

Meetings

Gamma Globulins: Structure and Control of Biosynthesis

Now that remarkable progress is being made in elucidating the structure of immunoglobulins, there is need for developing an understanding of the genetic mechanism for generation of their diversity and for relating this to the control of antibody synthesis and the clinical aspects of disturbed γ -globulin metabolism. For this reason the Nobel Foundation, in pursuit of its new goal to promote more effective scientific interchange in its chosen areas, called together a group of more than 50 protein chemists, immunologists, and clinicians from 14 countries to participate in a symposium on the Structure and Control of Biosynthesis of Gamma Globulins. This, the third Nobel Symposium, was held from 12 to 17 June 1967, at the Södergarn estate in Lidingö, Stockholm, Sweden—with support from the Bank of Sweden Jubilee Fund—under the sponsorship of the Nobel Committees on Chemistry and Medicine. Quite fittingly, the chairmen were Arne Tiselius, the discoverer of γ -globulins and a former president of the Nobel Foundation, and Jan Waldenström, the discoverer of macroglobulins and of the associated clinical syndrome that bears his name. The symposium took place just 30 years after the identification of γ -globulins by the electrophoretic moving boundary method, a discovery which had such an impact on biochemistry and medicine that Tiselius received a Nobel award.

Despite the heterogeneity of γ -globulins, which is the *bête noire* of immunologists, a number of giant steps have been taken in elucidating their structure through study of the homogeneous immunoglobulins produced in disease, especially through study of the Bence-Jones proteins excreted in multiple myeloma. These steps include (i) establishment of the subunit structure of all immunoglobulins as a pair

of heavy and a pair of light polypeptide chains; (ii) revelation that there are many kinds of heavy chains and light chains that combine pairwise to form the myriad molecules of normal γ -globulin, whereas patients or mice with multiple myeloma or macroglobulinemia produce a homogeneous γ -globulin with a single kind of heavy chain and a single kind of light chain, each apparently structurally unique for the individual; (iii) location of specific combining affinity of antibodies in a portion of the heavy chain (F_d fragment) plus the light chain; (iv) subclassification of γ -globulins into three major classes— γ G, γ A, and γ M (each determined by the kind of heavy chain, γ , α , or μ) and into two antigenic types K or L (determined by the light chain, κ or λ); (v) complete amino acid sequence analysis of κ and λ light chains, that is, of Bence-Jones proteins, which are identical to the light chain of the myeloma globulin or macroglobulin from the same patient and akin to normal light chains; (vi) demonstration that the amino-terminal half of light chains is highly variable in sequence whereas the carboxy-terminal or “constant” half is essentially invariant; (vii) extension of the sequence data and similar concepts to the F_d and F_c portions of heavy chains of several species; (viii) evidence for structural homology between light and heavy chains and among species. These advances were presented by N. Hilschmann (Max Planck Institute, Göttingen) who gave sequence data for two human κ -chains, including one with up to six extra residues, by F. W. Putnam (Indiana University) who reported the complete sequence of three human λ -chains, two of which had three extra residues, by R. R. Porter (St. Mary's Hospital Medical School, London), who gave extensive sequence data and the order of the CNBr fragments of human heavy γ chains, and by G. M. Edelman (Rockefeller University) who presented a pro-

cedure for complete sequence determination of a γ G myeloma globulin. The theme of the day was summarized by R. L. Hill (Duke University), who outlined a scheme for evolution of immunoglobulins through comparison of the sequence of light and heavy chains of different species.

The session on the structure and heterogeneity of γ -globulins brought out the complexities of the γ A globulins and failed to resolve the subunit structure of the γ M macroglobulins. However, Bennich (University of Uppsala) reported the discovery of an interesting new immunoglobulin class. An electron-microscopic study by R. C. Valentine (Mill Hill, London) led to a V-shaped model for γ G antibody molecules in which the F_c piece acts as the swivel and the two Fab pieces as the arms. Swedish workers (Höglund and Svehag) saw starfish-like structures for γ M antibodies. A lively discussion followed on the discrepancies in the interpretations of electron microscopic observations and of hydrodynamic measurements. In a summary statement, the electron microscopists half-jokingly stated that they had agreed on one thing, namely, not to criticize each other's pictures.

