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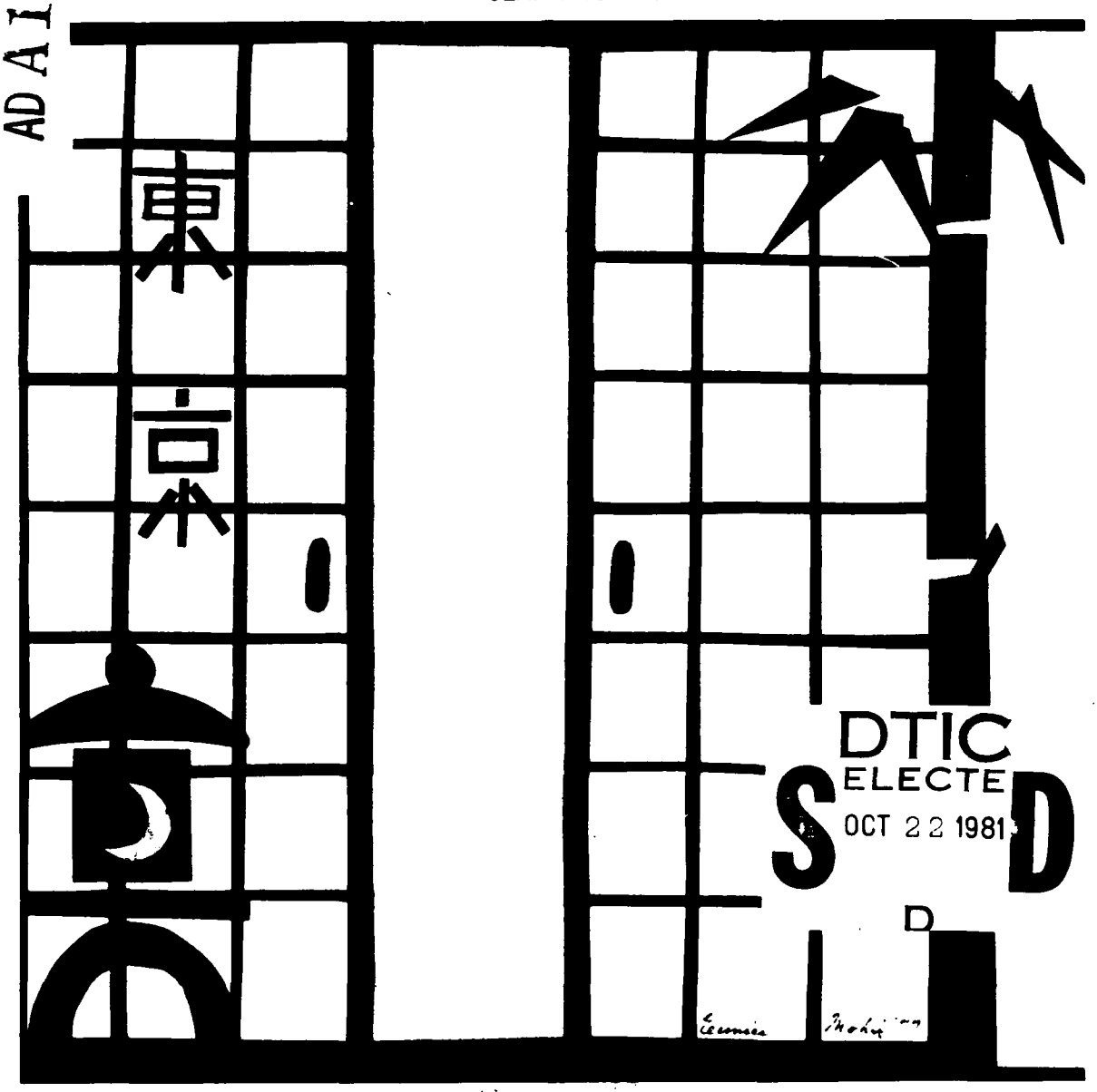
SCIENTIFIC MONOGRAPH

