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REVIEW OF THE ACTIVITIES OF THE PAHO/WHO  
IMMUNOLOGY RESEARCH AND TRAINING CENTER IN SÃO PAULO

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Introduction

The PAHO/WHO Immunology Research and Training Center in São Paulo was established in 1966 in the Department of Microbiology and Parasitology of the Escola Paulista de Medicina under the direction of Professor Otto G. Bier. In 1969, following an agreement between WHO, the Secretariat of Health of the State of São Paulo, and the University of São Paulo, the Center moved its headquarters to the Butantan Institute, where it now occupies an area of approximately 600 m<sup>2</sup>.

The present director of the Center is Dr. Ivan Mota, associate professor of the University of São Paulo. He succeeded Dr. Bier in May 1971. His scientific staff consists of three full-time immunologists provided by the Butantan Institute.

At the Ninth Meeting of the PAHO Advisory Committee on Medical Research in 1970, we reviewed the activities of the Center from 1966 to 1969. The present report deals with the activities of the Center in the last 4 years.

Objectives

The main objective of the Center is to provide candidates from Latin American countries with postgraduate teaching in basic immunology and to develop immunological research projects directly or indirectly related to health problems in the region.

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Annual Course in Basic Immunology

Since 1969 the Center's annual 8-month course in basic immunology has been condensed to 4 months to allow the staff enough time for research. This shortening of the course, far from being deleterious, proved to be beneficial: it is much easier to get good candidates to attend and visiting professors to teach the shortened course. On the other hand, the intensive, condensed course lends itself to an atmosphere of competition and excitement in which the potentialities of the students are clearly revealed. The schedule of the course given in 1971 is appended (Annex 1). Annexes 2 and 3 list the theoretical classes, laboratory work, and seminars held in conjunction with the 1972 course.

At the same time that the course was shortened, it was decided to offer to two or three of the best graduating students, the opportunity to remain at the Center for 8 more months to work on a scientific project. In his report to the Director General, a WHO consultant, who for several years had given tutorial lectures at the end of the course, and presided over final examinations at the Center, recommended that a relationship be established with the University of São Paulo to enable the best students of the Center to go on for a master's or a doctor's degree, while doing their thesis research at the Center. This recommendation has already been partially carried out, since both the University of São Paulo and the Escola Paulista de Medicina (a federal school) accept as full credits the immunology course and the master's or doctoral theses researched at the Center.

Up to 15 students are admitted to the 4-month course every year. The course is given entirely in English and comprises approximately 140 hours of theoretical lectures, 115 hours of seminars (critical analysis of immunochemical and immunological papers from the current literature), and at least 320 hours of laboratory work. Midway through the course, students are tested by each visiting professor. The examination consists of giving answers to selected questions, and analyzing scientific papers and laboratory work.

At the end of the course, a WHO consultant or one of the visiting professors is invited to give a final examination.

Students who failed in the partial examinations are allowed to attend the rest of the course as auditors, but do not receive the final examination and are therefore unable to get a certificate.

#### Immediate Consequences

As a result of the course given at the Center and of the stimulus brought by visiting professors, most of the students decisively focused their interests in immunology research. Some of them were sent abroad for further training in high-level laboratories in Europe and the United States. Two Uruguayans trained in England (1) and France (1); two Peruvians went to England and six Brazilians trained in England (2), France (1), and United States (3).

The solid background the students acquired at the Center served them in good stead in all these laboratories, so that the Center really fulfilled its role of selecting good candidates to become future leaders of immunology research in their respective countries.

The Center also influenced immunology research in São Paulo, as attested by the strong group of immunologists now working at the Biological Institute of the Secretariat of Agriculture of the State of São Paulo. In that institution, excellent projects on immunogenetics and on the immunoglobulins of different animal species are being conducted under the supervision of two visiting professors and of one former member of the permanent staff of the Center. As pointed out before, the Departments of Immunology of the University of São Paulo and of the Escola Paulista de Medicina are also being definitely influenced by the Center.

The next objective is to influence the host institution itself, the Butantan Institute. This institution performs an excellent job in preparing immunobiological materials for the State of São Paulo. The Pan American Health Organization has been of great help by providing

facilities for bringing the preparation of these products to international standards. However, there is a need of basic research to support these practical activities and the Center is anxious to cooperate towards this objective. The solution to this problem was given this year by the establishment, in the Institute, of a laboratory of immunobiology under the direction of a well-trained Brazilian immunologist who had been a visiting-professor at the Center. This laboratory will function in close association with the Center and, besides its research activities, will also take advantage of the facilities available at the Center to modernize the Butantan Institute's methods of preparation of immunobiological materials. For example, the preparation of snake antivenoms, now made according to old traditional methods will be entirely revised, from the schedules of immunization to the antiserum purification and standardization.

The Center has made a solid contribution to the etiology of pemphigus foliaceus in collaboration with one of the visiting-professors and is now engaged in immunological research in leprosy in cooperation with the leprologists of the Secretariat of Health of the State of São Paulo.

