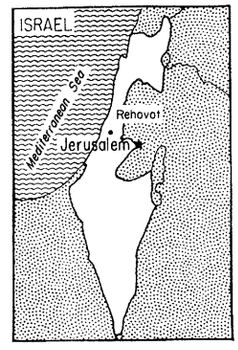

Fundamental Biology at the Weizmann Institute

Rehovot, Israel. Few research establishments make such an effort to avoid scientific parochialism as the Weizmann Institute of Science here. The effort has been essential to the creation, over the past 15 years, of one of the largest groups of vigorous scientists on this side of the Atlantic. The size of the group appears to be important. According to researchers in fundamental biology, continued progress in this field, which engages the largest number of Weizmann scientists, demands a laboratory large enough to provide association with men of many different backgrounds.

In search of money and continued full membership in the international scientific community, researchers at the Weizmann Institute have striven to give young scientists rapid promotion and to encourage collaboration between scientists of radically different backgrounds; to break down barriers between academic subjects; and to induce young scientists to return after periods of postdoctoral training in the United States. Research departments are set up—and given buildings—only when men of sufficient stature become available to head them.

The institute encourages foreign study; thus, at a given time, something like a sixth of the permanent scientific staff may be studying in another country. It welcomes visiting scientists; about 20 percent of the institute's nearly 300 scientists and 170 Ph.D. candidates are from overseas. Half of the visitors are from the United States.

There is a vigorous hunt for public and private grants, contracts, and gifts, led by Meyer W. Weisgal, head of the executive council of the institute. Weisgal has been a key figure in the institute's growth ever since the idea of a scientific research center for Israel began to take shape, in 1944. Chaim Weizmann, an organic chemist who led the world Zionist movement for many years and became Israel's first president, had long urged establishment of an institute where scientific problems of significance to Israel could be studied. With a group of Weizmann's friends in the United States, Weisgal began raising money for such an institute as a tribute to Weizmann on his 70th birthday. The predecessor of the new institute was the Daniel Sieff Institute, established in Rehovot in the 1930's, in a building donated by a family which operates a chain of department stores in England. The building was originally intended as a refuge for Jewish scientists fleeing Hitler. As it happened, few refugees came, so the building was used for a small institute, set up to do research on the use of Palestinian farm products. This building now houses the organic chemistry department of the Weizmann Institute.

Since its early days the Weizmann Institute has developed along lines somewhat different from those Weizmann envisaged. Weizmann himself was a scientist with a bent for applied work, and he intended that the new institute should focus on special problems of the new state of Israel (see *Science*, 5 March). Interruptions, such as the warfare in the late 1940's from which the state of Israel emerged, and the accident that most of the institute's early scientific leaders were interested in more fundamental problems have steered the institute primarily toward basic research.

Weisgal, who stays strictly clear of matters of scientific policy, played no direct role in this evolution. Scientific policy is worked out in a process which is less centralized than that at an American university, with its strong president, and less exclusive than the policy-making operation of a European university faculty. Weisgal has concentrated on keeping alive, among nonscientists, an enthusiasm for the institute that is essential to its growth. To this job he has brought a strong talent for public relations and money raising. For instance, he arranged a $25-million loan from the United States Government, to be used to build and equip a large number of urgently required buildings. The loan, which is being spent at a rate of about $4.5 million a year, was made in blocked Israeli pounds acquired by the United States from the sale of agricultural commodities. It is being paid back in dollars by friends of the institute from outside Israel, the blocked funds being thus repatriated.

Such a talent is vital, for the institute receives only about a fifth of its $6.5-million annual operating budget from the government of Israel and the Jewish Agency. Over a third of the budget comes from the Jewish Agency and from contributions from abroad. In addition to the $6.5 million, the institute scientists receive about $2 million yearly in grants. Most of these come from such U.S. agencies as the National Institutes of Health (which are not permitted to pay overhead costs abroad) and the U.S. Air Force. An important new contribution to the institute is a grant of $1 million a year from the West German ministry of scientific research. The money is earmarked for some 20 projects in physics and biology.