A visit to the Biochemical Institute at Uppsala included a demonstration of new methods of characterization of proteins and a program on the genetics of γ -globulins. The Gm groups discovered by Grubb (Lund) are a class of genetically determined antigens confined to the heavy chains of γ G molecules and now recognized as occurring in man and many mammals. H. Kunkel (Rockefeller Institute) has related the four heavy-chain subtypes to the Gm system and has located the Gm markers in various sections of the chain, and A. S. Kelus (Birmingham) has done the same for rabbit allotypes. These genetic markers provide a powerful method for structural study. One of the more exciting developments was the increasing evidence that certain myeloma globulins do have specific antibody activity, for these proteins have sometimes been called “antibodies in search of an antigen.” This aspect dominated the discussion on clinical aspects of the control of gamma globulin synthesis led by J. Waldenström (Lund) and E. F. Osserman (Columbia).

Members of three laboratory groups (C. Baglioni, Naples; B. A. Askonas, St. Mary's, London; and M. D. Scharff, Einstein) agreed that the heavy and

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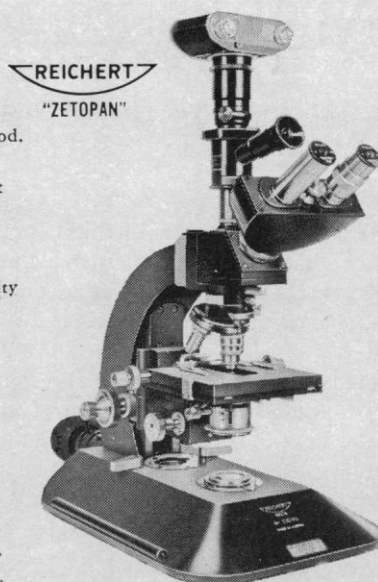
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light chains are synthesized in a continuous fashion from the amino- to the carboxyl-end without intermediates. This apparently precludes a separate synthesis of the variable and constant portions of the chains (with a later union) under the direction of many genes for the variable part and only one for the constant part. Two important concepts on the control of biosynthesis of antibodies were brought out by G. J. V. Nossal (Royal Melbourne Hospital, Australia) and others; first the concept of the committed cell which makes only one kind of light chain and one kind of heavy chain, and second, that the cell recognizes its own product, in a sense as if it were an antibody. M. Cohn (Salk Institute) in an elegant summary presented a genetic theory for the diversity of immunoglobulins which was contested by the proponents of the Smithies theory of antibody diversity and of other hypotheses of genetic recombination or multiplicity. M. Sela's dramatic arrival from Israel just after the "cease fire" catalyzed the sense of internationality of this gathering of scientists from many lands and diverse backgrounds. The proceedings of this excellent meeting will be published, before the year is out, as the Nobel Symposium III.

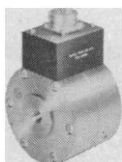
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MOLECULAR MECHANISMS OF TEMPERATURE ADAPTATION

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Molecular Mechanisms of Temperature Adaptation is a collection of papers on the general physiology of temperature adaptation in cold-blooded animals, plants, and microorganisms. Twenty-four contributors from the Soviet Union, Germany, Canada, Denmark, and the United States report recent research findings on the diverse molecular mechanisms of response, acclimation, and adaptation to heat and cold in bacteria, plant cells and tissues, insects, fishes, amphibians, and reptiles.

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Calendar of Events—November

National Meetings

20-21. **Manpower for Oceanography**, education symp., Houston, Tex. (American Soc. for Oceanography, 854 Main Building, Houston 77002)

20-22. American Physics Soc., annual New Orleans, La. (J. O. Kalliokoski, Dept. of Geology, Princeton Univ., Princeton, N.J. 08540)

20-22. American Physics Soc., annual **Fluid Dynamics** mtg., Bethlehem, Pa. (P. S. Klebanoff, Natl. Bureau of Standards, Connecticut Ave. at Van Ness St., NW, Washington, D.C. 20234)

20-22. **Geological** Soc. of America, annual mtg., New Orleans, La. (G. E. Murray, Texas Technical College, Box 4680, Technical Station, Lubbock, Tex., or Miss D. Curtis, Shell Oil Co., Box 60193, New Orleans 70160)

20-22. **Geochemical** Soc., annual mtg., New Orleans, La. (E. C. T. Chao, % U.S. Geological Survey, Washington, D.C.)

20-22. **Mineralogical** Soc. of America, New Orleans, La. (G. Switzer, % U.S. National Museum, Washington, D.C.)

20-22. **Paleontological** Soc. of America,