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ACTIVITIES OF THE PAHO/WHO IMMUNOLOGY RESEARCH AND TRAINING CENTER IN MEXICO CITY

ACTIVITIES OF THE PAHO/WHO IMMUNOLOGY RESEARCH AND TRAINING CENTER IN MEXICO CITY*

In January 1969 six laboratories engaged in immunology agreed to coordinate their activities, under the joint auspices of the Mexican Government and the Pan American Health Organization, to: (1) improve graduate training facilities for Mexican and foreign students; (2) exchange information on the individual research programs pursued in each laboratory; (3) establish a pool of locally available research resources such as: technical know-how, inbred-animal strains, scientific journals, rare and expensive reagents, and equipment facilities; (4) offer short courses on different areas of modern immunology to bring up-to-date the knowledge of interested investigators; and (5) establish a curriculum in immunology to adequately train candidates to the master's or doctor's degree.

Since 1969 four additional laboratories have joined the original group. The names of the 10 participating laboratories and of their heads are given in Annex 1.

Research programs carried out in the participating laboratories

1. Laboratorio de Inmunoquímica, Hospital Infantil de México:

   (a) Metabolism of Enterobacteriaceae antigens and their implications in diseases of children.

In regard to typhoid fever, the laboratory explored the correlation between the elimination of complete and fragmented antigens in feces and urine and clinical conditions such as: ordinary disease, complicated and fulminating forms, and the convalescent and chronic carrier stages.

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In infant diarrhea the amount of common antigen (Kunin) in Escherichia coli isolated from stools was inversely correlated to the clinical condition. In patients with diarrhea, E. coli strains had a low-content of common antigen whereas in convalescent and recovering patients, the antigenic content of E. coli increased significantly. The median lethal dose (LD_{50}) in chick embryo and the enteropathogenicity in rabbit ileal loops were lower in low-antigenic contents than in those of the same serotype but with higher amounts of the common antigen. There was no difference between the enteropathogenic and the nonenteropathogenic strains.

The common antigen biosynthesis is regulated by an episome that may be blocked by acridine orange. Enteropathogenic serotypes have a higher amount of somatic antigen (endotoxin) than the nonenteropathogenic O-types (13).

(b) Immunologic competence in severe protein-calorie malnutrition in children.

Research findings showed: dysgammaglobulinemic condition with normal IgG, increased IgA, and normal or increased IgM; antibody responses lower than those of well-nourished controls; leukocyte phagocytosis, bactericidal, and metabolic activities in a nitroblue tetrazolium medium within a normal range; a complement titer slightly lower than normal (some subcomponents, however, especially C1 were more than 50 percent decreased); normal beta-lysin and lisozyme values but a consistently depressed cell-mediated immunity. Laboratory models exhibited a diminution of "T" lymphocytes in the peripheral blood; the lymphoid cells from malnourished mice had a depressed ability to perform a graft-versus-host reaction compared with that of well-nourished controls; and malnourished Lewis rats were less susceptible to develop acute allergic encephalitis after they had received an injection of guinea pig spinal cord with complete Freund's adjuvant plus Bordetella pertussis (12).

(c) Materno-fetal exchange of proteins.

An active turnover of serum proteins such as albumin, transferrin, and IgG occurs in the amniotic fluid (8).

2. Laboratorio de Inmunología, Instituto Nacional de Cardiología:

(a) Mechanisms of immunologic tolerance with aggregated human gamma globulin.

Following injections of lymphoid cells from a donor unresponsive to human IgG, irradiated rabbits produced anti-IgG antibodies upon stimulation with a rheumatoid factor. On the basis of these findings, we postulated that "blocked" cells (live lymphoid cells with antigen in their surface) are the common substrate of unresponsiveness and of the proliferative phase of the immune response. If all cells are blocked, unresponsiveness ensues; whereas if only some are blocked, these are stimulated to multiply by antibody produced in others (5).

(b) Immunologic competence of C6-deficient rabbits found in Mexico City

Studies were conducted in relation to transplants, inflammatory reactions elicited by aggregated gamma-globulin and blood coagulation (14).

3. Departamento de Inmunología, Escuela de Ciencias Biológicas, I.P.N.:

(a) Immunologic studies in leprosy.

Immunochemistry of common antigenic determinants among polysaccharides of Mycobacterium tuberculosis, M. leprae, and Nocardia brasiliensis.

(b) Immune complexes in the circulation of patients with lepromatous leprosy.

These complexes were detected by means of $C1_q$ precipitation in agar gel. Tuberculoid leprosy patients and normal controls did not exhibit immune complexes (22).

