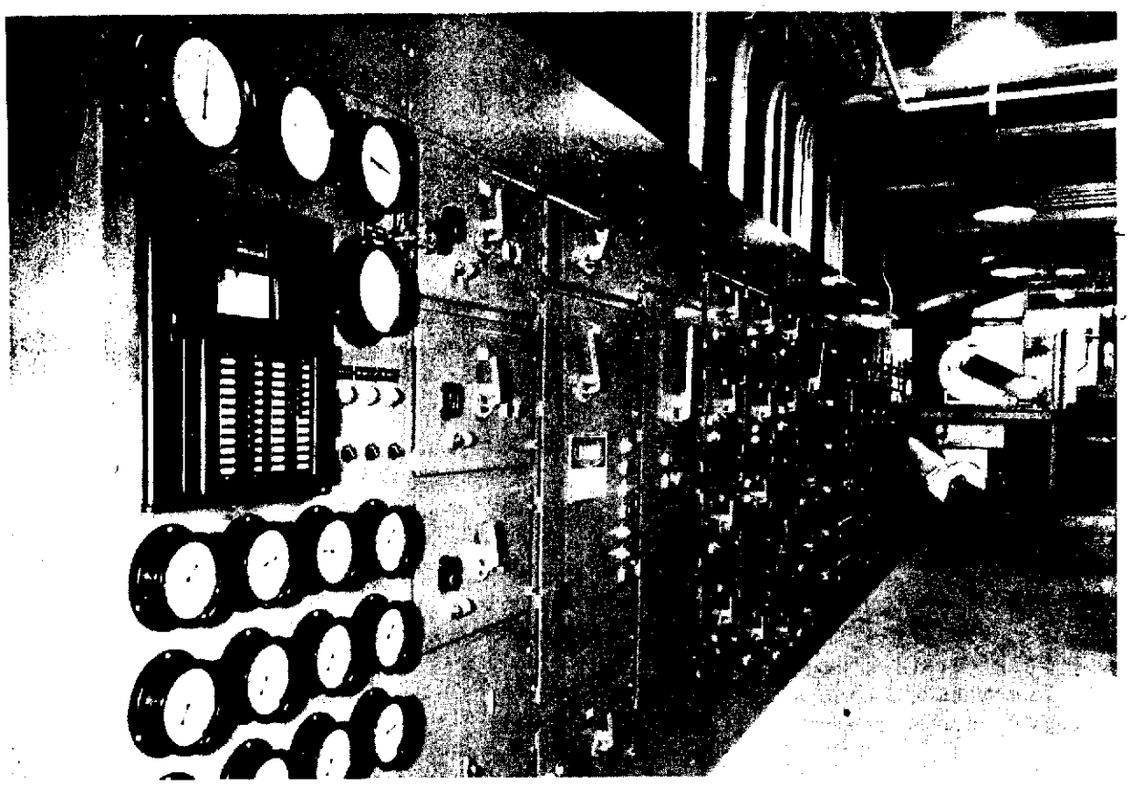
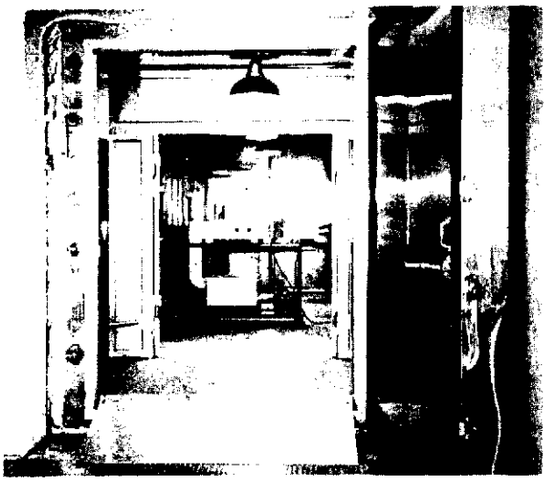


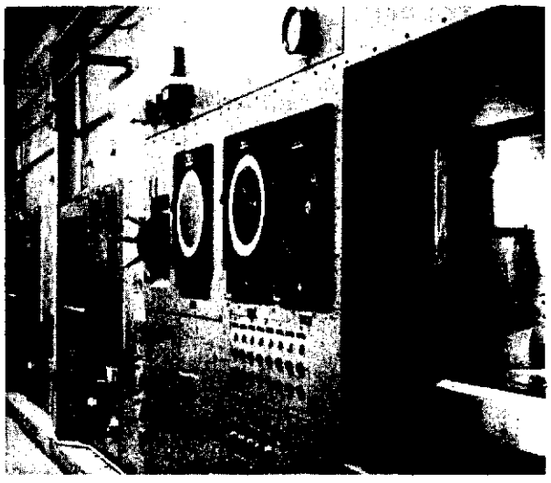
The completion of the Climatic Facility at Chemical Corps Medical Laboratories provides a unique instrument for toxicological research at any of the temperature and humidity conditions that may be encountered in military operations. The Facility is housed in its own building, and consists of a central structure with three principal climatic chambers and the air conditioning equipment, flanked on either side by supporting laboratories. Self-contained mobile units of a new design are a contrast to the fixed exposure chambers used previously in studies of toxic chemicals. The toxic chamber has a space 32 feet long, 9 feet wide, and 8 feet high, with a controlled temperature range from minus 70° to plus 100°F. High humidities are easily obtained over the whole temperature range. The all-weather chamber is 38 feet long, 19 feet wide and 15 feet high, and has the same temperature and humidity range as the toxic chamber. Water can be introduced to simulate rain from a light mist to a heavy downpour. The water can be precipitated at a controlled temperature, making possible a wide range of "weather" conditions from fog to powdered snow. A wind tunnel provides facilities for studies of the effects of air movement up to 45 miles per hour. Because of its interest in environmental physiology, the Physiology Division has taken the lead in planning the Climatic Facility and will have responsibility for coordinating the tasks to be carried out in it.



Control Panel for Refrigeration Equipment



View of mobile exposure chamber in toxic room of climatic facility.



Indicator panel and viewing windows into toxic room from observation corridor.

A research library of over 6000 volumes forms a working basis for the specialized medical-toxicological interests of the scientific staff. Much of this consists of bound journals. A current subscription list is maintained for some 300 journals, American and foreign. In addition, a document library of over 25,000 unpublished reports provides unusual literature search facilities in this vital area. Trained information specialists provide assistance to the staff in collecting data from this source.

A large and well-stocked animal colony houses several thousand laboratory animals. The chief species are mice, rats, guinea pigs, cats, dogs, pigeons, goats and monkeys. Modern methods of maintaining the health of these animals, and efficiency in providing suitable animals needed in the research program, have been an important factor in the success of the laboratories.

Equally important as the animal supply is the adequate instrumentation needed in modern biological research. Electronic equipment has to be kept in working order, special types of laboratory furniture and cages must be devised and constructed, autopsy tables need to be built. A complicated laboratory such as the climatic facility requires skilled refrigeration mechanics and engineers. Throughout Medical Laboratories the work of these technicians make possible the current research program and pave the way for future work.

VI. The Research Program

Research carried on at Chemical Corps Medical Laboratories is an important part of a national program involving many military and non-military government agencies as well as numerous industrial and university research groups, all of which have a vital interest in the hazards associated with the use of toxic chemicals. In addition to the chemical warfare agents these chemicals include insecticides, lubricants, propellant fuels and oxidizers, fire extinguishants and other compounds which present potential hazards. The pattern of the research program reflects the mission of Medical Laboratories as described on page 1.

Exchange of information on toxic chemicals is maintained with all other agencies working on similar problems, and results of Medical Laboratories' research are distributed promptly to other agencies on a "need-to-know" basis. There is a close correlation between the work done at Medical Laboratories and that carried out under the supervision of the Surgeon General, at the Army Medical Research Laboratory, in the Ordnance and Quartermaster Corps, the Corps of Engineers, and at the various arsenals and proving grounds. Close liaison is maintained with the office of the Air Surgeon, the School of Aviation Medicine, the Arctic Aero Medical Laboratory and the Air Research and Development Command. Similar liaison exists with the Office of Naval Research, Naval Research Laboratory, Naval Ordnance, Bureau of Medicine and Surgery, and other bureaus of the Navy which have an interest in poisoning by toxic chemicals.

The results of the Medical Laboratories' research program carried on by permanent staff members (civilian and military) are published as Medical Laboratories Research Reports (MLRR's). Each report represents termination of a significant task or test program in a given project. During 1953 eighty such reports were published and distributed to interested military and civilian agencies. Results of conferences, literature searches, and general activities are published as the occasion warrants, as Medical Laboratories Special Reports (MLSR's). About 30 of these appeared in 1953. Thus the publication program for a calendar year is approximately 120 reports.

A fundamental prerequisite for success of Medical Laboratories' research is continuous contact with civilian scientists who are authorities in specialized areas of the biological, biochemical and chemical sciences. Like many other government research organizations, Medical Laboratories makes use of specially trained scientists and unique university and industrial laboratories in order to enlarge its own research program economically and effectively. Some of this is accomplished by using these scientists as consultants. Other phases of research are assigned to "contractors"; in this way the Chemical Corps can accelerate such aspects of its program as may be necessary. The five-year cumulative funding of the Medical Laboratories contract program in effect in 1953 amounted to approximately $1,800,000.00; this was disbursed through contracts to the following:

Batelle Memorial Institute (Dr. Williams)
Brooklyn Polytechnic Institute (Dr. Gregor)
Columbia University (Dr. Slanetz)
Goodrich (B.F.) Company (Dr. Stevens)
Harvard University (Drs. Radford, Morris) - 2 contracts
Hazleton Laboratories (Dr. Watts)
Indiana University (Drs. Thacher, Robinson) - 2 contracts
Johns Hopkins University (Drs. Dethier, Grob, Richter) - 3 contracts
Lovelace Foundation (Dr. Reif)
Massachusetts General Hospital (Dr. Frazier)
Medical College of South Carolina (Dr. Walton)
Medical College of Virginia (Dr. Haag)
National Opinion Research Center (Dr. Marks)
Southern Research Institute (Drs. Montgomery, Skipper) - 2 contracts
Tufts College (Dr. Roeder)
University of Colorado, Medical School (Dr. Holmes)
University of Delaware (Dr. Clark)
University of Florida (Dr. Lauter)
University of Illinois (Drs. Gordon, Prosser) - 2 contracts
University of Maryland (Drs. Greenhill, Lindenberg) - 2 contracts
University of Michigan (Dr. Seevers)
University of Pennsylvania (Drs. Detweiler, Comroe) - 2 contracts
University of Pittsburgh (Drs. Buchsbaum, Hill) - 2 contracts
University of Utah (Dr. Jager)

University of Virginia (Dr. Chanutin)
University of Wisconsin (Dr. Busse)
New York Psychiatric Institute (Dr. Hoch)

Each contractor reports at periodic intervals to Medical Laboratories. Such reports as are of widespread interest are published as Medical Laboratories' Contract Reports (MLCR's) and distributed to all interested agencies.