Since the institute began to assume its present form, after the troubles of the late 1940's, it has given special attention to its ties to the United States.

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With the possible exception of some Japanese laboratories, the Weizmann Institute is the most distant group of laboratories to have developed such ties. Integration with the American scientific community is more noticeable here than it is even at the most active research centers of Western Europe. The strong ties to the United States arise in part from the institute's emphasis on fundamental biology. Departments working on biological problems have proliferated at the institute and account for well over a third of its scientists, although large groups in nuclear physics, applied mathematics, and organic chemistry have also sprung up. This emphasis on biology is not surprising in a basic-research institute which has developed during the recent flowering of biological studies in the United States, Japan, and Europe, but it creates a special need for good communications with scientists abroad. The drive to apply physical techniques to biological problems has broken down disciplinary boundaries. Certainly this situation has been a factor in the Weizmann Institute's interest in international exchanges of scientists and students.

There are other reasons for ties with the United States. Trained in European or American universities, the senior scientists here do not want to lose their Western contacts. Even the younger scientists, now moving up to run their own research groups and departments, studied abroad after receiving their doctorates in Israel, chiefly from the Hebrew University of Jerusalem.

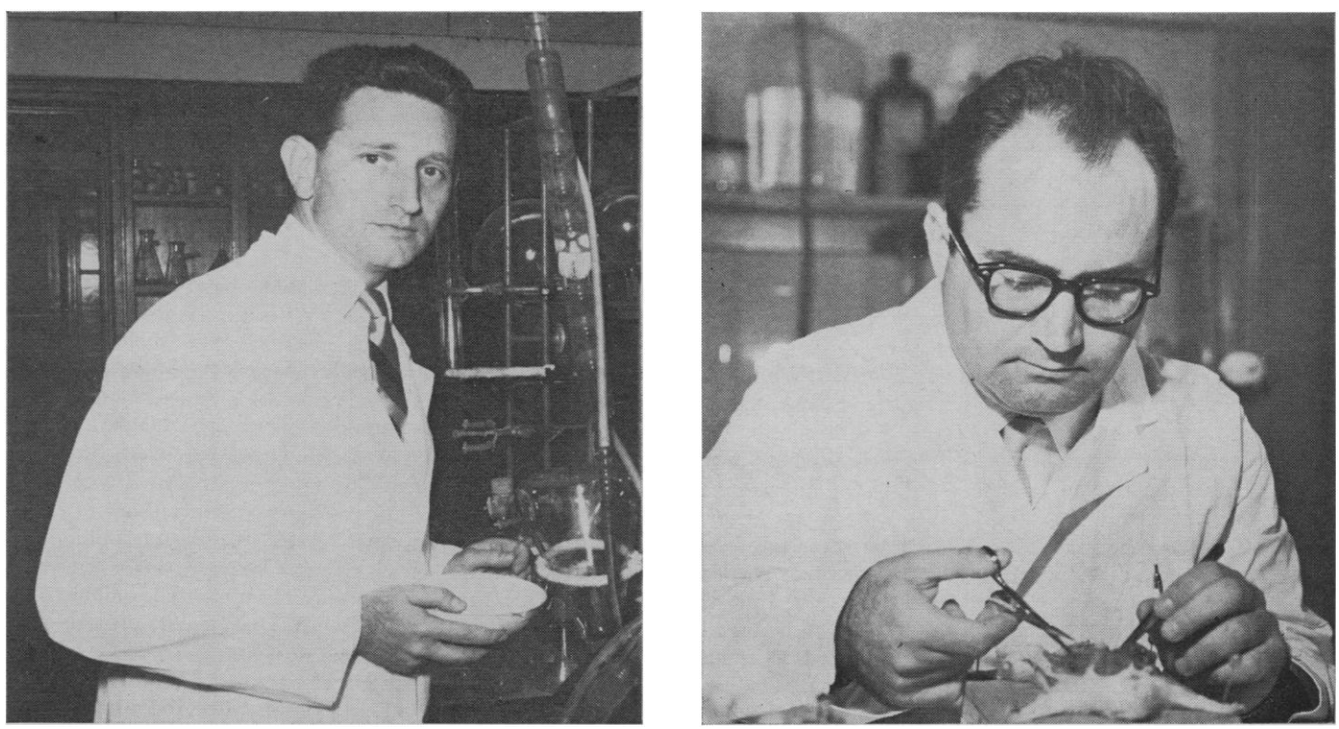
Scientists here hope that ties with laboratories in Western Europe will grow stronger. The institute is seeking more exchanges of scientists and graduate students with Europe and views the grant from Germany as a step in that direction. Ephraim Katchalski, head of the biophysics department, is one of the founders of the European Molecular Biology Organization (*Science*, 28 Aug. 1964).