#### Research Activities

The research activities of the Center in the last 4 years are summarized below.

##### A) Papers published or accepted for publication

1. Albuquerque, L. R., et al. Failure of insoluble antigens to elicit anaphylactic reactions. Int Arch Allergy Appl Immunol 41:797, 1971.
2. Beutner, E. H., et al. Immunofluorescent studies of auto-antibodies to intercellular areas of epithelia in Brazilian pemphigus foliaceus. Proc Soc Exp Biol Med 127:81, 1968.
3. -----, et al. Mem Inst Butantan 35:79-94, 1971.
4. Gennari, M. Estudo da ação do veneno de Bothrops jararaca sobre o complemento de cobaia. Master's thesis (oriented by Otto G. Bier), University of São Paulo, 1972.

5. Guercio, P., et al. Opsonic, cytophilic, and agglutinating activity of guinea pig  $\gamma$ -2 and  $\gamma$ -M anti Salmonella antibodies. Immunology 16:361-371, 1969.
6. Mota, I., and A. Perini. A heat-labile mercaptoethanol susceptible homocytotropic antibody in the guinea pig. Life Sci 9:923, 1970.
7. Passos, Helcio C., et al. Immunology. (Submitted for publication).
8. Perini, A. Estudo sobre o efeito adjuvante de endotoxinas e de ácidos nucléicos na produção de anticorpos da classe IgE em cobaias. Master's thesis (oriented by I. Mota), University of São Paulo, 1972.
9. -----, and I. Mota. Heterogeneity of guinea pig homocytotropic antibodies. Immunology 22:915, 1972.
10. -----, and -----. The production of IgE and IgG1 antibodies in guinea pigs immunized with antigen and bacterial lipopolysaccharides. Immunology, 1973. Submitted for publication.
11. Uriel, J., et al. Immunoelectrophoretic characterization of enzymes in the venom of Bothrops jararaca, Bull Soc Chim Biol 50:938-940, 1968.

B) Research programs in progress

1. T and B lymphocytes in circulating blood in the different clinical forms of leprosy.
2. Studies on the production of IgE antibody in B mice.
3. Stimulation of the immune system by single and double stranded RNA.
4. Adjuvant effect of LPS on IgE antibody production in guinea pigs.
5. Purification and biological properties of lymphocytosis-stimulating factor.
6. Role of the spleen in IgE antibody production: effect of splenectomy in mice and guinea pigs.

7. Separation by column chromatography of protective antigens from Bothrops jararaca venom.

8. Biological activity of the different IgG1 fractions obtained by linear gradient chromatography from guinea pig antiserum.

#### Concluding Remarks

The Immunology Center in São Paulo is accomplishing to the best of its ability the goals of training investigators and stimulating immunology research in Latin American countries. Its limited budget, however, definitely restricts research activities. These could be much greater if the Center employed a larger staff to make full use of existing laboratory facilities. The rather low salaries offered by the Butantan Institute, however, prevents the recruitment of scientific investigators who are drawn to the University of São Paulo where salaries are two to three times higher. A recent decree of the Government of the State of São Paulo somewhat ameliorated the situation by creating the Scientist Career. Nevertheless, measures must still be taken for the law to become effective. It is hoped that this will occur in the course of 1973.

WHO provides 15,000 dollars annually to run the Center and PAHO subsidizes the travel expenses of two visiting-professors and training grants for non-Brazilian students admitted to the course. This help is barely enough to maintain activities at the present level.

It would be desirable if the Center, besides the course on basic immunology which focuses on the identification of research talents, could also provide a short, one-month course on immunological techniques, given at the time of University vacations. This course would be intended mainly for immunology instructors in teaching institutions. It would involve only a small expense that could perhaps be covered by the Pan American Health Organization.

ANNEX 1

PAHO/WHO IMMUNOLOGY RESEARCH AND TRAINING CENTER

COURSE IN BASIC IMMUNOLOGY

16 August - 17 December 1971

Date	Lectures and seminars	Laboratory work
16-20 August	Elements of protein chemistry - J. L. Prado (3 hr)  Column chromatography. Gel-filtration - A. Takeda (2 hr)  Principles and applications of immunofluorescence - L. S. Prigenzi and M. E. Camargo (8 hr)	Fractionation of serum proteins by ammonium sulfate precipitation  Ouchterlony plate  Fluorescent labeling. Standardization of conjugates  Immunofluorescence demonstration of antibodies to microorganisms, intercellular and nuclear antibodies
23-27 August	Gene structure and function - W. Beçak (2 hr)  Protein biosynthesis - J. F. Lara (2 hr)  Introductory lectures in basic immunology - I. Mota (2 hr)  Nature of the forces involved in Ag-Ab interaction - M. E. Alves Pereira (1 hr)  Students' seminars (5 hr)	pH determination. Buffers  Visible light and UV spectrophotometry  Estimation of proteins by UV spectrophotometry, biuret, and micro-Kjeldahl  Immunization of animals
30 August to 3 September	Complement components and their functions in immune hemolysis - Wilmar Dias da Silva (4 hr)	Spectrophotometric titration of guinea pig and human complement



