oped areas; conversely, microbiologists often fail to seek advice on the economic consequences of their actions in the medical disciplines. A number of relevant examples and cases were cited. Moreover, often the skilled professional is not needed at all, and either paramedical personnel or sanitarians could as effectively and far more cheaply perform essentially the same functions. Thus, instruction in site selection for privies and in the construction of safe water supplies may be far more important than having a microbiologist routinely estimate coliform bacteria.

The role of microbiology in communicable disease control was assessed by M. M. Brooke (Communicable Disease Center, Atlanta). Brooke placed particular stress upon the availability of microbiological competence in the developing nations and the limited facilities or resources for the training of the required specialists or technicians. Without minimizing the value of the instruction received in the United States, there can be little doubt that these domestic programs alone probably never will be adequate to meet the extent of the problem. Frequently, as speakers at the symposium reiterated, U.S. educators present to overseas trainees concepts and facts that the teachers are interested in rather than those essential to the student upon his return home. It is only human for the trainees to lean toward sophisticated subjects and direct their attention to complicated equipment, particularly if obscurity tends to be associated abroad with status. Too often the drive for education and microbiological training is not directed to the requirements of the economy, and too commonly, it was pointed out, educational experiences formulated for Americans or individuals from advanced nations have no relevance in the economic and social contexts of the student's homeland. Each of the speakers emphasized the necessity for modifications in study programs in order to fit the educational levels and the medical, agricultural, and industrial requirements of the developing nations.

It was generally agreed by the participants in the symposium and aptly stated by Lamanna that after feeding upon a diet rich in manometers, microbial genetics, molecular biology, and, as a frosting upon the cake terminating the rich repast, a measure of intellectual snobbery—a snobbery often associated with an intolerance of the efforts of those not engaged in the newest research areas—the potential microbiologist will commonly not be in a position to assess the requirements or handle the issues facing his profession in a resource-limited, economically underdeveloped area. To cope with the problems of education, research, and the development of priorities, microbiologists themselves should take the initiative in suggesting means by which microbiological efforts can contribute to international assistance.

M. ALEXANDER
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Heterogeneity of Antibodies

Heterogeneity of antibodies was the topic of the 3rd annual midwinter conference of immunologists held in Pasadena, California, 26–28 January 1964.

During the first session, on theoretical considerations, Talmage discussed the question of how many different gamma globulins exist. Using as an analogy the combination of the relatively few letters of the English alphabet to form several hundred thousand words, he suggested that a relatively small number of different globulins, of the order of a thousand, present a few at a time in various combinations, might be sufficient to explain the known specificity properties of immunologic reactions. The number of possible combinations (which he called families) was calculated by means of the binomial coefficient $\binom{N}{F}$, N different globulins taken F at the time. He suggested that F might be determined from experimental observations and that the order of magnitude of other parameters might then be estimated. He also discussed certain consequences of this hypothesis concerning antibody synthesis and specificity.

A theory of electrophoretic transport of interacting systems was reported by Cann. He considered reactions of the type $A + nN \rightleftharpoons B$, where A represents a protein molecule in solution and B is its complex formed by binding of n moles of an electrically neutral constituent N of the supporting medium. The assumptions underlying this treatment were that the complex migrates with electrophoretic mobility different from that of the uncomplexed macromolecular ion, and that equilibrium between A, N, and B is established instantaneously. The conservation equations were solved numerically on a digital computer for the case where N is undissociated acetic acid. The theoretical electrophoretic patterns were shown to account for the essential features of the observed electrophoretic behavior of a number of proteins in media containing varying concentration of acetate buffer at *p*H 5.7 and 4.0.

Aladjem presented a new quantitative theory of the precipitin reaction. The theory describes the interactions between multivalent antigen and bivalent antibody; antibody is considered to be heterogeneous with respect to equilibrium constants. Heterogeneity is described in terms of a multivariate probability density function ($2f$ variate, where 2 is the valence of antibody and f the valence of antigen). He presented a method for finding this function from experimental measurements of the amount of antigen-antibody precipitate and the amount of soluble complexes. Briefly, the method consists of (i) making an initial estimate of the function and computing by means of the theory of distribution of complexes; (ii) comparing the computed distribution of complexes with the experimental data; and (iii) using the criterion of least squares and iterative procedures for consecutively better approximations, finding that distribution of complexes and hence that probability density function which best fits the experimental data. The theory suggests experiments and a new method of interpretation of the result.