Immunological Problems

Typical of the younger Weizmann Institute scientists trained first in Israel and then abroad is Michael Sela, head of the chemical immunology department. Recently his work with synthetic antigens has received wide attention.

The study of the reaction of special "immunologically competent" cells to the introduction of antigen has received new impetus with advances in understanding of the way in which cells manufacture proteins according to instructions carried in nucleic acids. Immunologists are asking whether the control system of antibody-forming cells includes equipment for learning how to make antibodies to any one of thousands or millions of antigenic substances, or whether the introduction of foreign substances creates conditions favorable to the selection of the only type of antibody-forming cell, among thousands or millions, which already "knows how" to make the specific antibody. Sela has emphasized what he sees as the difference between the ability of a foreign substance to elicit antibodies and the ability to react with antibodies. It is quite possible, he believes, that an antigenic protein which elicits an antibody could be degraded into smaller pieces which, when they were injected into an experimental animal, would not produce antibodies but would react against antibodies produced against the original antigenic protein. So, in this view, antigens can be thought of as having a general "immunogenic site" and a specific "antigenic site," just as enzymes can be thought of as having catalytic and specificity sites because they not only are adapted to making or breaking a particular bond but also select the substances for which they will perform this function.

Sela first tried to determine whether a protein—gelatin—which had less



Michael Sela, head of the chemical immunology department (left), and Michael Feldman, head of the cell biology department (right). [Ben-Zvi, Rehovot, Israel]

Uriel Z. Littauer (left) and David Elson (right) are heads of two of the groups in the institute's biochemistry department. [Ben-Zvi]

than the minimum requirements for an antigen could be converted into an antigen by the addition of chemical groups. He and his co-worker Ruth Arnon, now a research associate professor at the institute, found that the addition of as little as 2 percent of tyrosine to the gelatin molecule converted gelatin into an antigen. The antibodies elicited also reacted against untreated gelatin; thus Sela suspected that tyrosine had acted "as a kind of enhancer." Sela found that the addition of about 10 percent of tyrosine to the gelatin elicited antibodies that no longer reacted against untreated gelatin but, instead, reacted against proteins and copolymers enriched in tyrosine. The antibodies now appeared to be tyrosine-specific.

So Sela was led to ask whether gelatin was an essential starting material and whether a synthetic polypeptide might not serve as well. After much trial and error, Sela's group chose a multichain polymer in which DL-alanine groups were attached to a "backbone" of polylysine. By itself, this branched polymer was nonantigenic. Tyrosine and other materials were attached to the free amino groups in an attempt to create antigenic substances. The system did succeed in eliciting antibodies to the treated polymers.

Further experiments probed deeper into antigen characteristics. In a broad way, the shape of molecules has turned out not to be important: both dense and dilute branched polymers and linear polymers elicited antibodies. The known lower limit of size for antigenic substances continues to sink: substances with molecular weights well below 4000 have elicited antibodies. Optical configuration has been shown to have some importance for antigenicity.