DEPARTMENT OF THE NAVY OFFICE OF NAVAL RESEARCH TOKYO

AN OVERVIEW OF MICROBIOLOGY RESEARCH IN JAPAN, WITH NOTES ON MEDICAL HISTORY, EDUCATION AND HEALTH CARE

JEANNINE MAJDE



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REPORT DOCUMENTATION PAGE	READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER: ONRT M5	2. GOVT ACCESSION NO.: AD-A106 001
	3. RECIPIENT'S CATALOG NUMBER:
4. TITLE *(and Subtitle)*: An Overview of Microbiology Research in Japan, With Notes on Medical History, Education and Health Care,	5. TYPE OF REPORT & PERIOD COVERED: Scientific Monograph
	6. PERFORMING ORG. REPORT NUMBER: ONRT M5
7. AUTHOR(s): Dr. Jeannine A. Majde, Office of Naval Research, Branch Office, Chicago	8. CONTRACT OR GRANT NUMBER(s):
9. PERFORMING ORGANIZATION NAME AND ADDRESS: Office of Naval Research, Scientific Liaison Office, American Embassy, APO San Francisco 96503	10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS:
11. CONTROLLING OFFICE NAME AND ADDRESS: Office of Naval Research, 536 South Clark Street, Chicago, IL 60605	12. REPORT DATE: July 1981
	13. NUMBER OF PAGES:
14. MONITORING AGENCY NAME & ADDRESS *(if different from Controlling Office)*: Biological Sciences Division (Code 440), Office of Naval Research, Arlington, VA 22217	15. SECURITY CLASS. *(of this report)*: UNCLASSIFIED
	15a. DECLASSIFICATION DOWNGRADING SCHEDULE:

16. DISTRIBUTION STATEMENT *(of this Report)*

APPROVED FOR PUBLIC RELEASE: DISTRIBUTION UNLIMITED

17. DISTRIBUTION STATEMENT *(of the abstract entered in Block 20, if different from Report)*

18. SUPPLEMENTARY NOTES

Accession For
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DTIC TAB
Unannounced
Justification
By
Distribution/
Availability Codes
Dist | Avail and/or Special
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19. KEY WORDS *(Continue on reverse side if necessary and identify by block number)*

Medical history	Influenza virus	Smallpox virus
Medical education	Dengue virus	Rubella virus
Health care	Polio virus	Varicella virus
Chinese medicine	Shope papilloma virus	Mumps virus
Vaccines	Measles virus	Rabies virus

20. ABSTRACT *(Continue on reverse side if necessary and identify by block number)*

This monograph summarizes the research activities in medical microbiology at 19 leading medical schools and institutes in Japan. An emphasis is placed on ongoing work in infectious diseases and immunology. However, other disciplines including cell biology, physiology, and biochemistry, are covered when encountered. In addition, background notes on the development of medicine in Japan, the medical educational process, and the

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SECURITY CLASSIFICATION OF THIS PAGE *(When Data Entered)*

19. Key Words (cont.)

Rous Sarcoma virus
Japanese encephalitis virus
Sendai virus
Hepatitis virus
Herpes viruses
Avian leukosis agent
Epstein Barr virus
Adenovirus
BK virus
Epidemic keratoconjunctivitis
Isumi disease
Pertussis
Diptheria
Tetanus
BCG
Tuberculosis
Mycobacteria
Anthrax
Clostridia
Brucellosis
Cholera
Fusobacteria
Streptococci
Staphylococci
Klebsiella
Plague
Pseudomonas
Salmonella
Shigella
Listeria
Plasmids
Complement
Immunoglobulins
Autoimmune diseases
Cellular immunity
Idiotypes
Hypersensitivity response
Macrophages
Phages
Candida
Streptomyces
Rickettsia
Insect vectors
Toxoplasmosis
Malaria
Trypanosomes
Schistosomiasis
Clonorchiasis
Filariasis
Hookworms
Paragonimiasis
Onchocerciasis
Strongyloidiasis
Nitrosamines
Glyoxalase inhibitors
Enterotoxins
Endotoxins
DNA
Calcium
Aminoglycosides
Immunopharmaceuticals
Adjuvants
Adenyl cyclase
Aflatoxins
Acupuncture
Interferon
Liposomes
Lysozyme
Carcinogens
Immunology
Cytoskeleton
Cell biology
Neurobiology
Sleep
Circadian rhythms
High voltage electronmicroscopy

20. Abstract (cont.)

Japanese health care system are provided. Names and addresses of the researchers whose work is described in the monograph are provided in an Appendix to facilitate communication, and comprehensive indices are included.