Other sessions were devoted to chemical investigations of heterogeneity. Singer reviewed recent data relevant to the heterogeneity of antihapten antibodies. Hapten-protein conjugates, which are usually used as immunizing antigens, are very likely heterogeneous with respect to haptenic determinants; there may be many causes for structural heterogeneity of haptenic determinants. Singer emphasized the variations in the local environment on the protein surface and suggested that the points of covalent attachment of the haptenic groups on a given protein may be different. He concluded that the observed heterogeneity of combining sites of antihapten antibodies may therefore be due to antigenic heterogeneity and that heterogeneity of antibody-combining sites against a single determinant has not yet been demonstrated. Singer also reported some observations of Eisen. To minimize haptenic determinant heterogeneity, Eisen used as immunizing an-

tigen ϵ-41-mono-dinitrophenyl (DNP)-ribonuclease (only one DNP group per ribonuclease). By fluorescence quenching he observed as much ligand-binding heterogeneity with this antibody as with antibody to DNP induced by heterogeneously substituted DNP proteins. However, haptenic determinant homogeneity of DNP-ribonuclease has not been established.

Experiments relating to another type of heterogeneity were reported by Yagi, Pressman, and Kreiter. Antibody to *p*-azobenzenearsonate (R_p) was observed by radioimmunoelectrophoresis in three globulin components 6*S* γ-, 16*S* β_{2M}-, and 9–6*S* β_1. Globulins were separated on Sephadex G-200 and diethylaminoethyl cellulose. Antibody to R_p was also fractionated from R_p-cellulose columns by eluting the absorbed antibody with increasing concentrations of benzenearsonate. The fractions showed differences in binding constants and specificities toward haptens.

Frictional coefficient and intrinsic viscosity data on rabbit γ-globulin and its enzymatically derived functional subunits were reported by Buckley. He found that the intact molecule and dimer piece I had similar frictional properties but that pieces I and III are globular. Chromatography of tryptic digests of nonantibody and of purified antibody γ-globulins revealed that the greatest similarity in primary structure between the three pieces resides in piece III. He reported that univalent piece I of antibody protein could be renatured after complete unfolding in 6*M* guanidine hydrochloride.

Farr reported on the use and limitations of the ammonium sulfate technique for the study of heterogeneity of antibodies. I^{131}-labeled bovine plasma albumin, if combined with antibody in the form of a soluble complex, is precipitated by 50 percent saturated ammonium sulfate; free antigen stays in solution. Summarizing the work of several laboratories, he concluded that antiserums produced against crystalline bovine albumin are heterogeneous with respect to (i) the net affinity for bovine albumin-I^{131}, (ii) the association and dissociation rates between the labeled albumin and the antibodies concerned, and (iii) the efficiency of antibodies to cause secondary manifestations, such as precipitation, in the presence of the albumin.

Franklin discussed genetic control and biological activity of structural subunits of immune globulins. A number of antibody globulins from single individuals were found to be heterogeneous, since they were present in both type I and type II 7*S* and 19*S* γ-globulin fractions. In view of certain findings related to the synthesis of paraproteins found in the so-called "H-chain disease," and of certain other inconsistencies, he questioned the complete validity of current concepts of the structure of 7*S* γ-globulin. He suggested several possible alternate models for its structure.

