REPORTS

RESEARCH WORK ON CHEMOTHERAPY

AT the meeting of the Division of Chemistry and Chemical Technology of the National Research Council in Washington, D. C., in April, 1939, the opinion was expressed that research work should be stimulated in the field of quinine substitutes and synthetic antimalarials.

While quinine, plasmoquine, atebrine and a few other drugs have been useful, there is in the judgment of the medical profession, great need for something better. The present remedies leave much to be desired from a therapeutic point of view, and the price is higher than many can afford to pay. Further, so far as quinine itself is concerned, the world is practically dependent for its supply on Java and the Kina Bureau (its selling agent) and might be cut off from this supply or perhaps compelled to pay exorbitant prices if Java should be seized by some other nation. The trend is therefore toward synthetics as the direction which holds out the best promise of new and useful antimalarials.

Contrary to popular belief, malaria is still one of humanity's major scourges. India, with a population of some 320,000,000, has a yearly average of from 70 to 80 million sufferers, and President Fosdick, of the Rockefeller Foundation, in his recent annual report, has called attention to the threatening situation in South America. In certain tropical countries the incidence of this disease is 100 per cent. Throughout the world it is stated to be the direct cause of approximately a million deaths annually.

Dr. Herbert R. Moody, chairman of the division, was duly empowered to appoint a temporary committee to survey the field of malaria and antimalarials and to report back to the division whether or not it would be advisable to designate a regular standing committee of the division to study, in cooperation with the division of medical sciences, the whole problem of the chemistry and synthesis of antimalarials.

The temporary committee appointed by Dr. Moody, from the division of chemistry and chemical technology, consisted of Dr. Leonard H. Cretcher, assistant director of the Mellon Institute of Industrial Research, Pittsburgh; Dr. Lyndon F. Small, head chemist of the National Institute of Health, U. S. Public Health Service, Washington, D. C., and Marston T. Bogert, emeritus professor of organic chemistry in residence, Columbia University, New York, as chairman.

Later, on the nomination of Dr. Esmond R. Long, chairman of the National Research Council division of medical sciences, the following members for that division were added to the temporary committee: Dr. Lowell T. Coggeshall, International Health Division, Rockefeller Foundation, New York, and Dr. Torald H. Sollmann, dean, Western Reserve University School of Medicine, Cleveland.

The completed committee thus consisted of the following chemical and medical representatives: Lowell T. Coggeshall, Leonard H. Cretcher, Lyndon F. Small, Torald H. Sollmann and Marston T. Bogert, chairman.

As a result of this preliminary survey, the temporary committee reported unanimously that, in its judgment, a regular standing committee of the division of chemistry and chemical technology should be constituted by the National Research Council, to concern itself not solely with antimalarials, but whose function should be chemistry in the service of medicine and its title Committee on Chemotherapy, with antimalarials as its first assignment.

This broadening of the field to be covered by the committee will not reduce in any way its usefulness in an attack on the malaria problem but will permit it to offer its services in attempts to combat other diseases as well, particularly in those cases in which acute emergencies may arise and our help be welcome. Even in the investigation of antimalarials, other diseases are concerned, for example, the possible use of cinchona alkaloids or their derivatives in the treatment of pneumonia, a problem which has been under investigation by Dr. L. H. Cretcher at the Mellon Institute for a number of years.

At the meeting of the division of chemistry and chemical technology, National Research Council, November 18, 1939, in Washington, D. C., the report of the temporary committee was presented and adopted and the committee was discharged. The division then recommended that the same personnel be appointed as one of its regular standing committees, to be known as its Committee on Chemotherapy. This recommendation of the division was subsequently approved by the National Research Council, and Surgeon General Thomas Parran, Jr., of the U. S. Public Health Service, gave his prompt consent to the service of Dr. Small on the committee.

The Academy of Tropical Medicine, the American Society of Tropical Medicine and the National Malaria Committee met at Memphis, Tennessee, November 21–24, 1939, and unanimously endorsed the program of the committee. The council of the American Academy of Tropical Medicine also expressed its cordial approval of the selection of Dr. L. T. Coggeshall as a member of the committee.

The Symposium on Malaria, May 29–30, 1940, in Atlanta, Ga., called by Surgeon General Parran, for the purpose of a preliminary discussion of the malaria situation in our country, with special emphasis on chemotherapy, was attended by Drs. Coggeshall and Small of the committee.