Date	Lectures and seminars	Laboratory work
6-10 September	<p>Quantitative complement fixation - M. Hanashiro (3 hr)</p> <p>Diagnostic complement fixation - C. Fava Netto (2 hr)</p> <p>Conglutination and immuno-adherence - Lucia Mary Singer (1 hr)</p> <p>Nature and classification of hypersensitivity reactions of the immediate type - I. Mota (2 hr)</p> <p>Students' seminar (5 hr)</p>	<p>Quantitative C-fixation by the macromethod of Mayer et al.</p> <p>Preparation of EAC 142 and its decay to EAC 14</p> <p>Titration of C3 (relative units)</p>
6-10 September	<p>Arthus and similar reactions. Experimental serum sickness - O. G. Bier (2 hr)</p> <p>Experimental glomerulonephritis - M. Siqueira (2 hr)</p> <p>The role of complement in immunobiological phenomena - O. G. Bier (2 hr)</p> <p>Anaphylaxis - I. Mota (3 hr)</p> <p>Homocytotropic antibodies - I. Mota (2 hr)</p> <p>Allergy to drugs - Annelise Strauss (2 hr)</p> <p>Students' seminars (5 hr)</p>	<p>Conglutination and immuno-conglutination</p> <p>Systemic anaphylaxis, PCA and RPCA Dale test</p> <p>Degranulation of mastocytes</p> <p>Passive Arthus, direct and reverse</p>
13-18 September	<p>Quantitative study of the precipitin reaction - C. Moreno (2 hr)</p> <p>Immunochemical analysis by gel-precipitation - C. Moreno (2 hr)</p>	<p>Quantitative estimation of antibody and of antigen by the precipitin reaction</p> <p>Preparation of azo and DNP proteins</p>

Date	Lectures and seminars	Laboratory work
	<p>Immunoelectrophoresis - R. G. Ferri (3 hr)</p> <p>Students' seminars (8 hr)</p>	<p>Purification and quantitative estimation of anti-DNP antibodies</p> <p>Immunoelectrophoresis of human serum, normal and pathological</p>
20-24 September	<p>Agglutination - O. G. Bier (2 hr)</p> <p>Elements of carbohydrate chemistry. Dextran and levans - C. Moreno (4 hr)</p> <p>Pneumococcus polysaccharides, teichoic acids - C. Moreno (2 hr)</p> <p>Students' seminars (8 hr)</p>	<p>Passive hemagglutination</p> <p>Preparation of oligosaccharides from dextran</p> <p>Quantitative determination of hexose (galactose), methylpentose, glucosamine, and acetylhexosamine</p> <p>Nynhydrin micro N determination</p>
27 September to 1 October	<p>Salmonella O antigens - C. Moreno (2 hr)</p> <p>Endotoxin - O. G. Bier (1 hr)</p> <p>Exotoxins - O. G. Bier (1 hr)</p> <p>The toxin-antitoxin reaction - M. Gennari (2 hr)</p> <p>Cross reactions - C. Moreno (3 hr)</p> <p>Students' seminars (8 hr)</p>	<p>Preparation of oligosaccharides from dextran, concl.</p> <p>Partial purification of diphtheria toxoid</p> <p>Ramon flocculation</p> <p>In-vivo titration of antitoxin</p>
4-8 October	<p>Hapten-antibody interaction. Inhibition reactions - C. Moreno (3 hr)</p> <p>The nature of antigenic determinants and of the antibody combining site - C. Moreno (2 hr)</p>	<p>Equilibrium dialysis</p> <p>Hapten inhibition of precipitation</p>

Date	Lectures and seminars	Laboratory work
11-15 October	Heterogeneity and structure of antibodies and immunoglobulins - C. Moreno (4 hr)  Students' seminars (8 hr)	Quantitative precipitin curves of the reaction of rabbit antihem ovalbumin with hen and duck ovalbumins
11-15 October	Blood grouping - O. G. Bier (2 hr)  Genetic aspects of immunohematology - C. Moreno (2 hr)  Lectins - C. Moreno (1 hr)  Blood group substances - C. Moreno (3 hr)  Students' seminars (8 hr)	Separation of gamma-1 and gamma-2 antibodies from guinea pig serum  The antiglobulin test  Pepsin digestion of rabbit IgG  Acrylamide gel-electrophoresis of IgG chains
18-23 October	Delayed hypersensitivity - G. Biozzi (3 hr)  Regulation of antibody synthesis - G. Biozzi (2 hr)  PARTIAL EXAMINATION	Differentiation of 7S and 19S antibodies by mercaptoethanol treatment  Quantitative estimation of immunoglobulins by radial immunodiffusion
25-29 October	Cytodynamics of antibody formation - G. Biozzi (4 hr)  Genetic aspects of antibody formation - G. Biozzi (4 hr)  Students' seminars (8 hr)	Jerne plate  The "rosette" method  Macrophage migration inhibition
1-5 November	Radioactive methods of current use in immunology - G. Biozzi (2 hr)  Quantitative estimation of RES function - G. Biozzi (4 hr)  Students' seminars (8 hr)	Radioactive labeling of a bacterial suspension  Blood clearance of carbon particles

