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SOME BIOLOGICAL RESEARCH IN ISRAEL

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SOME BIOLOGICAL RESEARCH IN ISRAEL

This report is based on a rather extensive trip report that the junior author, H.B. Levine, wrote on Israel during summer and fall, 1968. During this period he spoke with 25-30 scientists in five different institutions. Because of the interesting nature of the material presented by him in his official trip report issued from his parent organization, the US Naval Biological Laboratory, Oakland, California, we have attempted to bring together this information in a narrative report. Primarily, this report deals in a limited way with some of the biological interests in two Israeli institutions, the Israel Inst. for Biological Research and the Hebrew Univ. of Jerusalem.

The Israel Inst. for Biological Research is located in Ness-Ziona, about ten miles southeast of Tel Aviv, in a lovely, tree-shaded area in the coastal lowlands about five miles from the sea. Founded in 1952, it is under the directorship of Dr. Sasson Cohen, who succeeded Dr. Robert A. Goldwasser in 1966. The latter is now back to full-time research in the laboratory. The Institute comes directly under the Office of the Prime Minister, and is engaged in both basic and applied research in a number of fields with particular emphasis on epidemiology, bacterial and viral infections, insect physiology and insect toxicology. It also has an interest in the synthesis and testing of new anti-cancer agents, psychotropic agents and general anti-metabolites. It publishes the OHOLO Annual Biology Conference reports, which reflect these interests. There are about a dozen separate departments or sections in the Institute, representing a wide variety of classical biological and chemical disciplines in addition to those in applied mathematics, biophysics and biotechnology. The main strength, however, lies in its microbiological research efforts.

Dr. Goldwasser, who is also on the faculty of the Hadassah Medical School, heads the Dept. of Virology, which is interested in the three arborviruses currently found in Israel: West Nile (WN), Sindbis, and Israel turkey meningo-encephalitis (ITME) viruses. The WN virus causes annual outbreaks among humans, and has been isolated by the Institute staff members from humans with West Nile fever. During surveys conducted between 1963-1968, staff researchers also demonstrated the existence of antibodies to the Group A and Group B arboviruses in a substantial proportion of wild birds, indicating that they are involved in the natural cycle of this virus. The Sindbis virus, which has been identified with human disease in South Africa, was isolated from Israeli turtle doves and mosquitoes by Institute members. No incidence of human infection

has been noted in Israel. The ITME virus was only recently identified at the Institute as the causative agent for epidemics of meningo-encephalitis among turkey flocks. Serological studies have shown that the organism belongs to the Group B arboviruses. No case of human disease has as yet been identified with this organism.

The Institute is very active in basic and applied studies on insect vectors that carry diseases to man. In order to obtain their blood meal from humans, these infected insects utilize various modes for the detection of their prospective victims. These involve specialized receptors for visual, thermal, moistural or chemical stimuli produced by the intended hosts. Dr. Rachel Galun has shown that in some insects, chemical compounds in the host blood such as ATP or glutathione activate chemoreceptors to induce the biting insect to suck and gorge itself. Some investigators at Ness-Ziona are studying the mode of action of these "blood receptors" with the hope of interfering with the stimulus to feed on the blood. This approach could lead to essential information for the development of anti-feeding compounds to protect the host from infectious bites without having to eliminate all potential insect vectors.

Among the insect vectors of human disease, mosquitoes of the genus Culex rank among the most important. In many parts of the world, including Israel, this mosquito, the vector for encephalitis, filiariasis, and other diseases, has developed resistance to the most potent insecticides such as the chlorinated hydrocarbons and organo-phosphorous compounds. Where resistance has developed, control operations have reverted to the old method of heavy applications of oils that kill off the larvae. This has given inadequate results.

Although no ready-made solution to the problem of resistance is yet available, the Institute hopes to undertake research to gather basic information on resistance patterns in field colonies, on the speed with which resistance develops in the field, and on the biochemical basis by which insects become resistant to various insecticides. In the latter category, preliminary studies on the effects of DDT on the biosynthesis of protein and RNA in houseflies has already been undertaken by Dr. A.S. Tahori. It appears that the pretreatment of flies with DDT stimulates these biosyntheses to a greater extent in resistant flies than in sensitive flies. It is felt, therefore, that the DDT could play an important role in enzyme induction.

