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13. ABSTRACT

In the five laboratories in Tel Aviv, Jerusalem and Rehovot which were visited, microbiology is studied very actively. At the University of Tel Aviv birth defects due to viruses, and antiviral proteins from Staphylococcus aureus, and at the Hebrew University, Dept. of Virology in Jerusalem the structure of arboviruses are studied. At the Government Central Laboratories in Jerusalem, National Centers for Cholera, Streptococci, Enterobacteriaceae and Immunohematology as well as the District Diagnostic Laboratory and the Serum and Vaccine Institute are situated. The Streptococcus Laboratory is particularly active in studying antibodies in patients and in typing strains of bacteria encountered in Israel. The hospital laboratory at Tel Hashomer provides an example of useful work under less than ideal conditions. The Weizmann Institute has three departments: cell biology, genetics and chemical immunology where basic research on cellular immunity, cellular differentiation and specificity of antibody formation is carried out. This institute has a staff which includes leaders in their fields of study. The work of this institute is considered among the best to be found in cellular biology in the world today.

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R-21-71

# OFFICE OF NAVAL RESEARCH

**BRANCH OFFICE LONDON ENGLAND**

MICROBIOLOGY IN ISRAEL

By GEORGE A. HOTTLE

18 June 1971





**UNITED STATES OF AMERICA**

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# MICROBIOLOGY IN ISRAEL

Visits were made to five laboratories in Tel Aviv, Jerusalem and Rehovot. In each of the places I visited there was evidence of great vitality and high motivation for carrying out research and for developing concepts and procedures to improve the health and condition of mankind. At the universities there was also a great interest in teaching of medical and science students. The atmosphere in the laboratories was very much like that seen in the US and the UK: there was a keen interest to get at the basic mechanisms of infection and immunity. Close ties to the US were evident. Much of the scientific equipment and instrumentation was made in the US, and many of the scientists had spent a year or more working in research laboratories there. Several instances were mentioned where professors at large universities in the US were induced to spend part of each year working or teaching in Israel while maintaining their positions at the home university. Under such situations there is little chance for stagnation, and they and their fellow staff members are stimulated to undertake challenging research problems and to pursue them vigorously.

The laboratories visited were: (1) Department of Microbiology, University of Tel Aviv, (2) Government Central Laboratories, Jerusalem, (3) Department of Virology, Hebrew University Medical School Jerusalem, (4) Weizmann Institute, Rehovot, and (5) Tel Hashomer Hospital, Tel Aviv.

## 1. DEPARTMENT OF MICROBIOLOGY, UNIVERSITY OF TEL AVIV

This Department occupies a modern isolated building in the new University area on the northern edge of Tel Aviv known as Ramat Aviv. The Department head, Prof. Emmanuel Eylan, has organized his work so that he can advise medical students and direct the research activities of the Department. The teaching responsibilities include 80 medical students plus a number of fourth-year science students.

The research program has received new impetus since Eylan was installed as head of the Department about two years ago. His own interest is in the antiviral effects of various biological materials. At the International Microbiological Congress in Mexico last year he reported on some work with antiviral proteins from Staphylococcus aureus. He found that an acidic extract of the bacteria reacted with the lipid envelope of certain viruses such as herpes virus and vesicular stomatitis virus, and inactivated them. He is also examining extracts of other bacteria and of plants for inhibition of herpes virus. Other studies are concerned with the interaction of two viruses in the same host tissue, and it was found that Sendai virus enhanced the growth and virulence of West Nile Virus. Virus yields have been increased by as much as 3 logs. The growth and plaque formation of toxoplasma are

being studied in cell cultures, and by using a special strain, which is not toxic for mice, Eylan is able to examine the effects of various viruses in increasing the virulence of the protozoa. Finally, a program for study of birth defects in man has been started. Serums are collected from pregnant women at three month intervals and stored until needed to investigate a fetal abnormality. Antibody levels in the serum specimens are determined against suspect viruses in order to discover any relationship with the progress of the pregnancy. Eylan has already found evidence of rubella virus involvement with birth defects.

2. COVERNMENT CENTRAL LABORATORIES, JERUSALEM

Located within the city of Jerusalem, this laboratory is well equipped and is staffed by capable, energetic scientists. Under the direction of Dr. Ch. B. Gerichter, National Centers for Cholera, Streptococci, Salmonella, Enterobacteriaceae, and Immunohematology and Blood Groups, the District Diagnostic Laboratory and the Serum and Vaccine Institute have been established at these laboratories.