Contacts with the scientific world are also maintained by exchange of information through articles in scientific journals, participation in national meetings of professional societies, and dissemination of information, within the restrictions of security, to all persons interested in the hazards resulting from the use of toxic chemicals. Some of this is carried out directly, some through such cooperating agencies as the National Research Council, National Institutes of Health, and the U. S. Department of Agriculture. The net result, however, is that the American citizen benefits directly, as well as indirectly, from Medical Laboratories research on toxic chemicals.

The current research program can be pictured as an advance on five scientific fronts. (1) In order to be able to devise protection against exposure to toxic chemicals, and treatment for cases of poisoning by them, the mechanism of action of the particular compound must be known. (2) Information gained on how the chemical affects the living body enables other scientists to devise protection against poisoning by toxic chemicals. (3) In cases of accidental exposure without such protection, or possible exposure of a military or civilian population to chemical warfare agents, first aid and treatment for exposure to toxic chemicals can be formulated on the basis of knowledge gained in mechanism of action studies. (4) Evaluation of wound ballistics and body armor is another front on which Medical Laboratories research makes significant contributions. (5) In the course of the foregoing programmatic research, much basic and incidental scientific knowledge is acquired; thus contributions to public welfare becomes another front, not an end in itself but a "bonus return" to the taxpayer on money spent for military-sponsored research. This five-fold aspect of Medical Laboratories research can be outlined in the following table.

CML C MEDICAL LABORATORIES RESEARCH PROGRAM
1. Mechanism of Action of Such Toxic Chemicals as: Chemical warfare agents Insecticides Other chemicals of military significance 2. Protection Against Toxic Chemicals by Means of: Protective ointments Protective clothing Gas Masks Decontamination of food and water 3. Treatment for Exposure to Toxic Chemicals by use of: Atropine Artificial respiration Personnel decontamination 4. Wound Ballistics and Body Armor. 5. Contributions to Basic Science and Public Welfare in: Clinical medicine Human physiology and biochemistry Insect physiology Development of special techniques and apparatus

1. Mechanism of Action of Toxic Chemicals

Chemical Warfare Agents. Medical Laboratories exists as a research facility of the Chemical Corps, and as such has a primary responsibility for increasing our store of knowledge - both theoretical and applied - concerning the medical aspects of the use of toxic compounds which can be used as chemical warfare agents. The nerve gases - a group of organic esters of phosphoric acid derivatives - are among the most potent of known chemical warfare agents; they are also most adaptable to long range attack upon civilian populations. For this reason considerable research has been carried out on these toxic chemicals by Medical Laboratories in order to prevent widespread disaster to the United States in the event of the use of nerve gases by a potential enemy. The history and action of the nerve gases are best described in MLCR 18 (Ref. 4), authored by two Medical Laboratories contractor-scientists, and in a paper from Medical Laboratories (Ref. 4A). Nerve gases act as "anticholinesterases"; their toxicity is due to their ability to inhibit the essential cholinesterase enzymes which control normal nervous, muscular, and glandular activities. The mechanism of action of such anticholinesterase compounds was reported in other Medical Laboratories reports (Ref. 3, 5, 6, 8).

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Medical Laboratories' technicians combine the skills of a chemist and those of a biologist in using animals for experimental purposes, to obtain answers on such questions as "why is chemical X toxic" or "what happens when chemical X reaches a certain organ or tissue"?

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In the Physiology Division, scientists measure the effects of nerve gas on respiratory rate, tidal volume, and various body functions. Here an animal subject is enclosed in a body plethysmograph, whose heart action is recorded on an electrocardiograph and blood pressure on a manometer. Such simultaneous measurements enable close correlation of rapidly-developing effects on important body functions, and furnish valuable clues to the type of treatment necessary.

A scientist in the Physiology Division tests the effects of nerve gas on the mechanical properties of exposed lungs of anesthetized guinea pig. The apparatus measures air pressures needed to inflate the lungs to constant volume in constant time.

The least toxic of these, known as DFP (di-isopropyl fluorophosphate) has been studied to increase our knowledge of basic nerve gas action (Ref. 9 thru 16). Mustard gas was one of the first chemical warfare agents, and the only one widely used in World War I. The biological action of mustard continues to be studied since it is an effective agent under certain circumstances. (Ref. 17 thru 21). Phosgene and phosphorus compounds were also studied for their toxicology (Ref. 22-24).

Insecticides. German scientists, in their search for a potent insecticide, discovered the nerve gases. Chemicals have been found man's greatest ally in his warfare against insects. Such chemicals are often also very toxic to man. Thus there is a close relationship between insecticides and the general field of chemicals toxic to man. Close relatives of the nerve gases are the currently used insecticides TEPP (tetraethyl pyrophosphate) and Parathion (diethyl-p-nitrophenyl thiophosphate). Both of these have presented hazards to agricultural users, and deaths have resulted. Studies have been made of these accidental deaths, and precautionary measures suggested (Ref. 25-28). The biological properties and toxicity to mammals of DDT were also subjects of Medical Laboratories research (Ref. 29-32).

Military Chemicals. At a recent tri-service conference on the health hazards of military chemicals, Colonel William E. R. Sullivan, at that time Deputy Commander of the Army Chemical Corps Research and Engineering Command pointed out the need for studies on the potential health hazards of handling certain of the new chemicals used by military and civilians alike.

"Many of the chemicals proposed for use by the military," Colonel Sullivan stated, "may be exceedingly toxic, and only through the investigations performed under this program can we determine the safety precautions which must be observed. All too often in the past, experience has demonstrated that some substances previously considered innocuous are actually harmful and present great danger to life and health. Consider the example of the all-purpose cleaner, carbon tetrachloride. This fluid is commonly used as a degreaser in many households, but it is toxic and the Army permits its use only if no other solvent is available - and then only with stringent safety precautions. The peril contained in this fluid was discovered a long time ago by accidental human poisoning. However, the military departments certainly cannot depend upon accidents to guide them in their handling of military chemicals."*

An important group of chemicals includes those used for the new types of fuels. The age of rockets and guided missiles has ushered in new concepts of transportation. These newer types of engines do not operate on the usual fuels; in their place are special fuels and the necessary "oxidizers" which are a prerequisite for ignition of these power-packed liquids.

By long acquaintance, men who have worked with gasoline engines and the familiar fuels they use have come to know the hazards involved and have learned to take the necessary precautions. But the newer liquids

* MLSR 48, August 1954.

which these power plants consume are far more dangerous. Not only do they provide more powerful explosive combinations, but in themselves they may be poisonous when splashed on the skin or eyes, or when inhaled. Rockets and guided missiles require fuels which have high energy and reactivity. In many instances these fuels, oxidizers and their decomposition products are poisonous, and conditions attending their use may present hazards to personnel.

The research staff of the Chemical Corps Medical Laboratories have had long experience in studying the toxic potentialities of chemical substances, in learning how to avoid dangerous contact, and the treatment measures to be taken in case of exposure to them. With the advent of these newer fuel requirements, the Medical Laboratories scientists are playing a leading role in applying their techniques to the study of toxic aspects of propellants, and in educating the public to the health hazards involved.

The toxicities of a number of propellant fuels have been studied by Chemical Corps Medical Laboratories personnel. Among them are aniline, several alcohols, and hydrazine. (Ref. 34-36, 61, 62-67).

Some oxidizers which are needed to burn these propellants are hydrogen peroxide, liquid oxygen, and red fuming nitric acid. (Ref. 69, 70, 72-75). Using animal subjects, Medical Laboratories scientists found that hydrogen peroxide, as a fine mist, can be a serious toxic hazard, causing tissue damage to the eyes and trachea. Red fuming nitric acid can produce severe burns, but it is also dangerous because it can produce poisoning by inhalation of the fumes.

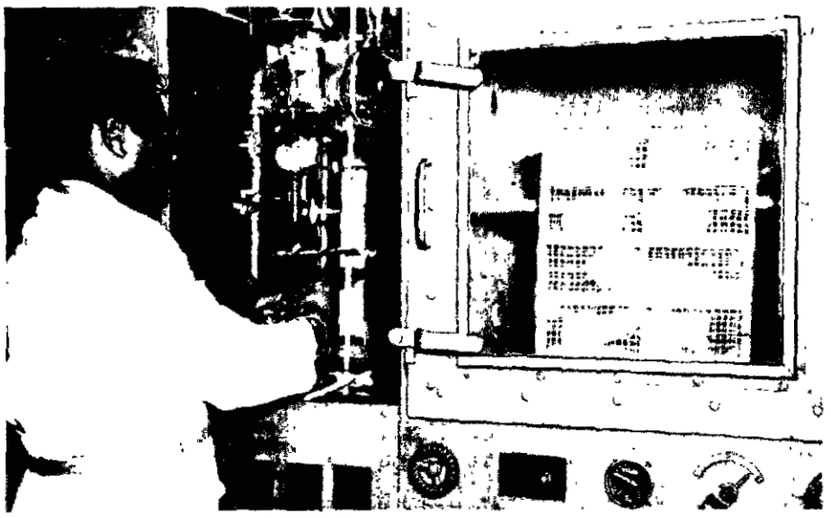
Other chemicals of military interest involve fire extinguishants such as bromomethanes and carbon tetrachloride; (Ref. 48, 49, 50, 58, 59); solvents; various intermediate and decomposition products (Ref. 79, 80) such as tetranitromethane and nitrogen dioxide. In addition, toxicity studies were carried out on diborane, pentaborane, decaborane, and boric acid (Ref. 37-47); on cyanides (Ref. 53-56) and chloropicrin (Ref. 51).