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AN OVERVIEW OF MICROBIOLOGY RESEARCH IN JAPAN, WITH NOTES ON MEDICAL HISTORY, EDUCATION AND HEALTH CARE

INTRODUCTION

The original goal of my three-month visit to Japan was to acquire an overview of biomedical research activities in one of the world's most highly developed countries. This goal might have been feasible 20 years ago; today Japan has over 80 medical schools, perhaps half of which conduct substantial basic research in numerous disciplines. The sheer volume of medical research in Japan quickly forced me to narrow my scope drastically. My activities were further limited to those subject areas in which common scientific interests transcended the language barrier. Thus this report is strongly weighted toward the field of medical microbiology, with an emphasis on infectious disease research and immunology. (Included in the latter is the new field of immunopharmacology, which will be covered only briefly here and in depth in a separate report in the ONR Tokyo [illegible].) However, I did acquire some information on cell biology and biochemistry; persons interested in those fields are urged to review the Table of Contents and the Index to locate projects of interest to them.

The institutions I visited in Japan group neatly into national university medical schools and institutes (supported exclusively by the Ministry of Education), private medical schools and institutes which may stand alone or be part of a private university (supported by student fees, government grants, industrial contracts, and royalties) and independent research institutes (with a variety of support, as will be discussed on an individual basis). My sample represents about 20% of the medical research institutions in Japan (excluding pharmaceutical firms), but is heavily weighted toward the most prestigious.

Because I emphasized medical institutions during my visits, I inquired of several of my hosts whether I should attempt to visit basic biological science departments outside of medical schools. Their opinion was that, apart from Tokyo University, very little important basic biomedical research of medical importance takes place outside of medical schools and their affiliated research institutes. I feel this is probably true as far as the classical disciplines are concerned; however, the medical schools appear to have little work in molecular biology, cell biology, or environmental biology. It is unlikely that these disciplines are being neglected in Japan, and interested persons will probably find such research in the basic science departments of the newer national universities and perhaps in some of the new medical schools in the smaller cities.

During my visits I attempted to learn about the Japanese system of medical education and medical care. The sections of this report discussing these aspects are in large part based on informal interviews, and may contain many factual errors and personal biases. They are included primarily to provide a context for the technical material which follows.

GENERAL BACKGROUND

Infectious disease research traditionally has dominated medical research in Japan as it did in the West until the age of antibiotics began in the 1940s. However, my impression is that it continues to play a prominent part in modern Japanese medical research, whereas in the West cancer research and molecular biology reign supreme. I suspect the reason for the persistence of infectious disease research in Japan is that the Japanese university organization, modeled on that of nineteenth century Germany (via Holland—see historical

sketch below), has a slow response time. Older universities have their departments organized around a single full professor who totally controls the research activities in his small, autonomous department until he retires (between the age of 58 and 65). As the end of World War II marked a transition point for all other social and economic aspects of Japan, it also gave rise to the current generation of full professors who are just now beginning to retire in significant numbers. (Indeed, my letters of introduction arrived just as many of their recipients retired prior to the start of the new fiscal year, 1 April.) Many of the larger research institutes and universities thus continue to emphasize infectious disease studies, much to my delight. It will be of interest to see if this emphasis will survive the new generation of microbiologists, who are attracted to the molecular orientation dominant in the U.S. and Europe.

It should be added that the need for infectious disease research is no greater in Japan than it is in the U.S. In fact, the general level of hygiene is higher, and preventive public health measures are more widespread than in the U.S. These conditions are reflected in the fact the Japan now has the highest life expectancy among industrial nations--73 years for men, 78 years for women. However, infectious diseases remain a social and economic burden for all nations, and the decline in infectious disease research leaves many serious gaps, especially in the area of viral, fungal, and parasitic diseases. Therefore, it is to be hoped that the excellent infectious disease research ongoing in Japan will not become outmoded as it has in the West.