The work of the national centers includes receipt and identification of strains of microorganisms from hospitals and public health officers of the entire country. In addition, diagnostic sera and other reagents are prepared for use by the center, and research on development of new diagnostic methods is carried out. Last year 500 strains of Vibrio cholerae were received for identification, and 4000 strains of Salmonella were examined for all O and H antigens. Recently when Salmonella blockley was found to occur in sporadic outbreaks of gastroenteritis in humans as well as in poultry and cattle, a phage-typing scheme was devised to identify individual strains of this species. By the use of a phage sensitivity test for each of three symbiotic phages and a lysogenicity test using three indicator strains, it was possible to obtain a framework of 64 theoretically possible phage types. With this scheme 1256 S. blockley strains were grouped into 14 types. In seven food-poisoning outbreaks, in which this scheme was used, all strains in each single outbreak were found to belong to the same phage type.

In the Streptococcus Laboratory Dr. Bergner-Rabinowitz has guided the work of her group in developing methods for identifying hemolytic streptococci. As a simple first step in classifying strains, they are inoculated on blood agar containing 5 units of bacitracin per ml. On this medium all group A strains of streptococci are inhibited but other groups will grow. The group A strains are then typed by agglutination with specific sera. Although this is more tedious than precipitin tests, it is possible to type practically all strains in this way. With the M substance only 15-20% of strains are typed by precipitin tests. Work was undertaken to determine the amount of protective (M) antibody in human sera. A simplified method for detecting type-specific antibodies for Group A streptococci in human sera was developed by using an in vitro phagocytosis system with mouse peritoneal leukocytes. The results with this technique compare favorably

with the bactericidal method, are simpler and provide an answer in a short time. In a recent study of 100 patients with glomerulonephritis caused by Group A streptococcus type 55 (a new type in Israel), antibodies against type 55 were found in the sera of a significant number of patients as compared with control individuals. Antibodies were detected two to three months after the initial infection and gradually disappeared six to seven months later. This study demonstrated the practical usefulness of the type-specific antibody test in nephritic patients.

The staff of the Vaccine and Serum Institute prepare five vaccines: cholera, plague, rabies, smallpox and typhoid fever, for use in the entire country. The cholera, plague and typhoid fever vaccines are killed bacterial suspensions prepared with the standard strains of bacteria. Rabies vaccine is made by the Semple method from infected rabbit brain suspensions which have virus titers of about $10^{6.5}$ LD 50 for mice. Smallpox vaccine is prepared in chick embryos. It is bacteriologically sterile and is distributed as a glycerinated suspension. Gerichter would like desparately to prepare a dried vaccine, but lacks a lyophilizer. In order to maintain the vaccine in a vigorous state to develop immunity in man, the seed is prepared in large amounts so that the vaccine is not more than three egg passages removed from a thoroughly evaluated seed preparation.

There is a need for rubella vaccine in Israel, and at present the importation of the vaccine is under consideration. A decision on the source of vaccine must be made among the following: vaccine prepared in duck embryos by Merck, in human diploid cell line WI 38 by Burroughs Wellcome or by Merieux.

## 3. DEPARTMENT OF VIROLOGY, HEBREW UNIVERSITY MEDICAL SCHOOL, JERUSALEM

This Department constitutes one of eight departments or units of the Institute of Microbiology which provides the administrative organization for all aspects of microbiology in the Faculty of Medicine. The Department of Virology headed by Prof. Nathan Goldblum is responsible for teaching 100 medical students, 50 biology students and 31 graduate students, six of whom are PhD candidates. The Department also does diagnostic work in virology for the University and City Hospitals. The research program developed by Goldblum includes the following areas: structure and composition of arboviruses, mechanism of SV40 virus induced cancer, selective inhibition of poxvirus replication by the antibiotic rifampicin, biological and molecular studies on foot and mouth disease virus, replication of herpes simples virus, and molecular and immunological studies of the trachoma agent.

Of specific interest to Goldblum is the structure of arboviruses. He has examined in detail the composition of the virion of Sindbis virus, one of the Group A arboviruses or togaviruses, by growing the virus in chick embryo fibroblasts. Purified virus particles prepared in this way were