2. Protection Against Toxic Chemicals

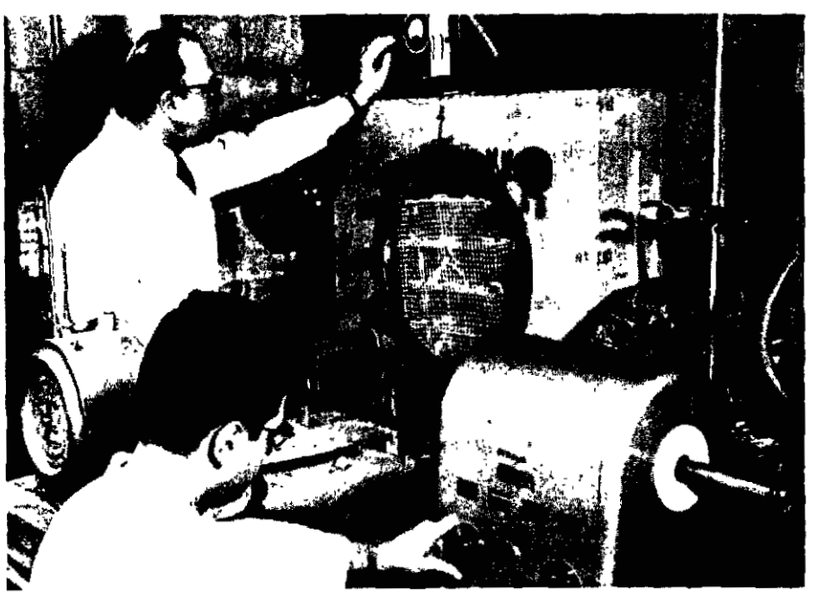
A chemical, in order to be toxic, must be able to gain entry into the body. There are three common routes of entry, each of which constitutes a hazard in exposure to toxic chemicals. One route is through the skin or other exposed surfaces of the body. Chemicals which are poisonous because of their ability to penetrate in this way are said to have percutaneous toxicity. Mustard gas is a chemical warfare agent of this type; the newer insecticides such as TEPP also are dangerous because of their percutaneous toxicity. Protective clothing is a safety precaution for those exposed to percutaneous hazards. Studies on the effectiveness of protective clothing, and the physiological effects on men wearing such clothing, act as a guide to development and improvement of protective clothing for our troops (Ref. 81-86).

Introduction of new fuels for aircraft requires new dispersion techniques in studying the health hazards of vapors from these fuels. On the left is the apparatus for producing the vapor under consideration. This vapor is then introduced in the gassing chamber (right center) containing the experimental animals whose response to the vapor can then be studied.

Considerable chemical analysis of contaminated atmosphere is essential in studies of the potential health hazards involved in manufacture of chemical warfare agents. The use of spectrophotometers (lower left) and photoelectric filter-type colorimeters (center) expedites this analytical work.



In a study of the health hazards of red fuming nitric acid vapor, the acid is allowed to drip over a surface in the column at the left. Vapors emanating from this surface are swept into the constant-flow gassing chamber on the right. The rats in the chamber will exhibit toxic signs depending on the concentration of the vapor and the length of the exposure time.



Medical Laboratories scientists investigate the hazards involved in handling hydraulic fluids. The instrument at the lower right heats the oil to 1500 F; resulting fumes are then cooled by the fins (center) and led into the gassing chamber containing the experimental animals. The instrument in the upper center is measuring the amount of carbon monoxide in the chamber. The instrument on the left measures the air flow.

Other chemicals present a toxic hazard when they are inhaled, either as vapors or aerosols. Inhalation toxicity studies are an important phase of Medical Laboratories research, since a great number of chemicals, other than the nerve gases, gain entry into the body through the throat, nasal passages and lungs. Gas masks are special protective devices to eliminate as far as possible the hazards of inhaling poisonous gases and fumes. The testing of gas masks as well as their wearability and effect on military tasks occupy the attention of special groups in Medical Laboratories (Ref. 87-90).

The poisoning of food and water supplies by chemicals is a constant hazard, both in peace and war. Development of detection and techniques, decontamination of such poisoned materials is another continuous program of the Medical Laboratories research staff (Ref. 91).

3. Treatment for Exposure to Toxic Chemicals

Considerable research has been carried on at Medical Laboratories in the development of first aid kits, therapeutic ointments, antidotes and procedures for use in cases of poisoning by chemical warfare agents. In the case of the nerve gases, such treatment depends upon the prompt use of adequate amounts of atropine. Numerous studies are under way, which have as their aim more accurate knowledge of how atropine and atropine substitutes can be used to prevent nerve gas casualties (Ref. 92-103). Artificial respiration is frequently necessary, as well as atropine therapy. Medical Laboratories has made notable contributions in this field, and in the development of resuscitators (Ref. 104-110).

Therapy for exposure to mustard (Ref. 125, 126) and the use of BAL ointment in poisoning by cadmium and mercuric chloride as well as by mustard (Ref. 120-124) have also been subject to evaluation (Ref. 111-119).

4. Wound Ballistics and Body Armor

Protection of the body against wounding as well as against exposure to chemical warfare agents, is another important aspect of Medical Laboratories research. Studies have been carried out on the effectiveness of steel armor and of nylon armor (Ref. 127, 128, 130, 131), and on the wound ballistics of rifle balls (Ref. 129).

The facilities and the skills which carry on this project are unique, representing a physical plant not duplicated anywhere else, and the integration of such diverse disciplines as electrical engineering, physics, chemistry, physiology, and medicine toward a coordinated solution of the problems. The very special standing of this organization is attested by the fact that all agencies of the Military Establishment as well as certain foreign nations among the free world rely upon this project as the one resource of information on wound ballistics and on certain important phases of body armor.

5. Contributions to Basic Science and Public Welfare

In any research program conducted by able scientists there will inevitably be by-products of public value. In the Army Chemical Corps Medical Laboratories this is certainly the case. An important mission of these laboratories, as the preceding pages demonstrate, is to develop practical procedures and equipment for the prevention and treatment of casualties caused by exposure to toxic chemicals. In order to accomplish this mission the research staff constantly has to acquire so-called "basic" scientific knowledge on the mechanism of action in the biochemical and physiological aspects of chemical poisoning before the more obvious "applied" results can be secured. There is no clear-cut boundary between basic and applied research; it is safe to say that few important contributions in applied research resulting in desired "end-items" have ever been made without the nourishment and stimulus of basic science. This is fortunate for the public who support research, for as a result in a military research program designed for specific objectives, the incidental basic research contributes by-products of value in all walks of life. As an illustration of how such military research can pay off, there is included as Section VII to this publication a revealing article by Colonel John R. Wood, written when he was Commanding Officer of Medical Laboratories (1949) and entitled "Contributions of Chemical Warfare Research to Clinical Medicine."

These by-products of Medical Laboratories research apply in a variety of areas: in clinical medicine, in human physiology and biochemistry, in insect physiology and the study of insecticides, in the development of special biological techniques and apparatus, and in other miscellaneous fields of scientific endeavor related to everyday living. A more complete and also more technical review of Medical Laboratories accomplishments from the period 1945 through 1952 is available (Medical Laboratories Special Report 25, July 1953), based on journal articles and unclassified reports. Some indication of the amount of this work can be gained from the fact that over the period covered (eight years) some 150 journal articles by Medical Laboratories scientists have appeared on clinical aspects of their research; 200 articles on insecticides and insect physiology; and 175 articles on application of our knowledge of toxic chemicals to civilian life.

The aggregate of these results is an impressive picture of the many advantages accruing to the public as an extra dividend on their support of a military research program such as that of Medical Laboratories.

Clinical Medicine. The effect of chemical warfare agents and many drugs on the nervous system has made it necessary for Medical Laboratories staff to study in detail the mechanism of action of toxic chemicals on the brain and the nerve-muscle apparatus. In the course of this work our knowledge of how the nervous system operates has been greatly increased, especially with regard to the pharmacology of the nervous system, cholinergic blocking agents, and related problems. (Ref. 133, 139A, 140, 141A, 142, 144, 145-149, 152, 152A, 152B). Pathological studies of

brain injury (Ref. 143), experimental medical physiology (Ref. 135, 138) and clinical data on insecticide poisoning (Ref. 136, 141) are other areas in which Medical Laboratories has made contributions to medicine.