(c) Immunochemistry of pneumococcus capsular polysaccharides.

(d) Immunogenicity of haptens from nucleic acids coupled to proteins.

Several derivatives (nucleosides and nucleotides) were explored. Method: We used periodic acid to open the furanose ring of pentose and the product was combined to the proteins; we then analyzed the specificity of the antibodies produced in goats and rabbits, through precipitin and inhibition of precipitation with the original and related antigens (haptens) (6).

(e) Conformational studies of ATP and FAD, using antibodies versus AMP (7).

4. Departamento de Inmunología y Reumatología, Instituto Nacional de Nutrición

(a) Ig levels in different populations of Mexico (4).

(b) Immunochemistry of antinuclear antibodies and provocation of antinuclear antibodies by drugs (1, 3).

(c) Immunopathology of autoimmune diseases (2).

(d) Role of the liver in the clearance of immune complexes from circulation.

5. Departamento de Bioquímica, Facultad de Medicina, U.N.A.M.

(a) Immunochemistry of pyridoxal coenzymes from liver and heart of pigs.

Antibodies to pyridoxal and pyridoxal-5'-phosphate were produced in rabbits by immunization with urease conjugated to the haptens, using bovine serum albumin conjugated to pyridoxal and pyridoxal phosphate. We analyzed the inhibition of precipitation with derivatives prepared by borohydride reduction of mixtures containing pyridoxal, or pyridoxal phosphate and aliphatic amines: ethylamine, butylamine, isobutylamine,

and hexylamine. The nuclear magnetic resonance indicated definite points of ligand interaction about haptens structures with the antibody sites. The specificity seemed to reside, (1) about the N atom in the ring structure, (2) in the covalent C-N link joining the aliphatic chain to the pyridine core, (3) in the methylene side chains of the carrier. Cross reactions were minimal because the phosphate residue seemed to be a definite antigenic point and antibodies induced with strong reactivity to phosphorylated conjugates were very unreactive with pyridoxal derivatives lacking the residue (21).

(b) Immunochemistry of the plant proteolytic enzymes, karatacin and hemispheric in (cathepsins).

After purification by gel electrophoresis and Sephadex, there was an evidence of isoenzymes with common and separate antigenic determinants.

6. Laboratorio de Investigaciones Inmunológicas, S.S.A.

(a) Immediate hypersensitivity in human onchocercosis.

(b) Development of techniques for the assessment of delayed hypersensitivity.

(c) Immune defects in Chediak-Higashi syndrome.

7. Departamento de Biología Celular, Instituto de Investigaciones Biomédicas, U.N.A.M.

(a) Analysis of IgG receptors and antigenic determinants in mammal macrophages.

There are antigenic differences between fixed and free macrophages, but no species differences, and the antigen probably resides in the membranes. An antibody specific for alveolar macrophages has been developed; it is not cytotoxic, does not interfere with glass adhesiveness, but decreases the phagocytosis of sensitized red cells. Experimental rats inoculated with BCG and having an acute lung inflammation

showed a marked increase of free macrophages, from 0 to 65 percent (using the specific antibodies versus fixed and free macrophages) (15).

(b) Antibodies versus mammal collagenase.

Labeling with ferritin permits the identification of the synthesis site and the collagenase secretion during acute inflammation.

(c) Effect of molar ratio: hapten/carrier in the immunogenicity and tolerogenicity of DNP-HSA.

The molar ratio influences the quality and magnitude of the immune response. A hypothesis has been formulated to predict the immune response in terms of the presence of specific receptors with three distinct properties: number, specificity, and K_m.

(d) In-vitro primary antibody synthesis.

8. Departamento de Ecología Humana, Facultad de Medicina, U.N.A.M.

(a) Delayed hypersensitivity to BCG and Nocardia.

Antigens isolated from these organisms have been studied to determine the ability of inoculated experimental animals and of human beings with the corresponding diseases to develop cell-mediated immunity to these organisms (16, 17, 18, 19, 20).

(b) Cellular kinetics of a precursor and early events of antibody-forming cells (9, 10).

9. Departamento de Inmunología, Unidad de Investigación del Centro Médico Nacional, I.M.S.S.

(a) Immunodeficiencies (11).

(b) Histocompatibility in human transplantation and cytotoxic antibodies in human lymphomas and solid tumors.

10. Banco Central de Sangre, Centro Médico Nacional, I.M.S.S.

(a) Serologic surveys in different Mexican populations to investigate the hepatitis-associated antigen, Chagas' disease, and amebiasis.