Date	Lectures and seminars	Laboratory work
8-12 November	<p>Opsonins. Cytophilic antibodies - G. Biozzi (2 hr)</p> <p>Phagocytosis. Nonspecific stimulation of resistance to infection - G. Biozzi (2 hr)</p> <p>Students' seminars (12 hr)</p>	<p>Autografts and allografts in guinea pigs and mice</p> <p>Autoallergic encephalomyelitis in the rat and in the guinea pig</p> <p>Experimental autoimmune thyroiditis</p>
16-20 November	<p>The morphology and ontogenesis of the immune system. Primary and secondary lymphoid organs - A. Szenberg (4 hr)</p> <p>Function of the lymphoid organs, lymphoid cell populations, and migration patterns of lymphocytes - A. Szenberg (4 hr)</p> <p>Students' seminars (8 hr)</p>	<p>Dissection and histology of lymphoid organs in mammals and birds</p> <p>Effect of thymectomy and of bursectomy on the immunoresponse in the mouse and in the chicken</p> <p>Thoracic duct canulation</p>
22-26 November	<p>Mechanism of immunological recognition - A. Szenberg (2 hr)</p> <p>Cell cooperation in the immune response - A. Szenberg (2 hr)</p> <p>Specific cell mediated immune reactions: GVH, Graft Rejection, Delayed Hypersensitivity, <u>in vitro</u> Models - A. Szenberg (4 hr)</p> <p>Students' seminars (8 hr)</p>	<p>Demonstration of GVH reactivity</p> <p>Autoantibodies in human thyroiditis</p> <p>Titration of rheumatoid factor</p> <p>Detection of Australia antigen</p>
29 November to 3 December	<p>Experimental models of autoimmunization - L. S. Prigenzi (2 hr)</p> <p>Mechanisms of autoimmunization - A. Szenberg (2 hr)</p> <p>Autoimmune diseases in man - Annelise Strauss (3 hr)</p>	<p>Leukocyte typing</p> <p>Histocompatibility tests</p> <p>Blast transformation by PHA and by antigen</p>

Date	Lectures and seminars	Laboratory work
	Leukocyte grouping and histocompatibility tests - F. Antonacio (2 hr)  Students' seminars (8 hr)	Reconstitution of irradiated animals
6-10 December	Immunogenetics of tissue transplantation. Histocompatibility antigens - N. Vaz (4 hr)  Students' seminars (8 hr)	Free
13-17 December	FINAL EXAMINATION	

## OBSERVATIONS

1. Lectures are given in the morning, starting at 9:00 a.m., from Monday to Friday. Seminars are usually held from 9:00 a.m. to 12:00 noon, Saturdays included. The period between 2:00 and 2:30 p.m. should be used for planning and beginning the experiments of the day, under the guidance of the permanent staff of the Center and of the visiting-professors. Students should work in the laboratory every day, except on Saturdays, from 2:00 to 6:00 p.m. The laboratory will also be opened in the evening for any supplementary work the students may need to do. Arrangements should be made for the use of the materials and equipment during extra hours of laboratory work.

2. A partial examination will be given on the 23rd of October. Students failing this examination will not be admitted to the final examination.

3. In all above activities, English will be the only language used for communication.

ANNEX 2

PAHO/WHO IMMUNOLOGY RESEARCH AND TRAINING CENTER

LECTURES AND SEMINARS GIVEN IN THE 1972 COURSE

I Introduction: Review of recent immunology advances (Dr. V. Nussenzweig, Pathology Department, New York University)

Antibodies

Theories of antibody formation

Antigen-antibody interaction: I

Antigen-antibody interaction: II

Suppression of synthesis of allotypically defined immunoglobulins and compensation by another subclass of immunoglobulin (seminar)

II Cellular Immunology (Dr. C. Bianco, Pathology Department, New York University)

The lymphoid system: I

The lymphoid system: II

Macrophages: I

Macrophages: II

Cell-mediated immunity

Cell cooperation: I

Cell cooperation: II

Tolerance

Specificity of T cells for transplantation antigens (seminar)

The mixed lymphocyte reaction (seminar)

Cell cooperation (seminar)

Triggering of lymphocytes (seminar)

Antigenic competition (seminar)

Transfer factor (seminar)

Are T cells essential for in vivo antibody formation? (seminar)

III Complement (Prof. W. Dias da Silva, Instituto Ciencias Biologicas, UFMG, Belo Horizonte, M.G.)