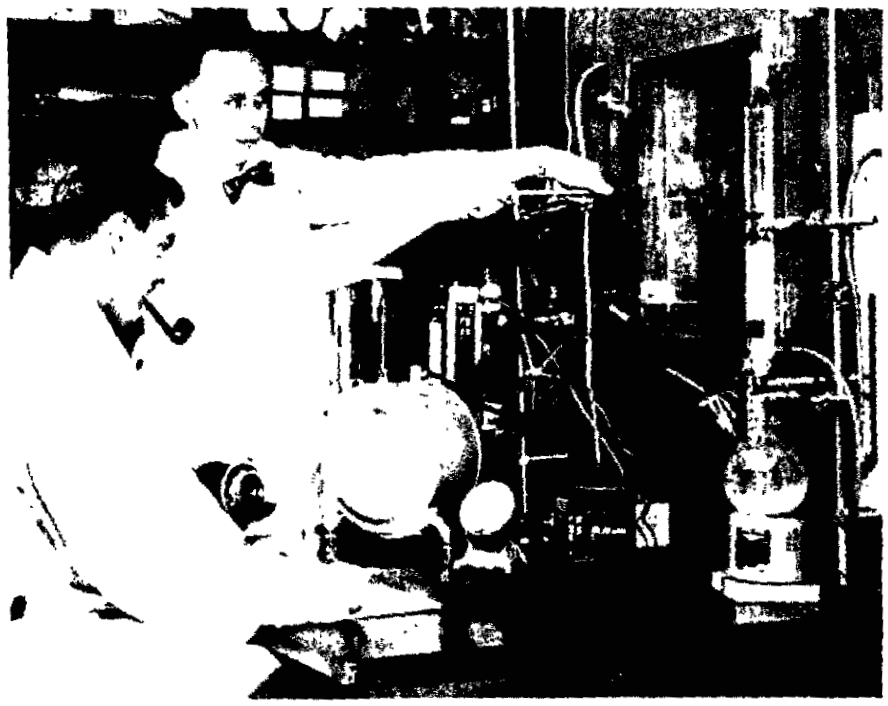
Human Physiology and Biochemistry. A unique advantage of Medical Laboratories is the close liaison effected by chemists and biologists in tackling problems which overlap both fields. This is particularly evident in mechanism of action studies on toxic chemicals carried out by the physiologists and the biochemists. In this area of mutual interest, scientists from these two disciplines join their efforts to solve some of the pressing enigmas of enzyme activity and inhibition (Ref. 159, 165, 167, 168, 171), biophysical phenomena (Ref. 156, 175), and aerosol behavior (Ref. 154-173). General physiological phenomena included studies on tolerance of animals to heat and cold (Ref. 153, 161, 163, 173) and effects of exercise (Ref. 177).

Insect Physiology. Agriculture is a major activity of a large percentage of mankind; the increasing demands of feeding growing populations have made it necessary to carry on a constant chemical warfare program against those insects which impair our agricultural yield. The nature of insecticides and their effect on insects constitute areas of research closely allied to those of Medical Laboratories. In addition, many insecticides are toxic to man as well as to insects. Human fatalities occur when careless operators are unfamiliar with the proper precautions of handling such dangerous insecticides as TEPP and Parathion. Biochemical and physiological studies of these insecticides have already been discussed (pp. 5, 13). Basic insect physiological studies have included chemoreception (Ref. 180, 182, 184, 191, 195, 201, 202); laboratory rearing methods (Ref. 178, 179); reaction of insects to radioactive compounds (Ref. 185, 186, 190, 192); cholesterol metabolism (Ref. 194, 203); DDT action (Ref. 181, 188) and factors influencing cholinesterase activity (Ref. 205, 206, 207).

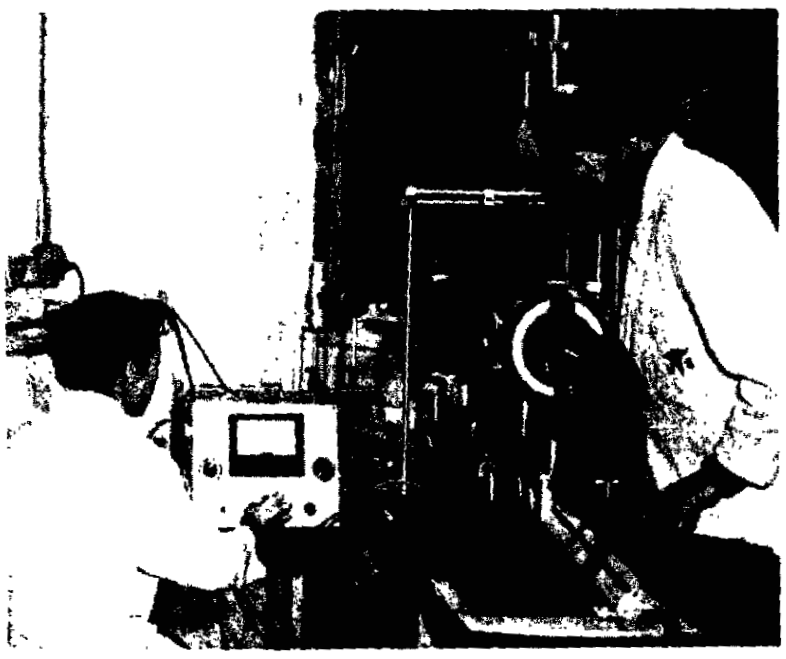
Special Techniques and Apparatus. In modern biological research, special equipment and techniques often have to be developed in order to solve a particular research problem. Instrumentation is particularly vital. Many of these newer biological techniques are of far-reaching importance to other laboratories working on similar problems. Techniques for determination of cholinesterase activity (Ref. 212, 217, 220); methods for determination of chlorides (Ref. 209, 210); micro-determination of chloropicrin (Ref. 214); development of a probe-type counter for detection of B-particles (Ref. 215); apparatus for determining retained doses of inhaled gases (Ref. 211); and an electrolytic method for determination of enzyme activity (Ref. 223) are a few of the contributions Medical Laboratories staff have made in this field.

Other Fields of Scientific Interest. As occasion demands, the research facilities of Medical Laboratories and its contractors are utilized to help in solving problems related to the Chemical Corps mission. The

importance of knowing how disasters, created by new weapons, might affect the military or civilian population, stimulated an investigation along these lines. (Ref. 225, 227, 228). Problems in maintaining an animal colony capable of meeting medical research demands were also investigated (Ref. 229, 230).

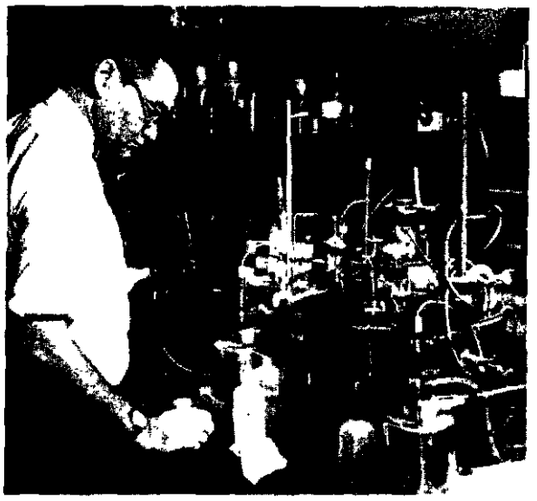


Laboratory technicians operate a toxic vapor-aerosol chamber in the Aerosol Branch.



The chief of the Physicochemical Branch, Toxicology Division, checks the calibration of an optical interferometer, used to measure the thickness of single molecular layers and to follow chemical reactions on those layers.

Enzymes which have been reactivated with radioisotope-labelled toxic agents and then partially digested are added to an ion-exchange resin column. The wash fluid in the bulb above this column then washes the enzyme fractions and separates them. Individual fractions are collected by an automatic device and analyzed. Such research aims to find the answer to the question "with which part of the enzyme does the toxic chemical combine"?



The blood sample under study is contained in a small beaker above the magnetic stirrer, and surrounded by a larger beaker which is maintained at a constant temperature by the apparatus at the right. Electrodes in this reaction vessel lead to the pH-meter in front of the investigator. Acidity in the mixture is kept constant by the addition of alkali from the microburette above the pH meter. The rate of addition of this alkali is a measure of enzyme activity.

Standard outfit and new designs in clothing used by the various branches of the Services are worn in contaminated air to determine their effectiveness in protecting against toxic agents.

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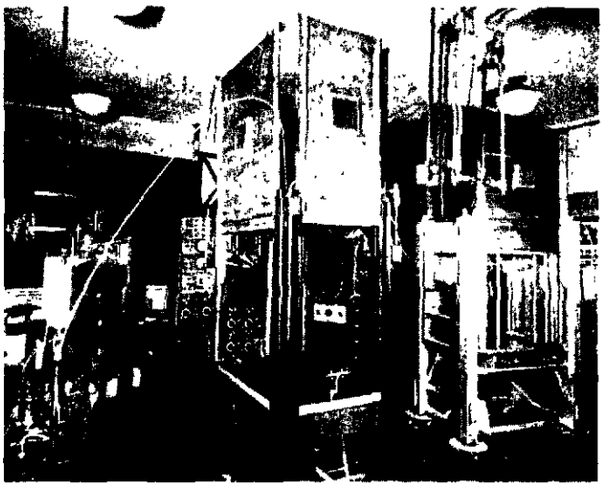

Electrical activity of the nervous system can be recorded by special laboratory equipment. This assembly provides simultaneous photographic recording of six independent phenomena displayed on cathode-ray oscilloscopes after adequate amplification. In the center and right foreground are two shielding chambers which permit two concurrent experiments. In the right background are the amplifiers. In the center background (partially hidden) are the cameras, oscilloscopes and accessory electronic equipment. In the left background is equipment for localization of radioisotopically labelled compounds which may be used.

Brain waves can be used as an index of nervous system activity. The brain waves (electroencephalograms) from a subject placed inside the ventilated shielding chamber at the right are recorded by the console-type instrument at the left center. Automatic frequency analysis of the brain wave is accomplished concurrently by the electronic equipment in the center background. The accessory equipment on the table at the right permits exposure of the subject to repeated, brief flashes of light in order to activate his nervous system.

VII. CONTRIBUTION OF CHEMICAL WARFARE RESEARCH TO CLINICAL MEDICINE

John R. Wood, Colonel, Medical Corps
Chief, Medical Division*

It is inevitable in any large scale research program, conducted by some of our most able scientists, that there will be by-products of public importance. In the chemical warfare program, this is fortunately the case in the field of clinical medicine.

Early in the war, the Oxford University group in England, under R. A. Peters, began an intensive search for an antidote for the toxic actions of lewisite, one of the arsenical blister gases. Like other active trivalent arsenicals, it combines rapidly and firmly with proteins.