Immunology has not yet expanded quite as fast in Japan as in the U.S., Western Europe, and Australia. This may also be a result of the slow response time generated by the rigid university structure. However, immunology departments are gradually taking shape as independent entities, and as in the U.S., immunologists are widely found in microbiology and cancer research laboratories. The Immunology Society of Japan currently has about 3,000 members.

The discipline of immunopharmacology is quite new throughout the world. Immunopharmacology includes the immunosuppressant drugs used for many years to treat organ transplant recipients and a host of natural and synthetic substances which enhance immunity. Where the latter are primarily being tested in cancer systems, they are also therapeutic for viral and fungal infections. Japan appears to be taking the lead in research and development in immunopharmacology, and, as this is my personal field of research, I sought out workers in this specific area. The results, as mentioned above, will appear in the ONR Tokyo *Scientific Bulletin*.

RESEARCH CONDITIONS

The almost universal organization of a Japanese laboratory, even in a nonacademic institute, is one headed by the professor or chief, with an associate professor (perhaps two), two assistant professors, and numerous postgraduate students, graduate students, and an occasional technician. Few academic laboratories have trained technical help; the only nonstudent labor is in the form of glassware washers and animal caretakers. The laboratories are almost always crowded with both equipment and people. The activity level is very high. Some equipment is from the U.S. (especially freezers), but most is produced by Japanese firms. It is usually quite modern, often in contrast with its surroundings. The physical plant appears almost totally neglected in the national universities and older private universities. Most of their buildings are prewar, and new buildings are being planned in many cases.

I found it interesting that shoe removal was optional in most situations except when

the presence of infectious organisms, cell cultures, or isotopes made it very reasonable. Another circumstance which invariably required shoe removal was the presence of a significant piece of equipment such as a computer or an electron microscope. I was assured that such equipment would be damaged by dirt brought in the room on street shoes.

Government regulations with respect to laboratory use of isotopes are very strict, reflecting the high level of public concern about radioactivity. The Japanese government enforces the U.S. guidelines on recombinant DNA work, at least in the universities. There appear to be few, if any, regulations relating to infectious agents, but laminar flow hoods and other containment equipment were commonly found.

Financial support, at least in the national universities, is adequate if not generous. All support of national universities is derived from the Ministry of Education through competitive grants. I got the impression that many private institutions were better off financially due to consulting agreements with pharmaceutical firms as well as service contracts with the government or industry for production or testing of biologicals and drugs.

A BRIEF HISTORY OF MEDICINE IN JAPAN

The earliest known exposure of Japan to medicine came by way of China and Korea in the fifth and sixth centuries. Japanese medical students were sent to China during the seventh century. During the eighth century laws were first formulated (but not promulgated due to widespread warfare) regarding medical education and practice. In the tenth century Chinese medical books became available in Japan.

The first exposure to Western medicine occurred when the Portugese landed in Japan in the sixteenth century. A Jesuit monk, Brother Luis d'Almeida, practiced and taught medicine beginning in 1556. However, during the Tokugawa period (1603-1868), the Christian missionaries were expelled and the only Westerners permitted in Japan were the Dutch.

In 1649, a Dutch ship's doctor, a German physician presumed to be Dutch, began to teach Western medicine in the Nagasaki area (southern Kyushu) and Edo (now Tokyo). Not until 1745, however, did a Japanese-Dutch dictionary become available to facilitate exchange of ideas. In 1771, Japanese physicians were finally shown by illegal demonstration (dissection was against Buddhist precepts and Japanese law) that human anatomy resembled that illustrated in a German atlas, but not that underlying Chinese medicine (Kampo). Japanese medical texts based on Western medicine began to appear in 1772. The first Japanese medical school was founded in 1837 in Osaka, followed by one in Edo in 1838. Smallpox vaccination was introduced in 1849, and a Vaccination Institute was established in Edo in 1858; this Institute was the forerunner of the Tokyo Imperial University Medical School. A German physiologist, Dr. Erwin Baelz, came to Tokyo in 1876 to teach there, and is frequently called the father of modern medicine in Japan. His arrival was an affirmation of the Imperial edict to adopt the German medical system (stressing the value of basic laboratory research rather than pure clinical observations) in Japan.