Little is known about the mechanisms of the effects of DDT on the enzyme systems or the effect of the enzymes on DDT. Recently, one of the investigators at the Institute, Dr. S. Akov, returned from leave of absence spent at the US Dept. of Agriculture research laboratories, Beltsville, Md., where she worked on the male sterilant, hexamethylphosphoric triamicide (hempa), which is effective against houseflies, fruit flies, mosquitoes, screw worms and various other insects of medical and economic importance. Hempa, she found, is demethylated by microsomal enzymes of the house fly, and that the demethylation can take place only in the presence of oxygen and NADPH (reduced nicotinamide adenine dinucleotide phosphate), and is inhibited by carbon monoxide. In these respects, the enzymatic reactions are similar to those mediated by mammalian liver extracts. She found further that the end products of N-demethylation are the same *in vitro* or *in vivo* and that they had lost the chemosterilant property of the parent molecule. Flies resistant to carbamate pesticides were shown to have a high level of N-demethylating enzymes, and they demethylate hempa much more rapidly than the pesticide-sensitive insects do. However, the sterilizing activity of hempa is not directly related to the rate of its metabolism by the insect; the mechanism of detoxication is therefore believed to be more complex. Of course, any further information on the metabolic rate of hempa would be most useful in devising new, improved compounds and/or in developing the most effective mixtures of pesticides and chemosterilants. Consequently, Dr. Akov proposes to continue these studies on the metabolism of hempa and other chemosterilants such as S-triazine.

Dr. S. Ben-Efraim at the Institute is concerned with the problem of early detection of insecticide-resistant mutants as well as a means to monitor sexually-deficient mutant insects. It has been proposed, in the latter consideration, that large numbers of sterile male *Culex* be raised and released. Since these males cannot produce offspring, it is anticipated that their release would cause the mosquito population to decline. However, if the males back-mutated to fertility, the mosquito problem could be augmented.

A novel approach to investigate and monitor mutational change and back-mutation is being considered by Ben-Efraim. He proposes to study, qualitatively and quantitatively, the enzymatic composition of insects by serological means. Hopefully, the appearance or disappearance of certain enzymes associated with resistance, mutation or back-mutation could be charted and used to indicate that genetic changes were occurring.

An important tick-borne disease in Israel, Boutonneuse Fever, has an endemic focus in a small, circumscribed area in the Sharon sub-district, about 15 miles north of Tel Aviv. It is caused by Rickettsia conori, and is transmitted to humans by the common tick, Rhiphicephalus sanguineus found on dogs. Clinically, the disease resembles murine and epidemic typhus except that it is characterized by an ulcerating lesion on the site of the tick bite and by the button-like appearance of the red, spotty eruptions. From observations made by Dr. M.A. Klingberg's team at the Institute, it seems that the disease is spreading in concentric circles from one village, Kfar-Vitkin, in the focus of the area plagued by Boutonneuse Fever.

Because of the increasing incidence of the disease over the past few years, there is a strong desire to carry out a comprehensive epidemiological survey. One of the key considerations is the development of reliable serological procedures for diagnostic purposes since none is available at present. For example, the complement-fixation test will not distinguish between Boutonneuse Fever and Rocky Mountain Spotted Fever.

The Hebrew Univ., Jerusalem, was opened in 1925 with a relatively small faculty and student body. Since the War of Independence in 1948 and the loss of its campus on Mount Scopus, a new main campus has been developed at Givat Ram in the new city of Jerusalem. There are now 11 different faculties and schools with a total student body of about 12,000. The old campus at Mt. Scopus has been reopened since the June 1967 war. Visits were made to the Hadassah Medical School, the Dept. of Zoology, and the Dept. of Entomology and Venomous Animals.

The recently completed Hadassah Medical School is part of the Medical Center at Ein Karem, Jerusalem. One of the striking features of the Center is a small chapel on the grounds which is surmounted by 12 beautiful, stained glass windows created by Marc Chagal. They are arranged in a rectangle and commemorate the 12 tribes of ancient Israel. The Medical School itself is housed in a new, modern well-equipped building.