As far back as the early nineteen hundreds, it had been postulated that trivalent arsenicals are toxic by reason of their attack on the sulfhydryl (SH) groups in vital body proteins. Time will not permit presentation of all of the interesting details. Very briefly it was proven that trivalent arsenic knocks out enzyme systems containing SH groups, which are vital to body oxidation reactions; the arsenic-sulfur bond thus formed is dissociable to some extent. It was reasoned that if a relatively nontoxic, synthetic mercaptan could be discovered, which would form a tighter bond with arsenic than that between arsenic and the SH groups of body proteins, two things might be possible. First, the synthetic mercaptan might compete successfully with body proteins for uncombined arsenic, and second, that it might be able to gradually reverse the combination between arsenic and body proteins. If the latter could be accomplished before the essential body proteins are destroyed, it might be possible to free the SH groups and restore the body proteins to normal.

A detailed biochemical study of available sulfhydryl compounds was therefore begun, both in the test tube and in the living animal. Finding that none met their criteria, research workers synthesized a series of monothiols and dithiols. It was soon apparent that the dithiols were more effective in competing for arsenic. This led to their discovery of 2, 3-dimercapto-propanol, which was given the code name, BAL, for British anti-lewisite. This compound not only strongly and successfully competes for free arsenic in the body, but, used early, it can actually "unscramble the eggs," by peeling arsenic off of the vital SH groups, and restore the essential body proteins to normal. BAL was highly effective in preventing or treating systemic arsenic poisoning in experimental animals, caused by lewisite. BAL therefore ranks as one of the few really specific remedies known to medicine.

The success attained in treating lewisite arsenical poisoning with BAL suggested that it might succeed in antidoting other forms of arsenic poisoning. The most immediately available cases were 7 individuals from

* written by Col Wood in 1949.

Army Chemical Center, Md., who had arsenical dermatitis due to the chemical warfare agent, DM. The cases were transferred to Dr. Longcope at Johns Hopkins Hospital and treated with BAL. The response was dramatic. All 7 cases were promptly cured in an average of 5 days.

With this spectacular beginning, BAL was placed at the disposal of first 40, later about 200, rapid treatment centers which were treating syphilis with arsenical drugs. Under the auspices of the U.S. Public Health Service, BAL was tried in these centers for a variety of the serious arsenical reactions, which occasionally follow the use of the arsenical drugs. The most alarming and highly fatal reaction is that due to poisoning of the brain, commonly called arsenical encephalitis. Out of fifty-five cases of this type, treated with BAL, fifteen were classed as mild, meaning that they were disoriented, had hallucinations, and were either in a semi-stupor, or were hyperexcitable. All of these responded promptly to BAL injections and recovered in 2 or 3 days.

Forty cases were severe, meaning that they were in convulsions, or deeply unconscious, and apparently progressing toward a fatal termination. Of these, 31 were treated with BAL within 6 hours of their initial seizure. Twenty-four of these recovered completely in 2 to 7 days, and 7 died; a mortality of 23%.

Another very grave reaction occasionally seen in these rapid treatment cases is agrnulocytosis, a condition in which all of the granular white blood cells are destroyed and the bone marrow injured. There were 11 of these cases treated with BAL. Ten of them recovered rapidly and only one died, which is a very favorable record for these serious cases.

One of the most frequent and distressing reactions seen in these cases is exfoliative dermatitis, in which large areas of the skin inflame, crack open, ooze serum, and develop pustules. The itching and discomfort are intense and the patient is toxic and often gravely ill. The severe cases which survive usually require from 2 to 3 months for the skin to heal. One hundred and thirty-three such cases have been treated with BAL according to reports from groups in this country and England. About 80% of these cases responded promptly to BAL, with marked relief from the distressing symptoms in about 3 days. They show 75% to 90% healing of the skin in 2 weeks. This probably represents the maximum benefit due to the neutralization of arsenic in the lesions by BAL.

Experimental work by the Medical Division and the University of Chicago Toxicity Laboratory has shown that BAL, or certain of its analogues, is very effective for the treatment of poisoning by other toxic metals, such as mercury, zinc and cadmium. Similar work by the Food and Drug Administration has shown BAL to be an effective antidote for poisoning by antimony, bismuth, chromium, nickel and mercury.

Based upon our experimental data on the favorable effects of BAL on mercury poisoning, Dr. Longcope made arrangements with the hospitals and Police Department of Baltimore to send all bichloride of mercury poisoning

cases to The Johns Hopkins Hospital, where he could treat them with BAL. Forty-three cases have now been so treated with only 2 deaths - an astoundingly low mortality.

But this is not the whole story. Mercury poisoning is often a lingering and extremely distressing illness, requiring weeks to months for recovery of the survivors. In striking contrast, the BAL treated cases improve in a few hours, and all cases treated within 4 hours were completely well in 2.5 to 7 days. Cases treated late recover more slowly, because of damage to the kidneys, which has already occurred. The longest case in this series was treated 19 hours after swallowing 3 bichloride tablets, but even this patient was completely well in 3 weeks.

Recently BAL has been applied to the treatment of gold poisoning. This sometimes occurs during the treatment of arthritis with gold pharmaceuticals. Toxic reactions to gold are quite serious and may result in severe exfoliative dermatitis, agranulocytosis, or encephalitis, remarkable like those seen in arsenic poisoning. Thus far, 12 cases treated with BAL have been reported from 3 clinics. Ten of these were exfoliative dermatitis. Nine recovered rapidly. One was a severe encephalitis case, who had also internal hemorrhages, and had lost all of his blood platelets. The patient dramatically improved under BAL treatment, with prompt regaining of consciousness and cessation of bleeding; he went on to rapid recovery. The other case was an agranulocytosis, whose granular white blood cell count dropped to practically zero and he became gravely ill. His recovery was rapid under BAL, and in just 12 days his blood count was normal and remained so.

Experimental work to date has shown that BAL is of no value for poisoning by lead, thallium, or selenium. In spite of this, BAL offers new hope, probably of a different order of magnitude, for the treatment of many of the common metal poisonings. BAL in oil is now commercially available from Hynson, Westcott and Dunning, Inc., Baltimore.

Some have considered it surprising that any of the war gases should prove useful as drugs. When it is remembered, however, that the term "highly toxic chemical" is practically synonomous with "highly active drug," there is less wonder that intensive studies of such compounds should reveal some of value to the physician. The nitrogen mustards are typical examples. Mechanism studies soon revealed that these compounds, when injected by vein, had a highly destructive effect on white blood cells, lymph glands and bone marrow. This suggested their use in the leukemias, in which there is an overproduction of white blood cells, and in Hodgkin's disease and lymphosarcoma, in which there are tumor growths of the lymph glands. These are all fatal forms of cancer. From a cautious beginning, the trial of the nitrogen mustards in cancer has now spread to at least 126 clinics, and hundreds of cases are now under treatment. More than 20,000 doses of HN-2 hydrochloride have been sent to these clinics, and more than 500 case reports have been collected by the National Research Council Committee on Growth. The nitrogen mustards

for this work were prepared by the Chemical Corps. The treatment sets are made up by Merck and Co., Inc., and are distributed for clinical study by the National Research Council Committee on Growth.

Clinical trials have been expanded to include a variety of types of cancer. The Committee on Growth is now compiling and summarizing data from the case reports, which will be published in due course. The first of these summaries has been released. It gives the results in 30 cases of various types of cancer of the lungs. Seventy percent of these cases obtained a definite favorable response, with remissions lasting 3 weeks to 6 months, but none was cured. All 21 cases had decreased or abolished cough and sputum, relief from shortness of breath and disappearance of bleeding from the lung. Most cases gained in strength, weight and appetite and in many the lung tumor greatly diminished in size. However, 30% of the cases obtained no significant benefit from treatment with HN-2.

Approximately 160 cases of cancer of all types, treated with nitrogen mustards, have now been reported in the medical literature. It is clear from the reports thus far that the nitrogen mustards probably do not cure any form of cancer, but they do prolong life in many instances, and bring about remarkable remissions in some cases. They are most effective in Hodgkin's disease and in certain forms of cancer of the lungs, where they appear to induce good remissions in about 70% of the cases. The response of lymphosarcoma is spotty, and the remissions are shortlived. They accomplish about as much in the leukemias as x-ray, but they are of less value than x-ray in most other forms of cancer.

It is too early yet to draw many final conclusions about the value of these agents in controlling cancer, but certain tentative ones appear to be justified. If the disease is widespread, or if it responds poorly to x-ray, the nitrogen mustards should be tried, either alone, or in combination with x-ray.

HN-2 merits consideration as the treatment of choice in 3 types of cases. First, in cases of Hodgkin's disease, when the cancer process is scattered widely over the body. In these cases sufficient x-ray to induce a remission cannot be given. X-ray to so extensive an area would endanger the life of the patient. Second, for cancer of the lung, when the main internal vein in the chest (the vena cava) is partially obstructed by pressure of the tumor. X-ray in these cases causes the tumor to swell and further compress the vena cava, resulting in dangerous edema. Nitrogen mustard does <u>not</u> cause the tumor to swell and avoids this risk. Third, the so-called "x-ray fast" cases, which no longer respond to x-ray or other forms of cancer therapy. HN-2 will induce a remission in at least some of these cases, and a few such cases have been reported as again becoming susceptible to x-ray, after HN-2 treatment.

Nearly 100 additional nitrogen mustards have now been prepared. They are being intensively studied as possible cancer drugs in a coordinated program. The work is being done by the Medical Division and Johns Hopkins University Medical School, in New York by the Memorial Hospital and

Sloan-Kettering Institute, in Chicago by the University of Chicago Toxicity Laboratory, and in Birmingham by the Southern Research Institute. Much of the work is supported by grants from the American Cancer Society.