The oldest extant institution of university-style higher learning in Japan, the private Keio University in Tokyo, was founded in 1858 by a student of the Dutch-trained physician, Ogata Koan, from Osaka. However, the medical school of Keio University was not established until 1917, by the great microbiologist Dr. Shibasaburo Kitasato, because medical education was restricted to Imperial universities until that time.

Dr. Kitasato, who might well be termed the Pasteur of Japan, deserves further mention. Born in 1852, he graduated from Tokyo University Medical School in 1883. He then studied in Berlin under Robert Koch from 1885 to 1891, where, together with Emil von Behring, he studied tetanus and diphtheria bacilli. In 1889, Kitasato first obtained a pure culture of the anaerobic tetanus bacillus. In 1890, he and von Behring demonstrated the therapeutic value of antitoxin in tetanus. Returning to Japan in 1892, he proceeded to discover the bacillus *Pasteurella pestis*, the agent of bubonic plague, simultaneously with the French bacteriologist Alexandre Yersin. His laboratory in Tokyo later (1899) became the Imperial Institute of Infectious Diseases, now the Tokyo University Institute of Medical Science. He went on to isolate the dysentery bacillus (1898) and to study vaccine made from killed bacterial cultures. He also investigated the mode of infection in tuberculosis. In 1914, he resigned from the Imperial Institute to found the Kitasato Institute (still extant) and then the Keio University School of Medicine. He died in 1931. Many Japanese feel that he deserved to share von Behring's Nobel Prize and might have had he remained in Germany.

For a more detailed account of the history of medicine in Japan, the reader is referred to the excellent book by Bowers.[1]

MEDICAL EDUCATION

Currently there are about 80 medical schools in Japan, nearly double the number present in 1964. The average class size is 110, turning out approximately 8,000 medical graduates per year to serve a population now at 112,000,000. A majority of these eventually enter private practice or serve as salaried physicians in hospitals. There is no shortage of primary care in the cities of Japan, but as in most countries, the rural areas are poorly served.

The high school student who successfully passes the rigorous entry examination for a medical school (approximately 1 in 40 succeed on the first try to a prestigious school like Tokyo or Keio) proceeds to two years of premedical training (which includes liberal arts courses), and four years of medical courses stressing classical subjects and basic science. There is little required clinical training. Whereas a one year rotating internship was at one time required, it was abandoned in 1973 as unproductive. About 20% of medical graduates go on for the four year postgraduate course, which emphasizes basic research and may provide clinical experience in some fields. The postgraduate degree is required for those seeking academic positions. (As recently as 1965, over 80% of medical graduates sought postgraduate research training, but as the result of some organizational changes hospitals now woo new graduates into highly paid clinical service.) Postgraduate students comprise the bulk of personnel in research laboratories, and their income from part-time clinical service often exceeds their professor's salary.

Specialty training in clinical medicine is conducted in much the same manner as in the U.S. and may be supplemented by a year abroad. Over 70% of medical graduates take specialty training. They are not required to pass licensing examinations to practice their specialities.

The German medical tradition was adopted in Japan for a number of historical

[1]Bowers, John Z., *Medical Education in Japan*. (Hoeber Medical Division, Harper Row, New York, 1965).

reasons outlined in the preceding sketch. It has been retained, it is said, because it suits the Japanese character. Its emphasis on basic research rather than clinical experience appeals to the deeply ingrained respect for scholarship that was carried from China to Japan. Many Japanese medical students aspire to the highly respected and very scarce faculty positions in the top-ranked medical schools. Only a handful achieve this goal. While this vigorous selection process favors maintenance of a strong research arm, many feel that care of the sick is neglected in all phases of medical training.

Another aspect of the German system that appeals to the Japanese is the omnipotence of the professor. The hierarchical structure thus derived is consistent with the highly structured society of Japan in general. The price is a reduced capacity to respond to changing directions in research, less freedom for the young researcher to pursue his own interests, and a structure which does not favor interdisciplinary efforts. Despite awareness of these limitations, no obvious effort is being made to change to a more flexible structure.

An aspect of the German system that appeals to students is the relative freedom from required class attendance; preparation for examinations is done independently. Most students work part-time for spending money, and devote considerable time to sports and social activities. Once admitted to medical school, there is little chance of failure.