obtained in concentrations up to $10^{10}$ per ml. By carefully disrupting the virions with SDS, mercaptoethanol and urea, the cell extract was found to contain two protein components which were separated on a sucrose gradient. These components are ribonucleoprotein (RNP) and lipoglycoprotein (LGP). The RNP is synthesized in the cytoplasm of the host cell following infection, and the LGP is part of the virus envelope which is acquired by a budding process from a cellular membrane synthesized in the infected cell. The enzyme, pronase, acts on LGP by splitting off three different glycopeptides with molecular weights of 1500 to 3000. Studies with three other group A viruses: eastern and western equine encephalomyelitis and Simliki Forest viruses have shown that proteins similar to those found in Sinbis virus are also formed. It is assumed that the basis for the identity of the large number of togaviruses which have been found lies in the glycopeptides which occur on the virus envelope. When LGP was subject to tryptic action, three components were released which reacted in gel diffusion tests with serums from rabbits immunized with LGP or with purified virions: (1) one component, molecular weight 200,000, is a hemagglutinin and also inhibits the neutralization of virus by rabbit antibody when measured by the infection of mice, (2) the second component, molecular weight 9000, fixes complement with rabbit antibody but does not hemagglutinate and (3) the third component neither hemagglutinates nor fixes complement. Goldblum plans to continue this work with West Nile Virus, a group B togavirus. He feels that the group A viruses examined so far are composed of one large molecule of ribonucleoprotein contained in a single molecule of envelope lipoglycoprotein.

In work with cell cultures which have been transformed by SV40 virus, but in which no infective virus nor virus antigen can be detected, studies have shown that by heating the cell culture to 45° C for 30 minutes and then incubating it at 34° C for two to three days, some of the cells start synthesizing viral antigen as shown by immunofluorescent staining. Up to 3% of the cells exhibited the viral antigen by this treatment. When the incubation medium of the heated cells was depleted of arginine, the percentage of cells in which synthesis of viral antigen was induced was increased to 11%. The data indicate that one of the repressors of the viral genome has been inactivated permitting some viral synthesis to occur. The effect of arginine depletion is difficult to explain since earlier studies had shown that it is essential for the synthesis of viral coat protein.

Other studies are being directed toward the action of the antibiotic rifampicin in the inhibition of vaccinia virus. This antibiotic has been shown to inhibit bacterial RNA synthesis by interacting with DNA-dependent RNA polymerase. The data to date show that it does not inhibit mammalian RNA polymerase. Dr. E. Heller, working with Goldblum, has shown that levels of rifampicin of 100 μg/ml will completely inhibit growth of vaccinia virus in mouse embryo cell cultures, but it will not inhibit vesicular stomatitis virus in the same host tissue. Although the mechanism of action of the

antibiotic is not known, it is noted that rifampicin has selective action on a DNA virus and not on an RNA virus. The action of rifampicin is reversible, i.e., inhibition is maintained only while it is present. When it is removed by washing the cells, virus replication starts up again.

## 4. IMMUNOLOGY AT THE WEIZMANN INSTITUTE OF SCIENCE, REHOVOT, ISRAEL

This Institute was founded in 1934 as the Daniel Sieff Research Institute by Dr. Chaim Weizmann, who later became the first President of Israel. Later the Institute was renamed in his honor, and at present is devoted to research and teaching in the natural sciences. Situated on a tract of more than 150 acres, the Institute consists of approximately 27 buildings erected over the period of its existence since 1934. Also associated with the Institute is the Yeda Research and Development Company which deals with commercial promotion of industrially-promising research projects developed at the Institute. The Institute is organized into 18 departments which are grouped into five faculties: Biology, Biophysics-Biochemistry, Chemistry, Mathematics, and Physics.

The staff of the Institute numbers about 1800 with a senior staff of 150 scientists and a total scientific complement of about 400, including long-term visiting scientists. The teaching function of the Institute has two facets: the Feinberg Graduate School with about 500 students working for the MSc and PhD degrees and a department for Science Teaching. The latter includes inservice training and Summer Institute for science and mathematics teachers and the preparation of materials for teaching of science in High School and in the technical and trade schools.

The work in immunology is centered in three Departments: Cell Biology, Genetics and Chemical Immunology.

In the Department of Cell Biology, Prof. Michael Feldman described some phases of the work on *in vitro* immune response: cellular immunity (graft reaction) and primary antibody response to chemically defined determinants. A new method for studying cellular immunity was developed by sensitizing rat lymphocytes to mouse fibroblasts. This sensitization is accomplished by plating the lymphocytes on monolayers of mouse fibroblasts. After the induction period, the transformed lymphocytes are separated from the mouse fibroblasts on an albumen gradient and the lymphocytes are plated on monolayers of $^{51}Cr$-labelled mouse fibroblasts. The immune cytolysis is measured by release of the label from the target cells. This system has provided unique specificity, because closely related mouse cells which cannot be distinguished *in vivo* are readily recognized as distinct by the transformed rat lymphocytes. Kinetic studies have shown that the reaction is of first order in the fibroblasts and in the rat lymphocytes. This means that one sensitized lymphocyte is needed to lyse one fibroblast. The kinetic studies also showed that each fibroblast died as a result of a single contact with

a sensitized lymphocyte and that there was no latent period for the lytic effect. Also the number of sensitized lymphocytes is not decreased during the lysis of target cells. They remain alive and active after a fibroblast has been killed. This sensitization is purely a cellular reaction; there is no antibody formation. If antibody to the mouse cells is added to the target cells, the sensitized lymphocytes have no lytic power. When hydrocortisone is added to the reaction mixture: during the sensitization phase, increased sensitization occurs among those cells which survive, but there is greater death of lymphocytes; during the effector stage lysis is suppressed somewhat.