Components of the complement system: methods of isolation and physicochemical characterization

Reaction sequence in immune hemolysis: the role of immunoglobulins - reaction and activation of the C1 component, formation of the C4b - C2a (C3 convertase) complex

Activation and cleavage of the C3 component: the role of C3b in immune hemolysis; reaction of the C5, C6, and C7 components; fixation of C8 on red-cell membranes and its activation by C9.

Ultrastructural changes produced on red-cells membranes in immune hemolysis: the role of C5 and C8 in the establishment of these lesions

Alternate pathway of the complement activation: the additional components and the complement's relation with the properdin system

Complement titration

The one-hit theory of immune hemolysis

Biologically active products formed during the complement activation: small fragments and enzymes

IV Immediate hypersensitivity (Prof. I. Mota, PAHO/WHO Immunology Research and Training Center, São Paulo)

Cytotoxic reactions

Biological activities of antigen-antibody complexes

Anaphylaxis

Mechanism of anaphylaxis: chemicals mediators

Mechanism of anaphylaxis: homocytotropic and heterocytotropic antibodies. Fixation of antibodies.

Mechanism of anaphylaxis. Target cells: mast cells, basophils, and platelets.

Serum sickness disease. Arthus reaction (O. G. Bier)

Mechanism of immunological injury of rat peritoneal mast cells (seminar)

Regulation of IgE-antibody formation (seminar)

Antigenic release of histamine from platelets (seminar)



Biological and immunological basis of the anaphylactic release of histamine: implication of C-AMP (seminar)

Mechanisms involved in the deposition of immune complexes in tissue (seminar) (Prof. A. Oliveira)

V Transplantation immunity (Prof. E. F. Potworowski, Institute of Hygiene, University of Montreal, Canada)

Transplantation antigens: I

Transplantation antigens: II

Typing sera: specificity determination

Genetics and family studies of transplantation antigens

Physical and chemical characteristics of transplantation antigens: significance in health and disease

Principles of immunofluorescence

Transfer factor

Lymphokinesis

Role of macrophages in humoral and cellular immunity

Lymphoid populations

T and B cell cooperation in immune response

Receptors on lymphocytes

Cellular events in immune response: I

Cellular events in immune response: II

The graft-versus-host reaction

Interaction in complex immunologic events

In vitro correlates of cellular immunity

In vitro correlates: critical review

Cell-mediated immunity

VI Immunogenetics I, II, and III (Prof. N. M. Vaz, Instituto de Biociências, IFMG)

VII Immunochemistry (Prof. Ruth Arnon, Weizmann Institute, Rehovoth, Israel)

A. Antigenes and Antigenicity

Introduction; definitions; proteins as antigen

Artificial antigens; polypeptidyl proteins; synthesis of polyamino acids and synthetic antigens

Synthetic antigens (role of composition, size, shape, locus)

Synthetic antigens (role of optical configuration and conformation), conformational determinants of proteins

Specific uses of synthetic antigens (size of active site, reverse charge relationship, genetic control of immune response)

Antigens with other specificities (sugars, lipids, nucleosides, steroids, hormones)

Antigenicity of polysaccharides; blood groups; nucleic acids

Immunochemistry of biologically active materials (enzymes, polypeptide hormones, toxins)

B. Antibodies

Structure of IgG (fragmentation; separation of chains)

Physical properties of IgG; domains, V and C regions

Diversity of immunoglobulins (isotypic, allotypic, and idiotypic); theories of origin of diversity

Combining site; properties of IgM, IgA, and IgE

C. Methods Used in Immunochemistry

Precipitins: turbidimetry; gel diffusion; Ag-binding capacity

Radioimmunoassay; hemagglutination; complement fixation; modified bacteriophage inactivation

Enzyme-labeled immunoabsorbent assay

Equilibrium dialysis; fluorescence quenching

Conjugation of molecules; purification of antibodies

Isolation of antigens and structural analysis; establishment of purity of antigens; localization of antigens in tissues and on cells; immunofluorescence, ferritin labeling.

LABORATORY WORK

Estimation of proteins by UV spectrophotometry, biuret, and micro-Kjeldahl

Spectrophotometric titration of guinea pig and human complement

Quantitative C-fixation by the macromethod of Mayer

Preparation of cell suspensions from lymphoid organs of the mouse

Isolation of lymphocytes from blood; stimulation of human lymphocytes with phytohemagglutinin

Mixed lymphocyte reaction

Cell separation with Ficoll-Hypaque gradient

Cytotoxic test by trypan blue exclusion

Autoradiography

Detection of B and T lymphocytes by immunofluorescence and cytotoxicity

Histology of the thymus dependent and thymus-independent areas of lymphoid organs

The graft-versus-host reaction in the chicken and mammals

Inhibition with anti-T cells

Histology of G. V. H. reactions (splenomegaly)

Delayed hypersensitivity in vivo: wattle reaction and skin test

Demonstration of antibody-producing cell (Cunningham assay): inhibition of antibody production by anti-B serum

Tissue typing techniques: microcytotoxicity - leucoagglutination - fluorescence assay