The cost to the student's family is quite modest if admission to a national university is achieved: An examination fee of about $40, a matriculation fee of about $250, and an annual tuition of about $600. (An average family gross income in Japan is about $24,000 per year, $17,000 net, with living expenses of about $12,000 and savings approaching $5,000.) Scholarship aid is available. Private medical schools, however, are very expensive. They subsist on tuition fees to a large extent, and charge essentially ten times the above rates. Many of the students in private medical schools are sons (or daughters, women comprising about 10% of medical entrants) of physicians who are expected to succeed their fathers.

HEALTH CARE

MEDICAL RESOURCES

Entering the lobby or hallways of a Japanese hospital provides no evidence of any gross distinctions between medical care in Japan and the West. Western-style uniforms and equipment are conspicuous. The patient may note some important differences, however, if his physician is freshly graduated, especially if he has graduated from a prestigious school. Such a new graduate will have had very little clinical training, and may have little interest in treating the sick. This image may be uncharitable but it is based on the structure of the medical educational system and the repeated statements by laypeople that I interviewed: Japanese doctors "are awful (?)," "give out too many pills," and are "too rich." Even some researchers with M.D. degrees supported these notions. The Japanese practitioner seems to share the status of his Western colleagues, who are respected but not admired.

An unusual feature of Japanese medicine is the continued presence of traditional Chinese medicine as an alternative mode of treatment. In some cases a Chinese-style hospital is located in the same complex as a Western-style hospital. Traditional Chinese medicine is limited to the now familiar acupuncture, moxabustion (where small cones of the powered herb mugwort are burned on specific sites of the skin, delineated according to the disease), and complex herbal drug therapy. Diagnosis is achieved through palpation of pulses. Training in Chinese medicine is achieved with a residency program following graduation from a Western-style medical school. While some people elect Chinese

medicine as their primary mode of treatment, it is generally used after Western medicine fails to solve the problem.

I inquired often whether any research was being done on the herbs used in Chinese medicine. A few institutions maintain gardens and greenhouses and even tissue cultures of Chinese herbs for chemical analysis of those with anticancer activity, but it seems that no one has succeeded in isolating the active agents. I was told that purification eliminates their activity. Because Chinese herbal medicine often requires several months to achieve its effects (in contrast to the "instant" effects of modern antibiotics), assay systems are probably complex. A substantial Research Institute for Wakan-Yaku (or herb medicine) is located in Toyama University in Toyama City, but I was unable to visit it. A visit to the Kitasato Chinese Hospital in Tokyo was made, however, with demonstrations of diagnosis and acupuncture, as well as a highly stimulating (olfactorily speaking) inspection of their very massive and unusual pharmacy.

Drugs, Western or Chinese, are more readily available to lay people in Japan than in the U.S. I have the impression that self-diagnosis and drug administration is widespread. Chinese-style pharmacists are also active in diagnosis and prescription of herbal remedies.

PUBLIC HEALTH

As previously mentioned, the general level of hygiene in Japan is very high. The Shinto religion, which emphasizes personal cleanliness, was established early and remains a significant cultural force. With the advent of modern sewage systems (and the replacement of human wastes with chemical fertilizers in agriculture), Japan has eliminated many of the infectious disease problems found in the rest of Asia despite the crowding of its cities. Perhaps the widely used "influenza mask" contributes as well as by reducing spread of respiratory diseases among commuters and office workers.

Supplementing these societal measures is a strong governmental program of preventive immunizations. Administered by the Bureau of Public Health of the Ministry of Health and Welfare, vaccinations are compulsory for all school children for the following diseases: tuberculosis vaccine (BCG), measles vaccine (live vaccine), rubella vaccine (live vaccine, in females only), and influenza vaccine annually until high school (split virus vaccine of the current epidemic strain or strains as determined the preceding March). Mumps vaccinations will be made compulsory soon. Compulsory for preschool children are standard pertussis/ diptheria/tetanus vaccine and polio (live type) vaccines. Japanese encephalitis virus vaccine (killed mouse brain extract purified by ultracentrifugation) is optional, and is encouraged in areas experiencing outbreaks of JEV in swine or humans.

The administration of these preventative services in Japan is the responsibility of the 47 prefectural governments and the more than 800 "health center districts" which serve the cities, towns, and villages. The expense is shared by these units.