The above work was done with lymphocytes from lymph nodes. When cells from rat spleen or thymus were used in this system, there was little or no lysis. However, when rat spleen and thymus cells were mixed, sensitization and lysis by transformed lymphocytes occurred. Studies are now being carried out to determine the role of both kinds of cells. Preliminary data indicate that thymus cells are sensitized by contact with mouse fibroblasts, and some filterable factor from spleen cells (an enzyme) is required for expression of the transformation and lysis of the target cells.

With the system described above, tools are now available for study of immunosuppression to permit graft acceptance and on the other hand for study of immune activation to enhance rejection of foreign tissue (tumor cells), either to prevent metastasis or to control rapidly growing transformed cells in the host.

The work in organ culture systems is directed toward study of antibody formation by spleen explants to a chemically defined determinant such as the 2, 4 dinitrophenyl (DNP) group. By utilizing systems which have been used for complex antigens in the past, primary antibody response to DNP, which has been attached to poly-L-lysine, can be obtained. Since minute amounts of antibody are formed, special methods are needed for its detection. This is done by studying the inactivation of T4 phage conjugated with DNP. The specificity of this reaction is shown by the lack of inactivation of the unmodified phage by the antibody formed to the DNP antigen. In these studies it is also possible to determine the types of immunoglobulins formed by the organ cultures.

In the Department of Genetics, Dr. Leo Sachs is interested in the properties of mammalian cells, and in mechanisms which regulate the growth and differentiation of blood cells. He is also curious about factors which determine the behavior of cancer cells. In work with the development of granulocytes in tissue culture it was found that spleen or kidney contain an inducer which stimulates the development of blast cells from bone marrow into mature granulocytes. The inducer must be present at all times in order for development to proceed. It is a protein and has been purified about 3000 fold. Mature granulocytes produce an inhibitor which stops the action of the inducer and prevents overproduction of the cells. In congenital neutropenia in man, there is a deficiency of mature granulocytes

in the blood. When the inducer from tissue culture was added to the cells in vitro, normal maturation occurred. Such normal maturation was also found with cells from patients with acute granulocytic leukemia and some cases of chronic granulocytic leukemia.

Other studies are directed toward determining the role of the cell membrane in control of growth. It was found that important parts of the membrane are carbohydrate chains which occur on the surface. Work with the carbohydrate-binding protein, concanavalin A (con A), has shown that tumor cells are agglutinated by this substance, but normal cells are not. Since normal and tumor cells have about the same carbohydrate content, the difference in agglutinability was found to be due to the number of exposed carbohydrate sites. This led to the finding that tumor cells have most of their carbohydrate sites exposed while in normal cells 85% were turned away from the cell surface. The use of con A has provided a new way for studying cell structure. Since it contains metal ions, it provides a means for labeling the protein and also the cell. In addition, it opens the door to a search for additional proteins with similar properties from soy beans, wheat germs and other natural products. The use of non-toxic proteins or their derivatives, with properties of binding to tumor cells, may offer hope for chemotherapy of cancer. An added advantage with these carbohydrate binding proteins is that the combination can be reversed by shifting the equilibrium with related sugar molecules of low molecular weight.

Dr. Ruth Arnon described the work of the Department of Chemical Immunology. Here studies of immunity at the cellular and molecular level are carried out. The work with lysozyme has provided interesting insight into enzymic action and antibody formation. A unique region of the enzyme molecule consisted of a di-sulfide bond between several amino acids. By isolating the peptide containing the di-sulfide bond, it was possible to carry out a number of experiments to show the role of a single site on an enzyme molecule. In addition, interesting insight into the genetic variation in antibody formation was obtained. When ten groups of mice of different genetic strains were immunized with lysozyme, each produced antibody which reacted similarly to the enzyme. When, however, inhibition of the antigen-antibody reaction was studied with the isolated di-sulfide peptide, it was found that serums from two of the groups of mice were not inhibited. This indicated that cells of different genetic make-up may selection different determinant sites for formulation of antibody reactive sites.