Another of the new chemical warfare agents, which has found its place in clinical medicine, is di-isopropyl fluorophosphate, now abbreviated to "DFP" in the scientific literature. Studies of the mechanism of action of this compound at the Medical Division and elsewhere revealed that it would destroy the enzyme, cholinesterase. This was a unique property, not possessed by any other known drug, since other drugs merely suppress the enzyme for a few hours.

Cholinesterase occurs in many tissues of the body, but it is highly concentrated in the nervous system, particularly in nerve ganglia and at the terminal ends of the nerves. In the passage of a nerve impulse, say from brain to muscle, the impulse must pass across certain gaps, or connections in the nerve path, called synapses. The passage of the impulse is made possible at these points by the liberation of tiny quantities of acetylcholine at the nerve endings. However, the acetylcholine must be quickly gotten rid of, or the nerve will continue to fire impulses past the synapse. This would cause the muscle to be overstimulated and go out of control. The rapid destruction of these tiny charges of acetylcholine is a function of the cholinesterase concentrated at these points. This enzyme splits acetylcholine to choline and acetic acid with extreme rapidity. Thus, only the main impulse passes, and the multiple sub-threshold impulses are stopped.

If all cholinesterase is knocked out, a variety of severe and distressing symptoms occur, followed by convulsions and death. If, however, only a fraction of the esterase is destroyed, then the effects which follow will depend upon the degree of depletion of the enzyme in the various parts of the nervous system. Thus, by controlling the dose of a drug like DFP, it is possible to reduce the cholinesterase more strongly in the most sensitive parts of the nervous system, without significant effects on the more resistant parts.

Studies of DFP indicated that the autonomic nerves which control certain involuntary smooth muscles were affected by the smallest doses of DFP. If the drug is injected, the muscles of the intestine and urinary bladder are very sensitive. If locally applied, either as a vapor or solution, two other sets of involuntary muscles are extremely sensitive. These are the muscles which control the size of the pupil of the eye, and the muscles which control the diameter of the smaller air passages in the lungs. In each of these systems, DFP causes a strong contraction of the muscles concerned. It is possible to counteract these effects by the use of atropine.

If atropine is used to control the effects of DFP on these sensitive structures, it is possible to give larger doses, until the more resistant parts of the nervous system begin to be affected. It was hoped in this way to be able to give enough DFP to affect the nerve endings in the muscles, or its too rapid destruction by too much cholinesterase at these points.

Considerable experience with a drug, called Prostigmine, which suppresses cholinesterase for several hours, had shown that this type of treatment is the only satisfactory one to induce a return of strength to the weak muscles. However, Prostigmine has two disadvantages. Its effects last such a short time that a severe myasthenic must take many doses per 24 hours. Prostigmine is also quite expensive, and the severe myasthenic must budget one to several dollars per day just for the purchase of the drug. DFP, on the other hand, has a very prolonged effect and it is quite cheap.

It was therefore with some enthusiasm that the staff at the Medical Division and a group at the University of Pennsylvania jointly undertook the clinical trial of DFP, first in normal men and then in myasthenic patients. Arrangements were also made with the Johns Hopkins Hospital to undertake similar studies, plus some very ingenious mechanism of action studies of DFP in human patients.

Trials in the normal subjects soon revealed that the dose of DFP which could be tolerated by man was very small, because of its high toxicity for the brain and other sensitive regions of the nervous system. Myasthenics similarly could tolerate only small doses. Seventeen myasthenics were carefully chosen for treatment, to represent all degrees of severity and distribution of the disease among the various muscle groups of the body. Of these 13 had appreciable gains in strength from DFP treatment. Two more were greatly improved, but it could not be certain whether the improvement was due to DFP, or to natural remissions which occur in this disease. Only 2 were not benefited at all.

Our next clinical application of DFP met with much greater success. There is a serious eye disease, called glaucoma, in which the pressure develops in the eyeball. This leads to marked impairment of vision, and unless the pressure is relieved, will cause blindness in a high percentage of cases. The only non-surgical treatment is the use of drugs which cause constriction of the pupil, thus affording better absorption of the excess fluids from the interior of the eyeball. Certain drugs, such as eserine and Prostigmine, will do this, but their action is of short duration, and they must be applied at frequent intervals. Local application of a very small amount of DFP in the eye causes the pupil to constrict to pinpoint size. Its action is also very prolonged, the pupillary constriction usually lasting one to several days in the normal eye.

Accordingly, arrangements were made to have a clinical study of DFP in the normal eyes and glaucoma at the University of Pennsylvania. The results in glaucoma have been very favorable. It has not failed once to control the disease in any case which could be controlled by any other drug, or combination of drugs. But more important, it succeeded in controlling glaucoma in 36 of 78 eyes when all other drugs had failed. In addition, the effects of DFP were so prolonged that its administration was required only one-fifth as often as other drugs, averaging less than 6 doses per week. It offers an economic advantage, too. The 0.1% solution of DFP costs very little. The other drugs are relatively expensive.

This ophthalmic solution may be obtained for clinical trial from Merck and Co., Inc., Rahway, New Jersey.

It is also true that small injected doses of DFP cause contraction of the intestine and urinary bladder. At the Johns Hopkins Hospital clinical studies have been made of DFP, for the treatment of conditions in which these organs are involved.

It was applied first for the relief of urinary retention and distention of the bladder, which often occurs after general anesthesia, and in invalids during prolonged confinement to bed. It has now been applied to some 60 such cases with excellent results. It fails only when the nerve supply to the bladder has been blocked or destroyed.

One of the most troublesome and frequent conditions following abdominal surgery is paralytic ileus, in which the motility of the intestine is lost and the bowel distends with gas. The condition also occurs in severe illness, such as pneumonia, peritonitis, and diseases of the spinal cord. Moderate cases make the patient miserable, with nausea, vomiting and abdominal pain. Severe cases are alarming, and may cause the patient to become toxic, or even proceed to shock and death. Available means of treatment have heretofore been quite disturbing to these ill patients and rather unsatisfactory in the severe cases.

DFP has now been applied to 64 cases of paralytic ileus. All of these were difficult cases, which had not been relieved by the usual measures; forty-six of them were severe cases.

DFP acts first to sensitize the non-motile, distended gut, and gives it tone. This occurred in a uniform manner in all 64 cases within 1 to 2 hours after an intramuscular injection of just 2 milligrams of DFP in peanut oil. If the case is a moderate one, rhythmic contractions of the intestine may start spontaneously, shortly after the gut becomes sensitized. The contractions are usually more gentle than the forceful contractions, which often follow the administration of other drugs, and painful cramping was rarely encountered. Due to the prolonged action of DFP, the rhythmic movements of the intestine continue for 2 to 5 hours, bringing striking relief of the distressing condition. Ordinarly, one or two more doses of just one milligram each of DFP, spaced 12 hours apart, is sufficient to give complete relief to these cases.

When a potential new war gas, such as DFP, can be directed to the relief of so much human misery, it is a source of satisfaction to be associated with chemical warfare research.

A Medical Library with some 7,000 volumes of bound journals and reference books provides research literature for the Medical Laboratories staff.

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APPENDIX 1

Research Personnel, Chemical Corps Medical Laboratories,
as of December 1954

Senior civilian research staff members arranged alphabetically are as follows:

*Anderson, Rupert S., Ph.D., Columbia, 1925: Chemistry (Enzyme). Wound Ballistics Branch. Special Interests: Enzyme and chemical physiology.

*Bales, Paul D., A.M., Indiana University, 1928: Physics. Applied Physiology Branch. Special Interest: Coordinator of operations of climatic facilities.

*Barry, Michael C., M.D., Yale, 1947: Medicine. Ass't Chief, Physicochemical Branch. Special Interests: Radioactive tracers in metabolism; clinical metabolism.

Bauer, Virginia E., A.B., Goucher College, 1940: Chemistry. Sanitary Chemistry Branch. Special Interest: Water purification.

*Bodenstein, Dietrich, Ph.D., University of Freiburg, Germany, 1954: Zoology. Entomology Branch. Special Interests: Insect endocrinology and developmental physiology.

*Chadwick, Leigh E., Ph.D., Harvard, 1939: Biology (Entomology). Chief, Entomology Branch. Special Interest: Insect physiology.

*Chambers, William H., Ph.D., Washington University, 1920: Physiology. Ass't Scientific Director and Chief, Physiology Division. Special Interests: Physiology, biochemistry, and toxicology of chemical compounds.

Clements, John A., M.D., Cornell, 1947: Medicine. Ass't Chief of Clinical Investigation Branch and Civilian Medical Deputy of Commanding Officer. Special Interest: Respiratory physiology.

Cornish, Edwin R., Jr., M.D., University of Pennsylvania, 1947: Medicine. Applied Physiology Branch. Special Interest: Medical physiology.

*Craig, Francis N., Ph.D., Harvard, 1937: Physiology. Chief, Applied Physiology Branch. Special Interest: Metabolism; environmental physiology.

*Dill, David B., Ph.D., Stanford, 1925: Biochemistry and physiology. Scientific Director. Special Interests: Applied Physiology; offensive and defensive problems of CW.

*Dziemian, Arthur J., Ph.D., Princeton, 1939: Physiology. Chief, Wound Ballistics Branch. Special Interests: Burn and traumatic shock; wound ballistics.

*Epstein, Joseph, M.S., University of Pennsylvania, 1940: Chemistry. Chief, Sanitary Chemistry Branch. Special Interests: Reaction kinetics; food and water chemistry.

Fleisher, Joseph H., M.S., University of Michigan, 1940: Chemistry. Enzyme Chemistry Branch. Special Interest: Effects of toxic chemicals on tissue metabolism.

Freeman, Gustave, M.D., Duke University, 1934: Medicine. Chief, Clinical Investigation Branch. Special Interest: Clinical investigation of chemical casualties.

Gordieyeff, Vladimir A., Ph.D., University of Warsaw, 1935: Chemistry. Aerosol Branch. Special Interests: Colloidal chemistry and spectroscopy.