Poulik reported studies on papain fragments of normal (7*S*) γ-globulins and (7*S*) myeloma γ-globulins by a combination of starch gel methods. Fragment *B*(F) contains at least 10 to 14 subcomponents and fragments A-C(S) at least 3 to 5 components. The subcomponents (thought to be intermediaries of the enzymatic cleavage) exhibit complex structures in two-dimensional starch-gel procedures (starch gel-urea starch gel; starch gel-urea mercaptoethanol starch gel). Immunological activities of the various subunits of the subcomponents were studied by a new immunoelectrophoretic technique performed directly from the urea starch gel or urea mercaptoethanol starch gel. The subunits of the A-C(S) and B(F) fragments already mentioned dissociated and separated in the gels gave precipitin lines with specific antisera. A possible new classification of the H(A) chain of the myeloma γ-globulins based upon these techniques was discussed.

Grossberg, using the paired label technique (I^{131} and I^{125}), presented evidence for existence of two different kinds of antibody sites against *p*-azobenzenearsonate; one kind contains an amino group, the other does not. He also found that antibody activity against *p*-azobenzenearsonate was associated with both H(A) and L(B) chains. Either polypeptide chain alone was only partially active, but when both chains were recombined, activity was fully restored. Antibody activity was measured by equilibrium dialysis and by radioimmunelectrophoresis; association of chains in the recombined fractions was demonstrated by radioimmunelectrophoresis and by ultracentrifugation.

Recent developments concerning heterogeneity of normal and pathological γ_{1A} globulins were presented by Vaerman, Fudenberg, Johnson, and Mandy. Two γ_{1A} paraproteins (7*S* and 17*S*) with different electrophoretic mobility were isolated (Sephadex G-200 and starch block electrophoresis) from the serum of a single patient with myeloma. The 17*S* component was converted to 7*S* on treatment with 2-mercaptoethanol. The 7*S* and 17*S* γ_{1A} proteins exhibited identical H- and L-chains on acid urea starch gel electrophoresis after reduction-alkylation, both with and without urea. The data suggest that 17*S* material is a polymer of the 7*S* γ_{1A}. Normal γ_{1A} globulins were isolated from a single individual and separated into 7*S*, 10.5*S* and a still heavier fraction containing 13*S* and (approximately) 16*S* γ_{1A} globulins. Again, L-chains of the γ_{1A} of the fractions differing by sedimentation rate were identical on gel electrophoresis. Passive transfer of reagin to weed extract was achieved with purified γ_{1A} globulin from an allergenic donor.

Biological aspects of heterogeneity were also discussed. Stavitsky reported on studies of the cellular origin of immune globulins during the primary and secondary response. The immunizing antigen was diphtheria toxoid in complete Freund adjuvant. Tissue culture, serological, and immunofluorescent methods were used to study spleens of immunized rabbits. The results were interpreted to indicate that cells resembling large lymphocytes synthesized 19*S* antibody and that subsequently plasma cells synthesized 7*S* antibody. He pointed out that the results did not exclude the possibility that large lymphocytes simultaneously or subsequently also synthesized some 7*S* antibody, that plasma cells synthesized some 19*S* antibody, or that large lymphocytes might be converted into plasma cells. S. Kaplan reported cross reactions, by complement fixation, between purified normal (wild type) tryptophan synthetase and extracts of point mutants of *Neurospora crassa* CRM+ or CRM−, with antiserum to purified tryptophan synthetase. The results indicate existence of at least three major species of antibody against the native molecule and were interpreted to reflect the existence of major antigenic regions on the surface of tryptophan synthetase. It was inferred that single amino acid replacements can lead to changes in the tertiary structure of protein antigens and also to marked change in immunologic reactivity. Most CRM− mutants give significant cross reaction with wild type tryptophan synthetase by complement fixation.

Vannier presented data which showed association of human skin sensitizing antibody with the $\beta_{2A}(\gamma_{1A})$-globulin fraction of human serum. Serum was fractionated by sequential diethylaminoethyl cellulose chromatography, Sepha-

dex G-200 gel filtration, and specific immune absorption with unispecific antiserums. Skin-sensitizing antibody was present in protein sedimenting slightly faster (7.7*S*) than human γ-globulin (6.8*S*).

