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Fifteen Years of the Harkness Research Fund

Five years ago a report was made summarizing ten years of research in immunochemistry carried out under the Harkness Research Fund. An outline was given (1) of progress made in the study of chemical substances chacteristic of the invading microbes of infectious disease, (2) of the isolation for the first time in the pure state of antibodies, the animal's blood serum defenses against invading microbes, and the certain characterization of these substances as proteins, and (3) of the clarification of two of the simpler but until then obscure immune reactions, or mechanisms by which combination of microbial substances and defensive antibodies occurs to produce a state of immunity.

While some of the questions that had been asked ten years before appeared to be satisfactorily answered, so many problems of immunity remained unsolved that it seemed preferable to attempt to extend the powerful new methods that had been devised in this laboratory to more complex but analogous problems, rather than to start researche in an entirely different field. The present report, therefore, deals with extensions of the earlier studies during the past five years.

Arrival of Dr. S. D. Henriksen, a bacteriological chemist from Norway, afforded the opportunity for continuation of the study of the proteins of streptococci and for the extension of the laboratory's quantitative method for the study of bacterial agglutination to this important group of disease germs. When this worker's return to Norway as head of the biochemical division of the Bacteriological Institute of the University of Oslo was prevented by the German invasion of his country, his stipend was continued by the Commonwealth Fund until the work could be brought to a conclusion permitting Dr. Henriksen's entry as medical officer into the Norwegian armed forces in Canada.

The study of antibodies was continued in a number of directions. In connection with Dr. Hattie E. Alexander's work at the Babies' Hospital on meningitis due

to influenza bacilli, the quantitative method was extended to rabbit antisera to these bacilli. As a result it was found possible to produce sera five to ten times as potent as were previously available and to purify the antibodies for administration in the disease. With adequate, measurable doses the mortality was reduced from almost 100% to 20% or 25%. A former graduate student is now collaborating in this laboratory with Dr. Alexander on extensions of the work under a grant from the Commonwealth Fund.

Antibodies produced by one species may function as antigens in another species and give rise to antibodies to the original antibodies. This peculiar phenomenon has been studied and brought into orderly relation with the mechanism of antigen-antibody reactions as now understood, and with the serum-protein fractions to which the various antibodies belong. The differing characteristics of antibodies produced by the same antigen in different species of animals have also been described and in part, at least, correlated and explained.

The quantitative precipitin method, as originally worked out, required amounts of antibody nitrogen ranging from 0.1 to 1 mg. for greatest accuracy. In order to extend the method to human sera, such as those of children recovered from influenzal meningitis, or of pneumonia patients after treatment with sulfa-drugs, it was necessary to use more sensitive procedures and these have now been worked out so that one-tenth of the above quantities may be estimated. A considerable body of precise data is being accumulated for the first time on the extent of the immune response in human beings.

Since the principal features of the two simplest immune reactions, the precipitin and agglutinin reactions, had been made clear, the methods developed were extended to a study of the reaction velocity. This was found to be very much more rapid than had been anticipated.

A study was also begun of complement, that hitherto mysterious and unstable group of substances in immune serum upon which depend the disposal of many invading bacteria by "lysis" or solution, the efficient disposal of others by phagocytosis, or destruction within the white cells of the blood, and also the successful issue of many

important diagnostic procedures, such as the Bordet-Wassermann test for syphilis. Like antibodies fifteen years ago, complement was considered an idea or a physical state, rather than a substance or group of substances. However, by a rigidly controlled extension of the quantitative precipitin method it was found that the fixation of complement in immune reactions actually adds measurable amounts of protein to the reacting system. With the help of this first method of weighing the amounts of complement present in sera the quantities entering into immune reactions were estimated. It was found that these amounts were compatible with the theory of immune reactions developed in this laboratory, and that for the first time a plausible explanation could be given, in modern scientific terms, of the unique properties of complement. It is hoped to continue this study after the war.

With the outbreak of the war in Europe it became obvious that our participation was inevitable. Six months before Pearl Harbor the laboratory started an investigation ~~for~~ of immunization against lobar pneumonia for the Surgeon General's office, and it is believed that the questions involved will have been answered and the project terminated by next July. Problems of immunity in malaria are also being studied under a Medical Research Council contract, and work on this was started months before the contract went into effect. In both of these problems the assistance of an already overworked staff of residents and internes and of a large body of medical students as volunteer subjects has been an inspiring feature. A third urgent problem has just come to the laboratory from the Government, so that very little but war work is now being carried out.

During the entire fifteen years the inspiration derived from close contact with colleagues of the Department of Medicine and other departments of the Medical School and Presbyterian Hospital has been an indispensible stimulus. Nor would such progress as has been made been possible without the unfailing encouragement and wise and understandin counsel of Dr. Palmer.

Since inception of the laboratory the following have been engaged in its activities:

	Dr. Michael Heidelberger	1928 -
	Dr. Forrest E. Kendall	1928 - 1936
	Mr. C. M. Soo Hoo (technician)	1928 -
*	Dr. Richard H. P. Sia (Peiping)	1929 - 1930
†	Dr. Arthur E. O. Menzel	1930 - 1938
	Mrs. John O'Neill (custodian)	1930 -
	Dr. Elvin A. Kabat	1933 - 1937
	Dr. Herbert E. Stokinger	1934 - 1939
	Dr. Henry W. Scherp	1934 - 1935
*	Dr. Torsten Teorell (Stockholm)	1935
*	Dr. D. L. Shrivastava (Calcutta)	1935 - 1936
	Dr. Henry P. Treffers	1936 - 1942
	Dr. A. J. Weil	1936
	Dr. Maurice Stacey (Birmingham, England)	1937
*	Dr. P. Grabar (Paris)	1937 - 1938
	Mr. Barnard Davis	1937 - 1938
†	Dr. Sulo A. Karjala	1938 - 1940
	Mr. Manfred Mayer	1938 -
	Dr. Bertil Josephson (Stockholm)	1939
‡	Dr. Sverre D. Henriksen (Oslo)	1939 - 1941
	Mrs. Catherine F. C. MacPherson	1939 -
¥	Dr. Otto G. Bier (Sao Paolo)	1941
**	Dr. Samuel Kaiser	1942
††	Miss Graciela Leyton-Ramirez (Santiago, Chile)	1942-
**	Miss Betty Robinson	1943 -

* Rockefeller Foundation Fellows
† National Tuberculosis Association Fellow
** On War Department pneumonia research project
‡ Fellow of the Norwegian Malthe and Pasteur Foundations; Commonwealth Fund Fellow.
¥ South American Fellow of the John Simon Guggenheim Memorial Foundation.
†† Kimball Fellow of Barnard College.

Approximately ninety papers from the laboratory have been published during the fifteen-year period.