Sela and his co-workers Hanna Ungar-Waron and Yael Schechter recently succeeded in eliciting antibodies to polypeptides with uridine, adenine, cytosine, or thymidine groups attached. They reported the work with uridine last year [*Proc. Nat. Acad. Sci. U.S.* **52**, 285 (1964)]. Sela thinks the production of specific proteins that react with nucleotides may be useful in studying the sequence of nucleic acids.

Sela, Israel Schechter, and others have launched studies of the structure and function of antibodies, and collaborate with John Humphrey's group at the National Institute of Medical Research at Mill Hill, near London, to determine the structure and function of antibodies, and the fate of antigenic material in immunologically competent cells. The studies of the effect of tyrosine added to nonantigenic material have been extended to problems of inducing or suppressing immunological tolerance. Such experiments, Sela thinks, show that the capacity of a material to induce tolerance is not parallel to its immunogenicity.

Arnon has become an independent researcher in Sela's department, but she continues to study problems arising from the experiments with synthetic antigens. In one set of experiments she has shown that although polylysine is not immunogenic, it will elicit the formation of specific antibodies when attached to rabbit serum albumin. This system was used for studying the size of the reacting site on the antibody.

She is also interested in the paradoxical phenomenon of protein-digesting enzymes eliciting the formation of protein antibody molecules which may serve as potential substrates for their antigens. In this work she collaborates with Gertrude E. Perlmann of the Rockefeller Institute, where Arnon worked from 1960 to 1963.

Cell Differentiation

Immunological questions also concern the cell biology department, headed by Michael Feldman. To Feldman (who heads one of three departments formed from cancer researcher Isaac Berenblum's experimental biology group), the most important concept in his work is the irreversibility of cell differentiation. How is the stability of the cell's function maintained? In the bacterial systems so intensely studied over the past two decades, he notes, β-galactosidase apparently is activated or repressed simply by the presence or absence of an inducer in the environment. But in the differentiated cells of higher organisms, the cell's particular function, once assumed, persists. This stability, Feldman thinks, could be maintained in either of two ways: the genes of the cell could be continuously "switched on" to permit continuous synthesis of the materials appropriate to a particular organ, or the genes could be "switched off" after they have manufactured sufficient quantities of stable messenger RNA.

To demonstrate the first of these proposed mechanisms, Feldman decided, it would be necessary to show continuous induction in adult organisms—say, in the differentiation of immunologically competent cells—after most of the organism's development had been completed. To demonstrate the second model it would be necessary to show that the pattern of development of a cell type—say, muscle cells in vitro—continued even though synthesis of messenger RNA had halted.

To investigate the differentiation of immunologically competent cells, Feldman and Amiela Globerson studied the thymus gland, which plays a major role in the immunologic development of a young animal. A series of experiments clearly indicated that the thymus also played an important role in regenerating the immune system of adult mice which had received large but nonlethal doses of radiation. Further experiments indicated that the thymus influences this regeneration by inducing or "instructing" cells of bone-marrow origin to differentiate, becom-

ing immunologically competent, rather than by manufacturing immunologically competent cells which later migrate. Thus, Feldman argues, continuous induction in the adult organism does take place in certain tissues.

Cloning of immunologically competent cells can be reliably achieved, Feldman reports, by injecting lymph cells into lethally irradiated mice of the same genetic composition as the mice from which the cells are obtained, using phytohemagglutinins to stimulate cell division. Feldman is testing the response of these clones to three different antigens. If all clones can respond to more than one antigen, Feldman notes, this would be evidence against F. M. Burnet's clonal selection theory of the immune response. Feldman feels that Burnet's theory has proved "very useful" because of the research it has stimulated.

In studying immunological tolerance, Feldman collaborates with David Nachtigal, and also with Sela's group. They have found evidence that natural and induced tolerance may involve similar mechanisms.