Ovary reported development of both iso- and autoagglutinins in a rabbit immunized with erythrocytes from a second rabbit. Antibodies responsible for the isoagglutinating activity were found to be of the 7*S* and 19*S* type and were reactive at 4° and 37°C. Antibodies responsible for the autoagglutinating activity were solely 19*S* antibody and were reactive only at 4°C. Benacerraf reported the separation of biologic activities in the fast and slow components of 7*S* antibodies of identical specificity in individual guinea pigs. Similar observations were made with purified mouse antibodies.

Raffel discussed reactivity of cells in delayed hypersensitivity. Small lymphocytes from guinea pigs sensitive to tuberculin or to a protein of nerve tissue were shown by fluorescent staining to bind these antigens. The nerve protein antigen is physically and antigenically homogeneous, and is localized in the myelin sheaths of nerve tissue; this antigen is associated with the induction of allergic encephalomyelitis, of delayed skin reactivity, and of lymphocyte reactivity in the absence of detectable circulating antibody.

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Forthcoming Events

August

16–24. **Human Economy**, conf., Inst. of Paper Chemistry, Appleton, Wis. (A. N. McLeod, IPC, Appleton)

17–20. American Assoc. of **Clinical Chemists**, 16th natl., Boston, Mass. (F. F. Ronan, AACC, 19 Bay State Rd., Boston 15)

17–20. **Natural Ultra Low Frequency Electromagnetic Fields**, symp., Boulder, Colo. (W. H. Campbell, National Bureau of Standards, Boulder)

17–21. **Combustion**, 10th intern. symp., Cambridge, England. (Combustion Inst., 986 Union Trust Bldg., Pittsburgh 19, Pa.)

17–21. **Cryogenic Engineering**, conf., Philadelphia, Pa. (K. D. Timmerhaus, Engineering Research Center, Ketchum 129, Univ. of Colorado, Boulder)

17–21. **Simulation in Space Technology**, Blacksburg, Va. (F. J. Maher, Virginia Polytechnic Inst., Blacksburg)

17–22. International **Astronomical** Union, symp., Thessaloniki, Greece. (Maj. B. R. Agins, Air Force Office of Scientific Research, SRMA, Washington, D.C.)

17–22. **Cardiology**, 4th European congr., Prague, Czechoslovakia. (H. Kafka, Karlovo nám. 32, Prague 2)

17–22. **Endocrinology**, 2nd intern. congr., London, England. (A. S. Mason, London Hospital, Whitechapel, London, E.1)

17–22. **Social Psychiatry**, 1st intern. congr., London, England. (J. Bierer, 7 Hollycroft Ave., London, N.W.3)

17–28. **Molecular Biophysics**, intern. inst., Squaw Valley, Calif. (Prof. Weissbluth, Biophysics Laboratory, Stanford Univ., Stanford, Calif.)

18–20. International Assoc. of **Milk and Food Sanitarians**, Portland, Ore. (H. L. Thomasson, P.O. Box 437, Shelbyville, Ind.)

19–21. Physiology of **Digestion in the Ruminant**, 2nd intern. symp., Ames, Iowa. (R. W. Dougherty, Box 70, Ames)

20–21. National **Council of Teachers of Mathematics**, Minneapolis, Minn. (J. D. Gates, NCTM, 1201 16th St. NW, Washington, D.C. 20036)

22. American Inst. of **Ultrasonics in Medicine**, 9th annual, Boston, Mass. (W. J. Fry, Biophysical Research Laboratory, Univ. of Illinois, Urbana)

22–24. **History of Astronomy**, symp., Hamburg, Germany. (B. Sticker, Institut für Geschichte der Naturwissenschaften, Universität Hamburg, Hartnungstr. 5, 2 Hamburg 13, Germany)

22–28. American Soc. of **Human Genetics**, Boulder, Colo. (S. H. Boyer, Johns Hopkins Hospital, Baltimore, Md.)

23. American Assoc. of **Electromyography**, annual, Boston, Mass. (M. K. Newman, 16861 Wyoming Ave., Detroit, Mich. 48221)

23–26. American **Phytopathological** Soc., Lafayette, Ind. (J. R. Shay, Purdue Univ., Lafayette)

23–26. **Soil Conservation** Soc. of America, 19th annual, Jackson, Miss. (SCS, 7515 Northeast Ankeny Rd., Ankeny, Iowa)

23–28. American Inst. of **Biological Sciences**, annual, Boulder, Colo. (AIBS, 2000 P St., NW, Washington, D.C.)