Dinitrophenylation of BSA

Passive hemagglutination

Precipitin reaction

Inhibition of precipitin with haptens

Immunodiffusion

Purification of antibodies

Digestion of IgG with papain

Digestion of IgG with pepsin

Reduction of IgG

ANNEX 3

LECTURES AND SEMINARS GIVEN IN THE 1972 COURSE

DURING AUGUST AND SEPTEMBER

Week 1

Tuesday  
1 August

Lecture: Introduction

Seminar 1: Recirculation of lymphocytes

- a. HOWARD, Jonathan C. The life-span and recirculation of marrow-derived small lymphocytes from the rat thoracic duct. J Exp Med 135:185, 1972.
- b. HOWARD, J. C., S. V. HUNT, and J. L. GOWANS. Identification of marrow-derived and thymus-derived small lymphocytes in the lymphoid tissue and thoracic duct lymph of normal rats. J Exp Med 135:200, 1972.

Wednesday  
2 August

Lecture: Antibodies I

Seminar 2: Antigen localization

- a. NOSSAL, G. J. V., A. ABBOT, J. MITCHELL, and Z. LUMMUS. Antigens in immunity. XV. Ultrastructural features of antigen capture in primary and secondary lymphoid follicles. J Exp Med 127:227, 1968.

Thursday  
3 August

Lecture: Antibodies II

Seminar 3: Are macrophages essential for the immune response "in vitro"?

- a. MOSIER, D. E. A requirement for two cell types for antibody formation in vitro. Science 158:1573, 1967.
- b. CHEN, C., and J. G. HIRSH. Restoration of antibody-forming capacity in cultures of nonadherent cells by mercaptoethanol. Science 176:60, 1972.

Friday  
4 August

Lecture: Theories of antibody formation

Seminar 4: One plasma cell-one antibody specificity

- a. GREEN, I., P. VASSALI, V. NUSSENZWEIG, and B. BENACERRAF. Specificity of the antibodies produced by single cells following immunization with antigens bearing two types of antigenic determinants. J Exp Med 125:511, 1967.

Week 2

Monday  
7 August

Lecture: Antigen antibody interactions

Seminar 5: Idiotypes

- a. ERICHMANN, K., and T. J. KINDT. The inheritance of individual antigenic specificities of rabbit antibodies to streptococcal carbohydrates. J Exp Med 134:532, 1971.
- b. BRIENT, B. W., J. HAIMOVICH, and A. NISONOFF. Reaction of anti-idiotypic antibody with the hapten-binding site of a myeloma protein. Proc Nat Acad Sci (USA) 68:3136, 1971.
- c. KUETTNER, M. G., A. WANG, and A. NISONOFF. Quantitative investigations of idiotypic antibodies. VI. Idiotypic specificity as a potential genetic marker for the variable regions of mouse immunoglobulin polypeptide chains. J Exp Med 135:579, 1972.

Tuesday  
8 August

Lecture: The complement system

Seminar 6: The alternate pathway for complement fixation

- a. GOTZE, O., and H. J. MULLER-EBERHARD. The C-3 activator system: an alternate pathway of complement activation. J Exp Med 134:90 [Suppl], 1971.
- b. MARCUS, R. L., H. S. SHIN, and M. M. MAYER. An alternate complement pathway: C-3 cleaving activity, not due to C142a, on endotoxic lipopolysaccharide after treatment with guinea pig serum. Relation to properdin. Proc Nat Acad Sci (USA) 68:1351, 1971.
- c. MULLER-EBERHARD, H. J. and O. GOTZE. C3 Proactivator convertase and its mode of action. J Exp Med 135:1003, 1972.

Wednesday  
9 August

Lecture: The lymphoid system, I

Seminar 7: Antibody-mediated cytotoxicity

- a. PERLMANN, P. and H. PERLMANN. Contactual lysis of antibody-coated chicken erythrocytes by purified lymphocytes. Cell Immunol 1:300, 1970.
- b. HENNEY, C. S., and M. M. MAYER. Specific cytolytic activity of lymphocytes. Effect of antibodies against complement components C2, C3, and C5. Cell Immunol 2:702, 1971.
- c. MOLLER, G., and S. SVEHAG. Specificity of lymphocyte-mediated cytotoxicity induced by in vitro antibody-coated target cells. Cell Immunol 4:1, 1972.

Thursday  
10 August

Lecture: The lymphoid system, II

Seminar 8: Origin of T cells

- a. OWEN, J. J. T., and M. C. RAFF. Studies on the differentiation of thymus-derived lymphocytes. J Exp Med 132: 1216, 1970.