Feldman's group also uses in vitro methods to investigate blood and muscle cells. Using a system developed in Canada for cloning blood cells, they study aspects of the feedback mechanism that regulates numbers of erythrocytes and other cells. With Yaffe, Feldman observes the differentiation of mononucleated myoblasts from newborn rats. Yaffe, who worked with Henry Kaplan in the department of radiology at Stanford University from 1959 to 1961, has studied the muscle cell system in detail, showing that the fibers are produced by association and not by division of single cells. He is interested in learning what sort of "language" leads the cells to agglomerate, and in finding whether the "language" is common to muscle cells of various species. He has obtained hybrid fibers containing (i) calf and rat cells, and (ii) chick and rat cells.

Cancer Research

For some years after Berenblum joined the Weizmann Institute he devoted much of his time to develop promising researchers in experimental biology. Berenblum had been invited, in the 1940's, to start a cancer research department at the institute but decided instead to establish a multidisciplinary biology department. By now, three of the units have become separate departments: cell biology under Feldman, fertility and fertility control under Moses C. Shelesnyak (recently housed in a new building donated by the Population Council), and genetics, under Leo Sachs, who has been on leave during 1964 and 1965, at the University of Cambridge and at the Salk Institute. Berenblum, Nechama Haron-Ghera, Nathan Trainin, and others study induction of cancer by hormones, by radiation, and by carcinogens such as urethane. In 1964, Berenblum, Trainin, Gabriel Cividalli, and a visiting scientist, M. E. Hodes of the University of Indiana, reported studies of a factor from sheep spleen which inhibited the development of one type of radiation-induced leukemia in mice [*Nature* **202,** 973 (1964)]. Trainin also studies the functioning of the thymus and has found that this organ liberates a hormone-like product that can carry out many functions of the thymus; his work is related to the problem of leukemia induction. Haron-Ghera studies the response of thymic grafts to radiation and other stimuli.

Many scientists have wondered, as they seek to understand the transformation of normal cells into cancer cells, if there is not some analogy between the impact of a virus on an animal cell and the behavior of bacteriophage nucleic acid, which acts as if it is incorporated into the genome of "lysogenic" bacteria. Although many virus-caused tumors are free of virus, still they have antigens over and above those they have in common with all cells of the infected creature. The idea of an analogy with lysogeny continues to hold interest despite repeated failures

Biological Science Building, Weizmann Institute. [Ben-Zvi]

to recover virus from virus-caused tumors.

Ernest Winocur of the genetics department has been studying this question intensely since 1962–63, when he worked under Renato Dulbecco at the California Institute of Technology. Winocur and others here have been studying tumors induced in mice and hamsters by the polyoma virus and the chemical benzpyrene. Is there a closer matching, or homology, between the nucleic acid of virus and of tumor cells than there is between that of virus and of normal cells? If the cancer-causing virus were actually incorporated into the nucleic acid of tumor cells, then the cancer-cell nucleic acid should have greater homology with the viral nucleic acid than with normal nucleic acid. Using labeled messenger RNA synthesized on the DNA from highly purified polyoma virus, Winocur so far has not been able to demonstrate any increased homology. A different method, the agar technique developed by Ellis Bolton and Brian McCarthy of the Carnegie Institution of Washington, seems to have been more successful. David Axelrod and Karl Habel, of the National Institutes of Health, and Bolton recently reported finding increased homology, in experiments with polyoma virus (*Science*, 11 Dec. 1964). Winocur has been studying homologies between the nucleic acids of viruses and normal cells. Although polyoma virus induces cancer in hamsters, rats, and mice, there is far less homology between its nucleic acid and the nucleic acids of rats or hamsters than between its nucleic acid and that of mice. There is some homology between the nucleic acids of Shope papilloma virus and rabbit, but none between those of vaccinia virus and mice and rabbits.

Winocur has developed a system for infecting whole cultures of kidney cells from suckling mice with virus. This system is being used in a study of synthesis and methylation of DNA in polyoma-infected cells of mice. Working with him on this study are Victor Stoller, a visiting Canadian researcher, and Alvin Kaye of Berenblum's department.