Undoubtedly, the most ambitious program is that of influenza vaccination of some 22,000,000 children annually, especially in view of the logistics of preparing new antigenic variants as they appear. However, the program reduces influenza by 50%-95% in vaccine recipients when the vaccine incorporates the epidemic strains, and is considered successful. A detailed analysis of the Japanese influenza vaccine program was recently published in an American journal.

[2]Dowdle, W.R., Millar, J.D., Schonberger, L.B., Ennis, F.A. and LaMontagne, J.R. *J. Infect. Dis. 141* (2), 258-264 (1980).

Turning to health problems other than infectious diseases, the patterns bear a close resemblance to those in the West. I was unable to acquire any statistics, but cardiovascular disease appears to be the most significant cause of death, followed by cancer and then trauma.

Among cardiovascular disorders, it is my impression that strokes associated with hypertension are more common than heart disease. The high salt content of the traditional diet may contribute to this, and the low animal fat intake probably protects the heart. (Beef and pork are very popular in Japan, but because of their high prices they are consumed less frequently and in smaller amounts than in the U.S.; fish still constitutes the primary source of protein.) Cigarette smoking is widely practiced, and probably contributes to cardiovascular disorders.

Stomach cancer is currently the most prevalent form of malignancy, but is being replaced by lung cancer. The cause for the high incidence of stomach cancer, presumed to be dietary, is still uncertain. However, epidemiological studies suggest that the high intake of pickled vegetables may result in carcinogenic levels of nitrosamines; possibly the low intake of ascorbate intensifies nitrosamine formation. The shift to lung cancer is thought to be a combination of reduced traditional diet (reducing the incidence of stomach cancer) and increased cigarette smoking, along with exposure to atmospheric pollution. My information on this is very uncertain as I encountered no one who professed knowledge about the situation or even appeared interested in it--in strong contrast with the widespread interest in causes of cancer and cardiovascular disorders found in the West. Probably interest is higher among cancer researchers and cardiologists, who were not included in my sample.

SECTION I

NATIONAL UNIVERSITIES

TOKYO UNIVERSITY

INTRODUCTION

Tokyo University is the largest and most prestigious university in Japan, termed "Harvard plus Stanford plus MIT rolled into one." It currently enrolls about 20,000 students. Founded by the amalgamation of two older institutions of higher learning and the Vaccination Institute in 1877, it is also the oldest national university, and exhibits the classical German 'chair' organization. The same organization holds for the affiliated research institutes. While in Tokyo I visited the Microbiology Department of the Tokyo University Medical School, the Institute for Applied Microbiology, and the Institute for Medical Research.

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Associate Professor Hideyo Yamaguchi, Acting Department Head (Professor Iwata having retired earlier in the month), served as my host. A major reconstruction of the laboratories was underway, so my visit was restricted to a discussion of the medical mycology under study by this very small group. Dr. Yamaguchi divided their work into four areas: mechanism of action of antifungal drugs; the role of cellular immunology in fungal infections; the biochemical basis of fungal morphogenesis; and pathogenic potential of industrial yeasts. Most studies are being conducted with the pathogenic yeast *Candida albicans*. My general impression is that this group looks to the U.S. for leadership in these areas, although the reorganization in progress may result in a shift in focus. In any event, this small department is overshadowed by the microbiology research conducted at the two large institutes described below.

INSTITUTE OF APPLIED MICROBIOLOGY

The Institute of Applied Microbiology was founded in 1953 on the main campus of Tokyo University at the recommendation of the Science Council of Japan "to perform coordinated research in microbiology, both fundamental and applied." Despite its relative newness, it is organized in the 'chair' mode.

It is noteworthy that fermentation is an ancient art in Japan, and fermented rice beverages (sake) and soy products (soy sauce, miso paste) are still significant components of the Japanese diet. The current high level of fermentation science in Japan originated with zymological research on soy sauces.