Friday  
11 August

Lecture: The lymphoid system, III

Seminar 9: Immunoglobulins on B cells, I

- a. PERNIS, B., L. FORNI, and L. AMANTE. Immunoglobulin spots on the surface of rabbit lymphocytes. J Exp Med 132:1001, 1970.
- b. TAKAHASHI, T., L. J. OLD, K. R. McINTIRE, and E. A. BOYSE. Immunoglobulins and other surface antigens of cells of the immune system. J Exp Med 134:815, 1971.
- c. UNANUE, E., H. M. GREY, E. RABELLINO, P. CAMPBELL, and J. SCHMIDTKE. Immunoglobulins on the surface of lymphocytes. II. The bone marrow as the main source of lymphocytes with detectable surface bound immunoglobulin. J Exp Med 133:1188, 1971.
- d. VITETTA, E. S., S. BAUR, and J. W. UHR. Cell-surface immunoglobulin. II. Isolation and characterization of immunoglobulin from mouse splenic lymphocytes. J Exp Med 134:242, 1971.

Week 3

Monday  
14 August

Lecture: Macrophages

Seminar 10: Immunoglobulins on B cells, II

- a. DAVIE, J. M., W. E. PAUL, R. G. MAGE, and M. B. GOLDMAN. Membrane-associated immunoglobulin of rabbit peripheral blood lymphocytes: allelic exclusion at the b locus. Proc Nat Acad Sci (USA) 68:430, 1971.
- b. GREAVES, M. F. The expression of immunoglobulin determinants on the surface of antigen-binding lymphoid cells in mice. I. An analysis of light and heavy chain restrictions on individual cells. Europ J Immunol 1:186, 1971.
- c. GREAVES, M. F. The expression of immunoglobulin determinants on the surface of antigen-binding lymphoid cells in mice. II. Allotypes of the Ig-1 locus. Europ J Immunol 1:195, 1971.

Tuesday  
15 August

Lecture: Cell-mediated immunity

Seminar 11: Antigen-binding cells (B) I

- a. WIGZELL, H., and B. ANDERSSON. Cell separation on antigen-coated columns. J Exp Med 129:23, 1969.
- b. RUTISHAUER, U., C. F. MILLETTE, and G. M. EDELMAN. Specific fractionation of immune cell populations. Proc Nat Acad Sci (USA) 69:1596, 1972.

Wednesday  
16 August

Lecture: Cell cooperation

Seminar 12: Antigen-binding cells (B) II

- a. DAVIE, J. M. and W. E. PAUL. Receptors on immunocompetent cells. I. Cell Immunol 1:404, 1970.
- b. DAVIE, J. M. and W. E. PAUL. Receptors on immunocompetent cells. II. J Exp Med 134:495, 1971.
- c. DAVIE, J. M., A. S. ROSENTHAL, and W. E. PAUL. Receptors on immunocompetent cells. III. J Exp Med 134:517, 1971.

Thursday  
17 August

Lecture: Tolerance

Seminar 13: Suppression of antibody formation by antiserum to immunoglobulin H chains

- a. LAWTON III, A. R., R. ASOFSKI, M. B. HYLTON, and M. COOPER. Suppression of immunoglobulin class synthesis in mice. I. Effects of treatment with antibody to  $\mu$ -chain. J Exp Med 135:277, 1972.
- b. PIERCE, C. W., S. M. SOLLIDAY, and R. ASOFSKI. Immune responses in vitro. IV. Suppression of primary  $\gamma$ M,  $\gamma$ G, and  $\gamma$ A plaque-forming cell responses in mouse spleen cell cultures by class-specific antibody to mouse immunoglobulins. J Exp Med 135: 675, 1972.
- c. PIERCE, C. W., S. M. SOLLIDAY, and R. ASOFSKY. Immune responses in vitro. V. Suppression of responses in primed mouse spleen cell cultures. J Exp Med 135:698, 1972.

Friday  
18 August

Lecture: Regulation of the immune response

Seminar 14: Suppression of antibody formation by antiserum to allotypic and idiotypic determinants

- a. DUBISKI, S. Suppression of synthesis of allotypically defined immunoglobulins and compensation by another subclass of immunoglobulin. Nature 214:1365, 1967.
- b. VICE, J. L., W. L. HUNT, and S. DRAY. Allotype suppression with anti- $b^5$  antiserum in  $b^5b^5$  homozygous rabbits fostered in uteri of  $b^4b^4$  homozygous mothers: compensation by allotypes at other loci. J Immunol 103:629, 1969.
- c. LYNCH, R. G., R. J. GRAFF, S. SIRISINHA, E. S. SIMMS, and H. N. EISEN. Myeloma proteins as tumor-specific transplantation antigens. Proc Nat Acad Sci (USA) 69:1540, 1972.

Week 4

Monday  
21 August

Seminar 15: Do T cells have immunoglobulins on the membrane?

- a. MARCHALONIS, J. J., R. E. CONE, and J. A. ATWELL. Isolation and partial characterization of lymphocyte surface immunoglobulins. J Exp Med 135:956, 1972.



- b. VITETTA, E. S., C. BIANCO, V. NUSSENZWEIG, and J. W. UHR. Cell surface immunoglobulin. IV. Distribution among thymocytes, bone-marrow cells and their derived populations. J Exp Med, 1972. In press.