Two years ago David Gershon collaborated with Sachs on a study of a somatic hybrid between cells of a polyoma tumor induced in one mouse strain and cells of a tumor arising spontaneously in another strain. Like Winocur, Gershon is interested in the biochemical events after infection of cells with virus. To initiate a viral genetics program, Gershon is now beginning the long-term job of isolating mutants, especially those which grow at temperatures above and below limits tolerated by wild-type virus.

For studies of tumors caused by the Rauscher leukemia virus, Dov H. Pluznik developed a rapid quantitative assay for virus, based on colonizing of cells in the spleen. This method allows the isolation of genetically homogeneous lines of virus.

Before leaving early this year to work with Irwin R. Konigsberg of the Carnegie Institution Department of Embryology, in Baltimore, Y. Berwald collaborated with Sachs in showing that carcinogenic hydrocarbons, such as 3,4-benzpyrene and 3-methylcholanthrene, would directly induce the change of normal cells to tumor cells, entirely in tissue culture. Cloning experiments showed that up to 20 percent of the cells forming colonies had been transformed.

Other Work

An example of the work of Katchalski's biophysics department is provided by Abraham Patchornik's studies of chemicals that will cleave peptide bonds as selectively as enzymes. The search for such chemicals has interested Patchornik ever since he received his Ph.D. under Katchalski in 1956 and went to work under Bernard Witkop of the National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland. Witkop and others have found various chemicals which will cleave proteins selectively. Patchornik, Witkop, and W. B. Lawson found the first of these reagents, *N*-bromo-succinimide, which cleave peptides at the tryptophan carboxyl-amide link.

Patchornik has been active in the Weizmann Institute's attempt to encourage sales of amino acid polymers and other amino acid derivatives through its Yeda company. On sabbatical leave in 1965–66, Patchornik will work in the laboratory of R. B. Woodward at Harvard.

In the institute's biochemistry department are groups headed by Uriel Z. Littauer, David Elson, Mordhay Avron, and R. Mitchell, respectively. Littauer studies nucleic acids; Elson studies enzymes and ribosomes; Avron works on photophosphorylation in chloroplasts, and Mitchell studies bacteria responsible for clogging the filtering sand used in sewage treatment.

Littauer has used a method developed by Katchalski and one of his students, Shulamit Simon, to study the transfer of RNA molecules. He has also studied for several years, in collaboration with groups at Stanford and Harvard, the function of methylation of selected bases in transfer RNA.

In studying enzymes that have been found associated with ribosomes, Elson has sought to "map" the components of the ribosome system. He has studied the enzymes detectable when the two major components of the ribosomes are packed together in a particle sedimenting with a velocity of 70 Svedberg units, and when the ribosomes dissociate into 30*S* and 50*S* subunits. Elson has also studied the linkage of soluble RNA to the ribosome and has shown that it is most tightly bound to the 50*S* particle. His group also studies several other aspects of protein biosynthesis.

This brief account of some of the biological research at the Weizmann Institute hardly begins to cover the range of scientific studies here. In the department of theoretical chemical physics, headed by Shneior Lifson, now serving as the institute's scientific director, Elson's wife, Pnina Spitnik Elson, studies ribosomal proteins. E. H. Frei of the electronics department studies magnetic properties with David Treves and other colleagues. Aharon Katzir of the polymer research department and his colleagues study membranes and the "mechanochemistry" of collagen fibers. In the physics department, Amos de Shalit has returned to his theoretical studies after a term as scientific director of the institute. Igal Talmi studies the theory of nuclear shells. Gvirol Goldring and many others are preparing to use a large new Van de Graaff accelerator, and a group headed by Gideon Yekutieli has begun a large-scale program of analyzing photographs of proton-proton interactions in bubble chambers; the photographs were taken at CERN in Geneva. The applied mathematics department, under C. L. Pekeris, an early associate of John von Neumann, works on the development of computers and the application of mathematics to geophysical problems.

Thus the biological researchers of the Weizmann Institute are closely associated with a large group of scientists in fields which have contributed many techniques and insights to biology in the past 20 years.

—VICTOR K. MCELHENY