Section N of the American Association for the Advancement of Science, at its Philadelphia meeting, December 27, 1940, to January 2, 1941, will hold a symposium on the human malarias, in which members of the committee will participate. The proceedings of this symposium when published will constitute an important review of present knowledge of this disease.

Active cooperation has been promised by an extensive list of educational and research institutions, scientific and technical organizations, manufacturers and individual scientific investigators, including the following:

Advisory Commission to the Council of National Defense, Edward R. Weidlein, executive, for Industrial Division C, Chemical and Allied Products, Industrial Materials Department (Edward R. Stettinius, Jr., commission member).

American Association for the Advancement of Science, Malcolm H. Soule, secretary of Section on Medical Sciences (N).

American Chemical Society, Divisions of Biological Chemistry, of Medicinal Chemistry and of Organic Chemistry.

American Drug Manufacturers Association, Carson P. Frailey, executive vice-president and secretary.

Army and Navy Munitions Board, Warren N. Watson, secretary, Chemical Advisory Committee.

Cinchona Products Institute, Norman Taylor, director.

Harvard University Committee on Pharmacotherapy, Soma Weiss, chairman.

Institut Pasteur d'Algérie, Algiers, Edmond Sergent, director.

Manufacturing Chemists Association, Warren N. Watson, secretary, and George W. Merck, chairman of Medicinal Chemicals Section.

National Conference on Pharmaceutical Research, John C. Krantz, Jr., secretary.

National Research Council Division of Medical Sciences, Lewis H. Weed, chairman, and Perrin H. Long, chairman of its Committee on Chemotherapeutic and Other Agents.

National Research Council Survey of Research in Industry, F. W. Willard, chairman.

School of Tropical Medicine, San Juan, Puerto Rico, George W. Bachman, director.

Tennessee Valley Authority, F. L. Roberts, University of Tennessee.

U. S. Department of Commerce, C. C. Concannon, chief, Chemical Division, Bureau of Foreign and Domestic Commerce.

U. S. Department of the Navy, Rear Admiral Ross T. McIntire, Surgeon General.

U. S. Public Health Service, Thomas Parran, Jr., Surgeon General.

U. S. War Department, Major General James C. Magee, Surgeon General.

The objects of the committee include:

1. Chemistry in the service of medicine, with special emphasis on the discovery of new and useful synthetic drugs.

2. To bring about a closer cooperation between chemists and pharmacologists interested in the same field. It often happens that an organic chemist synthesizes a new compound of therapeutic possibilities but does not know to whom to turn to have it tested. Similarly, a pharmacologist discovers that a certain chemical exhibits hitherto unsuspected physiologic effects but has no information as to which organic chemists could help him in the preparation of the compound and its more promising derivatives.

3. To help in this direction, the committee should function as a general clearing house for the collection and classification of information as to the chemists, manufacturers, pharmacologists and others in the United States who are now at work in this field, the special lines of investigation they are following and any other pertinent data. With this information in hand, and that accumulated last summer by the survey of research resources of educational institutions, in men and material, now classified and on file in the offices of the division of chemistry and chemical technology of the National Research Council in Washington, we should be able more intelligently to allocate and evaluate the various research problems to be investigated. In this way we can also be of some assistance in reducing the amount of unintentional duplication and overlapping in research work and suggest important problems for investigation where the need seems clearly indicated.

4. Not to undertake too ambitious a program at the outset, since the field of chemotherapy is a vast one. For the reasons explained in the foregoing pages, malaria has been selected as the first disease to be attacked.

5. To prepare a compact semi-popular presentation of the malaria situation throughout the world, particularly in our own land, including a summary of what is going on here and how it is retarded and handicapped by lack of funds, for the purpose of enlisting public appreciation and support.

6. To secure funds from interested individuals, institutions, foundations, firms and others for the support of the work of the committee, the establishment of research fellowships and such other activities as will advance and expedite the achievement of the results sought.

Such a survey is now being conducted to ascertain what investigations are under way or planned for the synthesis of new and useful antimalarials, to compile a list of individuals and firms interested in this field, just what they are doing and (as far as may be possible) in what other directions they are arranging to expand.

Simultaneously, bibliographies, reviews and digests of the literature covering various aspects of the problem are being compiled, but all this work can progress

but slowly under existing limitations, and speed is urgently needed; for the medical profession confidently predicts a malaria peak this year or next.