Dr. D.W. Weiss, Dept. of Immunology at Hadassah, is interested in the study of non-specifically-induced immunity. His work has centered on such immunity conferred on laboratory animals by a fraction of attenuated and avirulent tubercle bacilli. The fraction, designated (MER), is the residue of exhaustive methanol extractions at 55°C of phenol-killed, acetone-washed tubercle bacilli. In the dry state, it is stable for years, provided it is kept in cold storage. Although

MER is insoluble in water, it can be brought into suspension by various wetting agents. It is well tolerated by mice, rabbits and guinea pigs at doses several times greater than the optimally effective immunogenic quantity. MER is completely non-toxic and non-pyrogenic to mice. It can produce a high degree of resistance in these animals to a large number of bacterial and viral pathogens, including the agent of viral pneumonitis, as well as to normal homografts and tumor isografts. The non-specific protection is manifested shortly after a single, intra-peritoneal injection and lasts for many months. Experiments are under way to confirm findings which point to MER as a stimulator of phagocytic and antibody functions. Efforts are also being made in the purification and eventual characterization of the component(s) of MER. If the properties of MER hold true for man as well, this substance could provide a remarkable tool for dealing with sudden outbreaks of disease and an important protective adjunct to radiation therapy.

The mechanism of immune defense against large microorganisms is being investigated by Dr. Moshe Aronson of the Israel Inst. for Biological Research and Tel Aviv Univ. Medical School. He has found, with Cryptococcus neoformans, that rings of monocytes accumulate around the organism and function to restrict its multiplication. Such "rosettes" can be demonstrated on the omentum of mice and similar structures can be produced in vitro. Evidence that "rosette" formation can be augmented by vaccination has been obtained.

The Dept. of Entomology & Venomous Animals of Hebrew Univ. is located at Terra Sancta College, Jerusalem, under the chairmanship of Dr. A. Shulov. Shulov and his group are interested in the Reduvid bugs of the Holotrichus genus. These bugs are found frequently in the Sinai desert and have an extremely toxic venom which apparently exceeds the toxicity of most snakes and scorpions. To date, Shulov's group has bred these insects successfully in the laboratory to ensure a sizable quantity of venom for research purposes. They wish to continue preliminary studies on toxicity effects to include work on the basic physical, clinical and pharmacological properties of the venom. Despite the scarcity of pharmacological data on the venom, these investigators foresee the possibility of useful agents being developed from this material.

Another area of interest in Shulov's Department is that of bio-communications with special reference to insect communication mechanisms. Communication between insects is achieved through the use of receptors related to sight, smell, hearing or touch. To study these problems, the Department has a fair collection of electronic equipment (oscillograph, audiospectrometer, frequency analyzer and underwater transmitters) and recording equipment (film camera and tape recorder). In addition, they have an acoustic chamber and special aquaria for the recording and playing back of sounds to aquatic insects in them. Their laboratory studies have included sound recordings related to various behavioral patterns of Belostomid bugs of the Sphaerodema genus.

Communication between terrestrial insects is also of concern to members of the Department. In studying the desert locust, Schistocerca gregaria Forsk, they have found that these creatures employ a combination of olfactory, visual and tactile factors. Of the three, the olfactory one was found to be most significant.

An insect of fascinating experimental potential is the male cricket, Gryllotalpa gryllotalpa Linne, which occurs in two chromosomal forms. One, with 23 chromosomes, is limited in distribution to the desert region surrounding the Dead Sea, where the relatively moist soil has a high salt concentration. The other, with 19 chromosomes, is widely distributed throughout Israel. Shulov and his associates have been studying the habits and characteristics of these two forms, and intend to extend their research to cover the acoustic communication patterns. The intention is to play back to the insects recordings of the emitted sounds from members of their own chromosomal form, as well as from members of the alternative chromosomal forms. Behavioral patterns would be observed and correlated with the sounds. An interesting insight into the evolutionary and ecological processes could thus be obtained.

From the personal observations made during these visits, it is felt that the scientific competence among the Israelis is exceptionally high. Their facilities, laboratories, and research equipment rank with those found in the better laboratories in the US.

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A review is presented of the biological research interests of some staff members of the Israel Inst. for Biological Research and the Hebrew University of Jerusalem. Particular emphasis is placed on the research undertaken on viruses and insect vectors found in Israel.

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