(b) Immunohematologic analysis of incompatible blood transfusions.

Coordinated activities among the participating laboratories

1. Weekly seminars

The staff of the 10 participating laboratories meets weekly to: (a) critically evaluate the research programs that are in the planning stage; (b) report on the progress and on the final study results in every laboratory; (3) form a journal club; (4) discuss the future coordinated operation of the Immunology Research and Training Center; and (5) announce the availability of jobs, fellowships, courses, congresses, and new facilities.

2. Master's or doctor's degree curriculum in immunology

The Center, in association with the Graduate School of the Escuela Nacional de Ciencias Biológicas, I.P.N., offers graduate students master's and doctor's degree curricula in immunology. Candidates must have a professional title in medicine, microbiology, biochemistry, biology, or pharmacy. They must acquire a working knowledge of technical English and pass an examination on the subject. In addition, students in the last 5 years of their training must have accumulated several credit hours in analytical (qualitative and quantitative) and organic (intermediate) chemistry, and in statistics (introductory).

At the graduate level, credit requirements are: advanced immunology (1st semester); advanced biochemistry (1st part of the 2nd semester); immunochemistry (3rd semester); practical immunology (3rd and 4th semesters); cellular immunology (5th semester); and seminars on selected immunology topics (5th and 6th semesters).

After admission to the Graduate School, students are assigned to one or the other 10 participating laboratories where they will do research work under the guidance of a tutor. Students must produce

within 3 years an original work as a basis for a thesis which will be examined by an ad hoc committee.

Before working on his doctoral dissertation, a candidate must be able to translate technical subjects in a second language (French or German) and must pass a general written and oral examination on immunology. Some applicants do not enroll in the Graduate School. They remain as residents in the laboratory of their choice but must attend the interdepartmental seminar that is given weekly throughout the year. Laboratory residents must take some selected courses and at the end of their in-training, they receive a certificate listing the activities carried out during their residency period.

Every year visiting professors deliver lectures or give short courses of 1 to 2 weeks' duration on different subjects: immunochemistry of bacterial polysaccharides, complement component, and immunological damage.

In special instances candidates may spend some time in a laboratory outside Mexico if the subject of their work is inadequately covered at the Center and constitute an investment for future activities of one of the participating laboratories.

Up to May 1973, the Graduate School has produced four Ph.D's, three Ph.D's in the process of finishing their thesis, and nine trainees at different curriculum levels. Eight laboratory residents did not register in the Graduate School and concentrated in research work or in the methodological aspects of immunology.

Center activities have influenced several aspects of the immunology field in Mexico. The Center promoted: (1) the increase of training opportunities in immunology for Mexican and foreign fellows; (2) the improvement in the quality of undergraduate immunology courses in medical schools; (3) a better utilization of local available resources for research and teaching purposes; (4) the coordination of efforts to start a national program on transplants; and (5) the improvement in the diagnosis and treatment of immunologic disorders.

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ANNEX 1

List of Participating Laboratories

A. Original laboratories:

1. Laboratorio de Inmunoquímica, Hospital Infantil de México
   Head: Jesús Kumate, M.D., Ph.D.

2. Laboratorio de Inmunología, Instituto Nacional de Cardiología
   Head: Carlos Biro, M.D., Ph.D.

3. Departamento de Inmunología, Escuela Nacional de Ciencias Biológicas, I.P.N.
   Head: Sergio Estrada Parra, Ph.D.

4. Departamento de Inmunología y Reumatología, Instituto Nacional de Nutrición
   Head: Donato Alarcón Segovia, M.D.

5. Departamento de Bioquímica, Facultad de Medicina, U.N.A.M.
   Head: Felix Córdoba, M.D., Ph.D.

6. Laboratorio de Investigaciones Inmunológicas, S.S.A.
   Head: Prof. Mario Salazar Mallén, M.D.

B. New collaborating laboratories since 1969:

7. Departamento de Biología Celular, Instituto de Investigaciones Biomédicas, U.N.A.M.
   Head: Ruy Pérez Tamayo, M.D.

8. Departamento de Ecología Humana, Facultad de Medicina, U.N.A.M.
   Head: Librado Ortiz Ortiz, Ph.D.

9. Departamento de Inmunología, Unidad de Investigación, Centro Médico Nacional del I.M.S.S.
   Head: Roberto Kretschmer, M.D.

10. Banco Central de Sangre, Centro Médico Nacional del I.M.S.S.
    Head: Héctor Rodríguez Moyado, M.D.