The following societies will hold meetings in conjunction with the AIBS meeting:

American Bryological Society
American Fern Society
American Fisheries Society
American Microscopical Society
American Society for Horticultural Science
American Society of Human Genetics
American Society of Parasitologists
American Society of Plant Physiologists
American Society of Plant Taxonomists
American Society of Zoologists
Biometric Society ENAR-WNAR
Botanical Society of America
Ecological Society of America
Genetics Society of America
Mycological Society of America
National Association of Biology Teachers
Nature Conservancy
Phi Sigma Society
Phycological Society of America
Society for Industrial Microbiology
Society for the Study of Development and Growth
Society of Nematologists
Society of Protozoologists
Tomato Genetics Cooperative

23–28. American Congr. of **Physical Medicine and Rehabilitation**, Boston, Mass. (G. Gullickson, Jr., 30 N. Michigan, Chicago, Ill.)

23–28. **Conservation Education**, conf., Tacoma, Wash. (C. Boyce, Office of the Superintendent of Public Instruction, Olympia, Wash.)

24–26. American Inst. of **Aeronautics and Astronautics**, Los Angeles, Calif. (AIAA, 1290 Sixth Ave., New York, N.Y.)

24–26. Society for **Cryobiology**, annual, Washington, D.C. (V. P. Perry, Tissue Bank Dept., National Naval Medical Center, Bethesda, Md.)

24–26. **Education in the Nuclear Power Era**, conf., Gatlinburg, Tenn. (M. L. Nelson, Education Div., Oak Ridge Natl. Laboratory, P.O. Box 117, Oak Ridge, Tenn.)

24–26. **Mathematical** Assoc. of America, summer meeting, Univ. of Massachusetts, Amherst. (H. M. Gehman, Univ. of Buffalo, Buffalo 14, N.Y.)

24–27. American Soc. for **Pharmacology** and Experimental Therapeutics, Univ. of Kansas, Lawrence. (E. B. Cook, The Society, 9650 Wisconsin Ave., NW, Washington, D.C.)

24–27. **Biological Photographic** Assoc., annual, New York, N.Y. (C. H. Weiss, 81 Bedford St., New York 14)

24–27. American **Hospital** Assoc., Chicago, Ill. (E. L. Crosby, 840 N. Lake Shore Dr., Chicago 11)

24–27. **Toxicology and Occupational Medicine**, 4th inter-American conf., Miami Beach, Fla. (W. Machle, Univ. of Miami School of Medicine, Coral Gables, Fla.)

24–28. International Council of the **Aeronautical Sciences**, 4th congr., Paris, France. (American Inst. of Aeronautics and Astronautics, 2 E. 64 St., New York, N.Y. 10021)

24–28. **Astrodynamics Guidance and Control**, conf., Los Angeles, Calif. (K. Watanabe, 4731 B Engineering Building III, University of California, Los Angeles 24)

24–28. American **Astronautical** Soc., military space applications symp., Stanford, Calif. (AAS, 516 Fifth Ave., New York, N.Y.)

24–28. Society for **Industrial and Applied Mathematics**, Amherst, Mass. (W. S. Dorn, T. J. Watson Research Center, I.B.M., P.O. Box 218, Yorktown Heights, N.Y.)

24–28. Scandinavian **Mathematical** Congr., Copenhagen, Denmark. (Secretariat, The Congress, c/o Mathematical Inst., H. C. Ørsted Inst., Universitetsparken 5, Copenhagen Ø)

24–28. American **Mathematical** Soc., New York, N.Y. (G. L. Walker, AMS, 190 Hope St., Providence, R.I.)

24–28. **Preventive Cardiology,** first intern. conf., Burlington, Vt., (W. Raab, Preventive Heart Reconditioning Foundation, 206 Summit St., Burlington, Vt.)