Those individuals, organizations, institutions and manufacturers who are willing to cooperate by supplying the information suggested in the foregoing pages are requested to communicate with the chairman of the committee, whose address until September 20 will be Belgrade Lakes, Maine; after that, Havemeyer Hall, Columbia University, New York.

As this committee has been for some time in touch with many others interested in antimalarials both in this and in other countries and has accumulated considerable information of value, it seems to us wise to publish this statement, in order that confusion and duplication of effort may be avoided and national preparedness advanced more speedily, for we have been informed that other committees and groups have been or are about to be organized to cover much the same field, evidently unaware of the existence of our committee and its activities.

LOWELL T. COGGESHALL
LEONARD H. CRETCHER
LYNDON F. SMALL
TORALD H. SOLLMANN
MARSTON T. BOGERT, *Chairman*

SPECIAL ARTICLES

THE ISOLATION IN PURE FORM OF THE INTERSTITIAL CELL-STIMULATING (LUTEINIZING) HORMONE OF THE ANTERIOR LOBE OF THE PITUITARY GLAND

SHORTLY after proof of the secretion of gonadotrophic hormones by the anterior lobe of the pituitary body had been offered by the work of Smith,[1] Zondek and Aschheim,[2] and a number of later investigators,[3] it was suggested that the effects of implants or crude extracts of the pituitary on the gonads should be attributed to at least two hormones (follicle-stimulating and luteinizing hormones). This view-point was supported by Fevold, Hisaw and their collaborators and, more recently, by work in this laboratory and in that of H. M. Evans. However, some investigators are not satisfied that more than one gonadotrophic hormone can be extracted from the gland and have awaited the isolation of pure hormones which should satisfactorily correct the existing confusion with regard to the possible number and effects of the gonadotrophic hormones postulated by others. In New Brunswick,[4] considerable progress had been made in isolating a hormone[5] stimulating the interstitial cells of the male or female gonads. This material was not chemically pure but was found to be free of other pituitary hormones. The work here reported describes the isolation of this hormone as a pure protein.

[1] P. E. Smith, *Anat. Rec.*, 32: 221, 1926.
[2] B. Zondek and S. Aschheim, *Klin. Wschr.*, 6: 248, 1927.
[3] H. B. van Dyke, "The Physiology and Pharmacology of the Pituitary Body," Chicago, I, 1936; II, 1939.
[4] R. O. Greep, H. B. van Dyke and B. F. Chow, *Jour. Biol. Chem.*, 133: 289, 1940.
[5] Evans, Korpi, Simpson, Pencharz and Wonder (*Univ. Calif. Pub. Anat.*, 1: 255, 1936) isolated an interstitial cell-stimulating fraction which was considered not to cause luteinization. Later, Evans, Simpson, Tolksdorf and Jensen (*Endocrinology*, 25: 529, 1939) concluded that the same fraction can bring about both interstitial cell-stimulation and luteinization.

The initial extraction of gonadotrophic hormones from the pituitary glands of swine was undertaken by a method already described.[6] The interstitial cell-stimulating extract free from other hormones was then isolated by a second procedure.[4] Electrophoretic studies were carried out on this preparation in a Tiselius apparatus,[7] using the scanning method of Longsworth[8] for obtaining the electrophoretic patterns. Experiments were performed over a range of pH values from about 4.5 to 8.0 at a constant ionic strength of 0.05, using the monovalent buffers, acetate, cacodylate and diethylbarbiturate. The results showed the presence of three components (Fig. 1 A). After

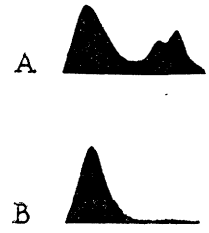

FIG. 1. Electrophoretic patterns at pH = 7.85. A—Before final purification. B—After final purification.

sufficient separation of the electrophoretic boundaries it was possible to isolate two fractions, one containing the major component, the other the two minor ones. The biological activity was found to be entirely in the main component. A plot of mobility against pH showed the isoelectric point of this main component to be at pH 7.45. The isoelectric points of the contaminating, inert components fell between pH 4 and 5.

This information made it possible to secure the pure hormone by isoelectric precipitation. To a concen-

[6] B. F. Chow, R. O. Greep and H. B. van Dyke, *Jour. Endocrinol.*, 1: 439, 1939.
[7] A. Tiselius, *Tr. Faraday Soc.*, 33: 524, 1937.
[8] L. G. Longsworth, *Jour. Am. Chem. Soc.*, 61: 529, 1939.