Grossman, David, B.S., Rensselaer Polytechnic, 1940: Electronics. Chief, Research Instruments Branch. Special Interest: Research instrumentation.

*Hart, E. Ross, Ph.D., California, 1940: Pharmacology. Chief, Neurology Branch. Special Interest: Nerve impulse transmission.

*Hassett, Charles C., Ph.D., Johns Hopkins University, 1941: Physiology. Ass't Chief, Entomology Branch. Special Interest: Insect physiology.

*Herget, Carl M., Ph.D., Johns Hopkins, 1940: Physics. Chief, Biophysics Division. Special Interest: Biophysics of body mechanisms.

*Horton, Richard G., Ph.D., Cornell, 1937: Physiology. Ass't Chief, Field Toxicology Branch. Special Interest: Physiology and toxicology of the nervous system.

*Hylander, Clarence J., Ph.D., Yale, 1925: Biology (Botany). Chief, Technical Information Office. Special Interests: Technical writing and dissemination of scientific information.

Innes, James R. M., Ph.D., Cambridge University, Emmanuel College, 1931. Chief, Pathology Branch. Special Interests: Pathology of diseases of man, animals and laboratory animals with particular reference to diseases caused by bacteria, viruses, protozoa and worms.

Jacobson, Keith, Ph.D., University of Cincinnati, 1949: Biochemistry. Gassing Branch. Special Interest: Industrial toxicology.

*Jandorf, Bernard J., Ph.D., Harvard, 1942: Biochemistry. Chief, Enzyme Chemistry Branch. Special Interests: Tissue metabolism and isolation and properties of enzymes.

Joffe, Milton H., Ph.D., Ohio State University, 1949: Physiology. Field Toxicology Branch. Special Interest: Respiratory physiology.

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*Kondritzer, Albert A., Ph.D., Cincinnati, 1938: Biochemistry. Chief, Pharmaceutical Chemistry Branch. Special Interest: Pharmaceutical Chemistry as related to CW.

Krackow, Eugene H., B.A., Johns Hopkins, 1934: Chemistry. Chief, Toxicology Division. Special Interest: Inhalation toxicology and aerosol therapy.

Krauss, Max, Ph.D., California Institute of Technology, 1949: Biology. Ass't Chief, Wound Assessment Branch. Special Interest: Histophysics of wounded tissue.

*Krop, Stephen, Ph.D., Cornell, 1942: Pharmacology. Ass't Chief, Physiology Division. Special Interests: Pharmacology and physiology of circulation and respiration. Coordinator of Military Chemicals Project.

Kunkel, Anne M., M.S., University of Maryland, 1940: Pharmacology. Pharmacology Branch. Special Interest: Therapy of chemical warfare agents.

*Light, Frederick W., Ph.D., Johns Hopkins University, 1948: Mathematics. M.D., Johns Hopkins University, 1930: Medicine. Chief, Wound Assessment Branch. Special Interest: Pathology of trauma.

*Marrazzi, Amedeo S., M.D., N.Y.U. College of Medicine, 1928: Medicine. (Physiology and Pharmacology). Chief, Clinical Research Division. Special Interests: Nerve impulse transmission and localization of drug action in nervous system.

*Marzulli, Francis N., Ph.D., Johns Hopkins, 1940-41: Physiology. Chief, Field Toxicology Branch. Special Interests: Toxicology, respiratory physiology.

McGrath, Francis P., M.S., Georgetown, 1938: Biochemistry. Ass't Chief, Gassing Branch. Special Interests: Inhalation toxicity and physiology of chemical compounds.

*McNamara, Bernard P., Ph.D., Maryland, 1942: Pharmacology. Chief, Aerosol Branch. Special Interests: Mechanism of action of CW agents and methods of therapy.

*Michel, Harry O., Ph.D., Duke, 1938: Biochemistry. Ass't Chief, Enzyme Chemistry Branch. Special Interest: Kinetics of enzymatic reactions.

*Oberst, Fred W., Ph.D., State University of Iowa, 1930: Organic Chemistry. Chief, Gassing Branch. Special Interest: Inhalation toxicology.

*Odell, Floyd A., Ph.D., Yale, 1940: Biology (Anatomy). Ass't Chief, Biophysics Division. Special Interest: Biophysics of wound ballistics and body armor.

O'Leary, John J., Ph.D., University of Rochester, 1951: Pharmacology. Pharmacology Branch. Special Interests: CW mechanism and military chemicals.

O'Neill, John J., M.S., University of Maryland, 1953: Organic chemistry. Medicinal Chemistry Branch. Special Interest: Biochemistry of enzymes and their organic chemical models.

Plapinger, Robert, Ph.D., University of Maryland, 1951: Organic chemistry. Medicinal Chemistry Branch. Special Interest: Reactions of organic compounds with enzyme inhibitors.

*Robinson, Ellis J., Ph.D., N.Y.U., 1934: Physiology. Wound Ballistics Branch. Special Interest: Biophysics of body mechanisms.

Rosenblatt, David H., Ph.D., University of Connecticut, 1950: Chemistry. Pharmaceutical Chemistry Branch. Special Interest: Development of analytical organic methods.

Rosenthal, Robert W., Ph.D., University of Wisconsin, 1949: Organic chemistry. Sanitary Chemistry Branch. Special Interest: Reactions of CW agents.

Rubin, Leonard S., Ph.D., N.Y.U. Graduate School of Arts & Sciences, 1950: Psychology. Applied Physiology Branch. Special Interest: Psychophysiology.

*Saunders, Jack P., Ph.D., Maryland, 1953: Biochemistry. Ass't Chief, Pharmacology Branch. Special Interest: Pharmacology as related to CW and therapeutic agents.

Schaffer, Norwood K., Ph.D., Harvard, 1936: Biochemistry. M.D., Western Reserve, 1943: Medicine. Enzyme Chemistry Branch. Special Interest: Chemistry of drug action.

*Snyder, Fred M., Ph.D., University of Wisconsin, 1940: Entomology. Entomology Branch. Special Interest: Development of resistance in insects.

Steinberg, G., Ph.D., Purdue, 1945: Organic chemistry. Ass't Chief, Medicinal Chemistry Branch. Special Interest: Organophosphorus compounds.

Stewart, George M., Ohio State University, 1929-32. Body Armor Branch. Special Interest: Engineering.

*Summerson, William H., Ph.D., Cornell, 1937: Biochemistry. Chief, Biochemistry Division. Special Interests: Metabolism of normal and cancer tissue and effect of drugs on isolated enzyme systems.

Trurnit, Hans J., M.D., Berlin University, 1931. Chief, Physicochemical Branch. Special Interest: Chemistry of surfaces.

Wagner-Jauregg, Theodor, Ph.D., University of Munich, 1926. Chief, Medicinal Chemistry Branch. Special Interest: Medicinal chemistry.

Ward, Dorothy M., M.S., Catholic University, 1939: Biochemistry. Ass't Chief, Technical Information Office. Special Interest: Documentation of scientific reports.

*Weiss, Charles M., Ph.D., Hopkins, 1950: Biology. Ass't Chief, Sanitary Chemistry Branch. Special Interest: Aquatic biology.

*Wilber, Charles G., Ph.D., Johns Hopkins, 1942: Physiology. Chief, Animal Ecology Branch. Special Interests: Comparative and environmental physiology; biochemical evolution.

*Wills, J. Henry, Ph.D., Rochester, 1940: Physiology. Chief, Pharmacology Branch. Special Interests: Pharmacology of CW and therapeutic agents.

Senior military personnel, arranged alphabetically, are:

*Elton, Norman W., Col, Medical Corps, Commanding Officer. M.D., Boston University, 1926.

Gittes, Hyman R., Major, Cml C. Ass't to Chief, Clinical Research Division. B.A., Chemistry, New York University, 1937. First Chemical Officers Special Orientation Course, 1950. Clinical Research Division.

Micheau, Charles G., Lt Col, Cml C, Deputy. B.S., Chemistry, Ohio State University, 1937; Command and General Staff College, 1949.

Romanchek, Joseph J., Major. Officers Associate Advance Medical Field Service School. Technical Services Division.

Ross, Martin A., Lt Col, VC. D.V.M., Ohio State University, 1939. Pathology Branch.

Savage, Ledru H., Lt Col, Cml C, Executive Officer. M.S., Agriculture (Plant Pathology), New Mexico A&M College, 1933. Advance Class Chemical Corps School, 1943.

Werne, Jacob, Lt Col, Medical Corps. M.D., Baylor University, 1926.

Wheeler, Harold W., Lt Col, Cml C, Deputy Program Planning. B.S., Chemistry, Fletcher College, 1939. 4th Advance Class, Chemical Corps School, 1949-1950. 1st Strategic Intelligence Course, MID, 1945.

* Inclusion in the American Men of Science.

APPENDIX 2

Representative Publications, Chemical Corps *Medical Laboratories*, 1944-1954

CHEMICAL WARFARE AGENTS

NERVE GASES.

1. Biochemical detection of G-agent poisoning. Zvirblis, P. and D. B. Dill. MDR 146. 1948.

2. Mydriatics in nerve gas poisoning. Seed, J. C. MDRR 50. 1951.

3. Histochemical detection of fatal anticholinesterase poisoning. Bergner, A. D. and S. H. Durlacher. MDRR 59. 1951.

4. Effects and treatment of nerve gas poisoning. Grob, D. and A. M. Harvey. MLCR 18. 1953.

5. Conference on the neuromuscular blocking action of anticholinesterase compounds. MLSR 27. 1953.

6. Variation in red blood cell cholinesterase activity in personnel handling nerve gas. DeArmon, I. A., T. M. Frazier, W. J. Ludlow, W. J. Wayne. MLRR 174. 1953.

7. Mechanism of action of DFP and TEPP on the patellar reflex. Beck, R. et al. Fed. Proc. 12:596. 1953.

8. The mechanism of action of anticholinesterase compounds. McNamara, B. P. MLSR 46. 1954.

DFP.