Other studies have been concerned with the fractionation of spleen cells to determine antibody response of cells bearing an acidic or a basic charge. By injecting negatively-charged spleen cells into irradiated animals, the animals were found to respond to antigens having only positive charges, and only negatively-charged antibody molecules were formed.

The striking feature of the work at the Weizmann Institute is the cross-fertilization of ideas which occurs among scientists in all Departments.

Certainly in the biological sciences the collaboration between workers in various Departments was evident. One of the reasons for this is the intense interest which the scientists have in their work. Another reason is, as Dr. Albert Sabin, the President of the Institute pointed out: living quarters are provided for the scientists on the Institute grounds. This means that opportunity for informal discussion is ever present. Also, with the frequent visiting scientists from Europe and America, new viewpoints are obtained for the problems at hand. In this vibrant, highly-motivated society of scientists the objectives of research become sharply focused and attainable.

5. TEL HASHOMER HOSPITAL, TEL AVIV, ISRAEL

The Bacteriology Department of the laboratory of this 1000-bed hospital is directed by Dr. G. Altmann. The hospital is located about 10 miles east of the center of Tel Aviv, occupying a number of single-story buildings which were constructed during WWII. These buildings had served as a general hospital and rehabilitation center for the US Army during the Mediterranean campaign. Since that time, there have been some modifications to the buildings, but in general, the problems of communication between the numerous hospital wards and clinics in separate buildings impose many difficulties on the laboratory staff. Altmann and his coworker, Dr. Bianke Bogokowski, have maintained an active program of surveillance of bacterial diseases in this hospital. They work closely with the Government Central Laboratory in Jerusalem, and have kept in touch with other international laboratories such as the WHO Neisseria Reference Center at Marseilles and the National Communicable Disease Center in Atlanta when special problems have arisen.

In discussing the questions of meningitis with Altmann, he stated that it is not a serious problem in Israel. They have about 50 cases per year. From these cases the meningococci isolated were mainly Group C with some Group B. He described some work done several years ago in which two groups of young women were studied as carriers of meningococci. One group was composed of 50 women who were admitted to a nurses training school. The other group was composed of the same number of women who entered army training. Both groups represented women of the same ages and the same types of backgrounds. In following these individuals by nasopharyngeal cultures for meningococci, it was found that the nurses who lived two in a room had a very low carrier rate, and the army women who lived as a group in a single large room in the barracks had a carrier rate over 60%. There was no meningitis in either group. This study confirmed other work which showed that crowding of individuals resulted in a high carrier rate for meningococcus. It also showed that some other factor is responsible for the disease, because a high carrier per se does not always mean that the disease appears.

Because meningitis is a relatively rare disease in Israel and there is no national reference center for meningococci, Altmann would like to keep in touch with microbiologists in other countries to compare data on diagnosis of meningitis. He has prepared grouping serums for this work, and would like to receive some serums from other laboratories for comparison with his. The commercial serums which he has obtained have not given good results in his hands. When strains of meningococci are isolated here, he has sent them to Atlanta and to Marseilles for confirmation of antigenic type. This has worked out satisfactorily in some cases.

Another phase of the work has been the treatment of typhoid carriers. The use of antibiotics has not been successful in eliminating the carrier state in many people. Therefore, a study is made of each patient in order to determine the nature of the excretion of the bacilli by each individual. When urinary excretion is found, a careful examination of the kidneys is made by X-ray to determine any pathology which is present. Often stones or abscesses are seen. In these cases surgery is indicated. At the same time, a massive antibiotic therapy with ampicillin or other suitable drug is instituted two days before surgery. Antibiotic treatment is continued up to the time of surgery in order to provide a high drug level to prevent spread of the infection when the tissue or abscess is cut. This avoids establishments of new infected foci. Antibiotic treatment is continued until cultures are negative.

When fecal excretion of the bacilli is found, a similar study is made of the liver and gall bladder. When gall stones, or liver abscess are seen, surgery is indicated and the antibiotic therapy as outlined for kidney infection is instituted. With this approach there have been very good results in eliminating typhoid carriers and permitting these people to function as normal members of society.

There are plans for the construction of a new modern hospital at Tel Hashomer. However, with the many requirements of this growing nation, it may be difficult to make arrangements for the replacement of the present numerous small buildings which are meeting a need today. This means that Altmann and his staff will continue to operate the laboratory of the hospital in the best way they can. For most of the back-up for their work in bacteriology or parasitology, they look to the Government Central Laboratory and for virology to Hebrew University Medical School in Jerusalem, which provide the services for identifying streptococci, staphylococci, salmonella and other bacteria and viruses isolated in this hospital.