Tuesday  
22 August

Seminar 16: Specificity of T cells for soluble antigens

- a. ROELANTS, G. E., and B. A. ASKONAS. Cell cooperation in antibody induction. The susceptibility of helper cells to specific lethal radioactive antigen. Europ J Immunol 1:151, 1971.
- b. BASTEN, A., J. F. A. P. MILLER, N. L. WARNER, and J. PYE. Specific inactivation of thymus-derived (T) and non-thymus-derived (B) lymphocytes by  $^{125}\text{I}$ -labeled antigen. Nature (New Biol) 231:104, 1971.

Wednesday  
23 August

Seminar 17: Specificity of T cells for transplantation antigens

- a. GOLSTEIN, P., E. A. J. SVEDMYR, and H. WIGZELL. Cells mediating specific in vitro cytotoxicity. I. Detection of receptor-bearing lymphocytes. J Exp Med 134:1385, 1971.
- b. BERKE, G., and R. H. LEVEY. Cellular immunoabsorbents in transplantation immunity. J Exp Med 135:972, 1972.
- c. WEKERLE, H., P. LONAI, and M. FELDMAN. Fractionation of antigen reactive cells on cellular immunoabsorbent factors determining recognition of antigens by T-lymphocytes. Proc Nat Acad Sci (USA) 69:1620, 1972.
- d. SPRENT, J., and J. F. A. P. MILLER. Interaction of thymus lymphocytes with histoincompatible cells. II. Recirculating lymphocytes derived from antigen active thymus cells. Cell Immunol 3:385, 1972.

Thursday  
24 August

Seminar 18: The mixed lymphocyte reaction

- a. WILSON, D. B., and P. C. NOWELL. Quantitative studies on the mixed lymphocyte interaction in rats. V. Tempo and specificity of the proliferative response and the number of reactive cells from immunized donors. J Exp Med 133:442, 1971.

- b. WILSON, D. B., and D. H. FOX. Quantitative studies on the mixed lymphocyte interaction in rats. VI. Reactivity of lymphocytes from conventional and germ-free rats to allogeneic and xenogeneic cell-surface antigens. J Exp Med 134:857, 1971.
- c. WIDMER, M. B., and F. H. BACH. Allogeneic and xenogeneic response in mixed leukocyte cultures. J Exp Med 135:1204, 1972.

Friday  
25 August

Seminar 19: Cell cooperation

Note: Deadline for research projects.

- a. KRETH, H. W., and A. R. WILLIAMSON. Cell surveillance model for lymphocyte cooperation. Nature 234:454, 1971.
- b. CLAMAN, H. M., and E. A. CHAPERON. Immunologic complementation between thymus and marrow cells: a model for the two cell theory of immunocompetence. Transpl. Rev 1:92, 1969.

Week 5

Monday  
28 August

Seminar 20: Triggering of lymphocytes

- a. TAYLOR, R. B., W. P. H. DUFFUS, M. C. RAFF, and S. PETRIS. Redistribution and pinocytosis of lymphocyte surface immunoglobulin molecules induced by anti-immunoglobulin antibody. Nature 233:225, 1971.
- b. SINGER, S. J., and G. L. NICOLSON. The fluid mosaic model of the structure of cell membranes. Science 175:720, 1972.

Tuesday  
29 August

Seminar 21: Antigenic competition

- a. BRODY, N. I., and G. W. SISKIND. Studies on antigenic competition. J Exp Med 130, 821, 1969.

Wednesday  
30 August

Seminar 22: Transfer factor

- a. RAPAPORT, F. T., H. S. LAWRENCE, J.W. MILLAR, D. PAPPAGIANIS, and C. E. SMITH. Transfer of delayed hypersensitivity to coccidioidin in man. J Immunol 84:358, 1960.

- b. LEVIN, A. S., L. E. SPITLER, D. P. STITES, and H. H. FUDENBERT. Wiskott-Aldrich syndrome, a genetically determined cellular immunologic deficiency; clinical and laboratory responses to therapy with transfer factor. Proc Nat Acad Sci (USA) 67:821, 1970.

Thursday  
31 August

Seminar 23: Regulation of antibody formation

- a. BYSTRYN, J., N. W. GRAF, and J. W. UHR. Regulation of antibody formation by serum antibody. II. Removal of specific antibody by exchange transfusions. J Exp Med 132:1279, 1970.
- b. PINCUS, C. S., M. E. LAMM, and V. NUSSENZWEIG. Regulating of the immune response: suppressive and enhancing effects of passively administered antibody. J Exp Med 133:987, 1971.

Friday  
1 September

Seminar 24: Are T cells essential for antibody formation in vitro?

- a. FELDMAN, M., and A. BASTEN. The relationship between antigenic structure and the requirement for thymus-derived cells in the immune response. J Exp Med 134:103, 1971.

Week 6

Monday  
4 September

Written examination

Tuesday  
5 September

Discussion of research projects

Wednesday  
6 September

Discussion of research projects