9. Myanesin in the treatment of poisoning by DFP. McNamara, B.P., D. Stabile, J. Wills, S. Krop. MDR 222. 1949.

9A. Skin penetration of radioactive anticholinesterases - a direct quantitative method of study. Hart, E. R., J. H. Fleisher, A. S. Marrazzi. Fed. Proc. 8:300. 1949.

9B. Distribution of radiophosphorus in rabbit tissues after injection of phosphorus-labelled DFP. Jandorf, B. J. and P. D. McNamara. J. Pharm. Exptl. Therap. 98:77. 1950.

10. Mechanism of respiratory failure following administration of DFP in dogs. Ortega, L. G. and W. P. McShane. MDRR 54. 1951.

11. Mechanism of seizures induced by DFP. Bouzarth, W. F. and H. E. Himwich. MLRR 73. 1951.

11A. The measurement of skin penetration by the use of subcutaneous probe counter in conjunction with radioisotope labelled material. Gittes, H. R., E. R. Hart and A. S. Marrazzi. Fed. Proc. 10:50. 1951.

12. Some aspects of the mechanism of respiratory failure in DFP poisoning in dogs. Berman, B. MLRR 182. 1953.

13. Influence of dehydration on the toxicity to mice of DFP and KCN. Esposito, E. J. MLRR 161. 1953.

14. Effect of DFP on the muscular contractions produced by ATP. McNamara, B. P. and M. Quille. MLRR 158. 1953.

15. Morphologic alterations in the spinal cord of cats after subacute exposure to DFP. Lindenberg, R. MLRR 235. 1954.

16. Some effects of DFP poisoning at the myoneural junction in rats. Berman, B., M. Asbornsen, T. F. Young. MLRR 268. 1954.

MUSTARD.

17. Study of the reaction rates of various amines and related compounds with mustard for decontamination purposes. Comstock, C. C. and W. H. Edwards, Jr. MDR 153. 1948.

18. Effectiveness of nitrogen mustards in retarding the growth of Sarcoma 180. Goldin, A., B. Goldberg, L. G. Ortega, E. B. Schoenbach, R. Fugmann, F. Faiman. MDR 212. 1949.

19. Some relationships of structure to biological activity in the nitrogen mustards and related compounds. Goldin, A., H. A. Noe, B. H. Landing, B. Goldberg, R. A. Fugmann. MDR 170. 1949.

20. An attempt to produce anaphylactic phenomena in guinea pigs with sulphur mustard treated homologous plasma. Albert, P. A. MLRR 242. 1954.

21. Toxicity and antigenicity of homologous plasma treated with sulphur mustard, and toxicity of cathode-irradiated plasma in animals. Freeman, G., J. R. Trimble, B. S. Cohen, P. A. Albert. MLRR 299. 1954.

PHOSGENE.

22. Residual effects of phosgene poisoning in human subjects. Galdston, M., J. A. Luetscher, and W. T. Longcope. MDR 49. 1945.

23. Studies on the toxicology of phosgene. I & II. Karel, L. and R. E. Weston. MDR 70, MDR 75. 1946.

PHOSPHORUS COMPOUNDS.

24. Quantitative analysis of phosphorus-containing compounds formed in WP burns. Walker, J., J. Wexler and M. L. Hill. MDR 37. 1945.

INSECTICIDES

PARATHION.

25. Report of three new cases of parathion poisoning. McKusick, V. A. and D. Grob. MLCR 5. 1952.

26. Clinical data on organic phosphorus insecticide poisoning. Freeman, G. MLSR 16. 1952.

27. Physiological action of parathion in goats. Wilber, C. G. and R. A. Morrison. MLRR 269. 1954.

TEPP.

28. Skeletal muscle fasciculation produced by TEPP. McNamara, B.P., E. F. Murtha, A. D. Bergner and L. J. Edberg. MLRR 273. 1954.

DDT.

29. Review of the biological properties and insecticidal applications of DDT. Philips, F. S. MDR 13. 1944.

30. Toxic effect of prolonged ingestion of DDT on dogs. Haymaker, W., A. M. Ginzler, C. L. Boyers, and R. L. Ferguson. MDR 79. 1946.

31. Studies on the chronic toxicity of DDT in the dog. Bing, R. J., B. P. McNamara and F. H. Hopkins. MDR 58. 1946.

32. Studies on the pharmacology of DDT. I, II, and III. Philips, F. S. and A. Z. Gilman. MDR 50, MDR 51, MDR 52. 1945.

MILITARY CHEMICALS

ACETYLENE.

32A. Acetylene-induced ventricular fibrillation. Kunkel, A. M., A. H. Oikemus, B. P. McNamara, and J. H. Wills. MLRR 63. 1951.

33. Ventricular fibrillation induced by epinephrine during asphyxia. McNamara, B. P., E. A. Fine, and J. H. Wills. MLRR 129. 1952.

ANILINE.

34. The inhalation toxicity of aniline, furfuryl alcohol, and their mixtures in rats and mice. Comstock, C. C. and F. W. Oberst. MLRR 139. 1952.

35. Chronic toxicity of aniline vapor by inhalation in dogs, rats, mice and guinea pigs. Hackley, E. B., C. C. Comstock and F. W. Oberst. MLRR 222. 1953.

36. The penetration of aniline through polyethylene films proposed for protective clothing. Conn, L. W. and R. G. Horton. MLRR 169. 1953.

BORANES.

37. Literature survey on the toxicity of boric acid and sodium tetraborate. Kunkel, A. M. MDSR 2. 1950.

38. The cardiovascular effects of decaborane. Walton, R. P., J. A. Richardson and O. J. Brodie. MLCR 7. 1952.

39. Decaborane inhibition of utilization of glucose by living yeast cells. Hill, D. L., et al. Fed. Proc. 12:217. 1953.

40. The median detectable concentration of diborane, pentaborane, and decaborane by odor for man. Comstock, C. C. and F. W. Oberst. MLRR 206. 1953.

41. Toxicity and pharmacology of the boron hydrides. Wills, J. H. MLSR 15. 1953.

42. Boron analysis and toxicity. Hill, W. H. and Svirbely, J. L. Reports on Contract DA 18-108-CML-3910. 1953-1954.

43. Decaborane poisoning and its possible therapy. Cole, V. V. et at. Fed. Proc. 12:312. 1953.

44. Toxicity and health hazards of boron hydrides. Krackow, E. H. A.M.A. Arch. Indust. Hyg. & Occ. Med. 8:335-337. 1953.

45. Quantitative determination of diborane in air. Feinsilver, L. MLRR 170. 1953.

46. Inhalation toxicity of diborane in dogs, rats, and guinea pigs. Comstock, C. C., L. Feinsilver, L. H. Lawson, and F. W. Oberst. MLRR 258. 1954.

47. The cardiovascular action of decaborane. Walton, R. P., J. A. Richardson and O. J. Brodie. MLCR 34. 1954.

BROMOMETHANES.

48. Monochloromonobromomethane inhalation toxicity, pathology, and symptomatology in rats and mice. Comstock, C. C., J. K. MacNamee, E. E. Ozburn, R. W. Fogleman, and F. W. Oberst. MLRR 113. 1952.

49. Toxicity of inhaled trifluoromonobromomethane and difluorodibromomethane vapors from subacute and chronic exposures of rats and dogs. Comstock, C. C., J. Kerschner and F. W. Oberst. MLRR 180. 1953.

CARBON TETRACHLORIDE.

50. Comparative inhalation toxicities of carbon tetrachloride, monochloromonobromomethane, difluorodibromomethane, and trifluoromonobromomethane to rats and mice in the presence of gasoline fires. Comstock, C. C. and F. W. Oberst. MLRR 107. 1952.

CHLOROPICRIN.

51. Microdetermination of chloropicrin vapor in air. Feinsilver, L. and F. W. Oberst. Anal. Chem. 25:820-821. 1953.

CHLORINE TRIFLUORIDE.

52. Report on chlorine trifluoride. Hazleton Laboratories Reports on Contract DA 18-108-CML-4399. 1952, 1953. MLCR 12, 1952. MLCR 22, 1953.

CYANIDES.

53. Residual lesions of the central nervous system in cyanide-poisoned animals. Ferguson, R. L., A. M. Ginzler, O. Bodansky, C. L. Boyers and B. J. Jandorf. MDR 39. 1945.

54. Oral toxicity of cyanogen chloride in water to rats. Leitch, J. L. and V. Bauer. MDR 19. 1945.

55. Pathology of cyanogen chloride by inhalation. Ginzler, A. M., O. Bodansky, R. L. Ferguson, B. J. Jandorf, C. L. Boyers. MDR 34. 1945.

56. Intravenous toxicity studies on cyanogen chloride and sodium cyanide in dogs, goats, and rabbits. Pratt, H. J. and R. G. Horton. MDR 26. 1945.

56A. Estimation of microquantities of cyanide. Epstein, J. Anal. Chem. 19:272. 1947.

ETHYLENE OXIDE.

57. The acute toxicity of inhaled ethylene oxide vapor. Hackley, E. B. and K. H. Jacobson. MLRR 296. 1954.

FIRE EXTINGUISHANTS.

58. An investigation of the toxicity of proposed fire-extinguishing fluids. Chambers, W. H., E. H. Krackow, C. C. Comstock, F. P. McGrath, S. B. Goldberg, L. H. Lawson and J. K. MacNamee. MDRR 23. 1950.

59. Method for estimating toxicity limitation on selection of candidate fire-extinguishing fluids. Krop, S. MLSR 26. 1953.

FLUOROACETATES.

60. Splitting of fluoroacetate esters by plasma. McNamara, B. P., D. Stabile, E. Murtha and J. H. Wills. MDRR 2. 1950.

FURFURYL ALCOHOL.

61. Pharmacology of furfuryl alcohol. Fine, E. A. and J. H. Wills. MDR 223. 1949.

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