I was fortunate to meet with Professor Nobuo Tanaka, Director of the Institute and an active researcher into the mechanism of action of antibiotics with antitumor activity. Dr. Tanaka was a student of the much revered Professor H. Umezawa, discoverer of the aminoglycosides kanamycin and neomycin. Dr. Umezawa has retired from the University of Tokyo and now heads the private Institute of Microbial Chemistry (see below). Dr. Tanaka is still investigating the sub-cellular effects of the aminoglycosides (which include streptomycin and the currently popular gentamycin) in terms of ribosome binding and tubulin binding. The latter is a result of the basic nature of aminoglycosides and results in binding to microtubules and cytoskeletal actin, with toxic consequences for certain cell

types. Dr. Tanaka is also interested in the family of anthracyclic antibiotics, such as adriamycin, currently used in cancer therapy. Adriamycin is limited in its use by its cardiotoxicity; a new variant, aclacinomycin, lacks cardiotoxicity and appears equally carcinostatic in animal systems. Aclacinomycin is currently being tested clinically in Japan. Carcinostasis by the anthracyclics is achieved by DNA intercalation, which blocks DNA polymerase activity. The cardiotoxicity of adriamycin appears to be due to induction of free radicals in microsomes, which cause membrane lipid peroxidation.

Although the Institute stopped screening for new antibiotics for several years, they resumed such screening two years ago both for antibacterials and for anticancer drugs. Most attention is paid to the streptomycetes, which appear to be a limitless resource of such drugs. They recently incorporated a screening for immunopotentiating drugs as well, using cultured lymphocytes stimulated by the mitogen phytohemagglutinin as an assay system. This is a small scale effort at this time. A much more vigorous program for isolation of immunopotentiators from microbial products is in progress under the direction of Dr. Umezawa at his Institute for Microbial Chemistry (see below).

In addition to Dr. Tanaka's antibiotic division, the Institute has 11 other divisions: molecular biology of bacterial structure (penicillin action); microbial genetics; bacterial physiology; bacterial toxonomy and culture collection; enzymology; algal physiology; microbial chemistry; fermentation technology; fungal genetics; bioengineering; and biological activity of microbial products. The staff totals 12 professors, 12 assistant professors, 24 research assistants and 80 technicians or graduate students.

INSTITUTE OF MEDICAL SCIENCE

This Institute, located some distance from the Tokyo University Medical School, was founded in 1892 as a private Institute for Infectious Diseases. It was incorporated by the University in 1916. After World War II, it split into the National Institute of Health (equivalent to the U.S. Bureau of Biologics; see below) and its current more generalized medical research activity. The Institute of Medical Research has 32 divisions (or 32 full professors), a third of which are concerned with infectious disease, and the rest split between oncology, radiology, surgery (including organ transplantation), genetics, molecular biology, pathology, and support facilities. An affiliated hospital with 180 beds is used for clinical research.

A sketch of the research activities of these divisions (abstracted from a 1977 brochure) is given below, followed by some details of the work of the six researchers I interviewed.

- Allergology - Professor Tyoku Matsuhashi: immunological and physicochemical study of immunoglobulins; mechanisms of antibody production; antitumor action of microbial substances.

- Animal Pathology - Professor Kosaku Fujiwara: pathogenesis of Tyzzer's disease and murine viral hepatitis; pathology of canine brucellosis; epizoology of indigenous infections in laboratory animals; vertical transmission of maternal antibodies.

- Bacterial Infection - Professor Iwao Kato: pathogenesis of staphylococcal infections and staph toxins; molecular aspects of R plasmids in [illegible] ; mechanism of salmonella-phage interaction.

- Bacteriology - Professor J. Yuzuru Homma: immunogenicity of pseudomonas structural components and pseudomonas toxins; clinical application of a 3-component pseudomonas vaccine; relationship of *Propionibacterium acnes* to sarcoidosis; immunochemical and biological properties of *Mycoplasma pneumoniae* membranes and *Pseudomonas aeruginosa* L-forms; analyses of human immunoglobulin idiotypes.

- Cancer Cell Research - Professor Hajim Katsuta: chemical carcinogenesis in cell culture; interactions between cocultured normal cells and tumor cells; definition of toxic metabolites produced by cancer cells.

- Carcinogenesis and Cancer Susceptibility - Professor Iwao Hirono: investigation of the interaction of natural and synthetic carcinogens with genetic factors of target cells; metabolic activation of chemical carcinogens; cytopathology of early events in cells treated with carcinogens.

- Cell Chemistry - Professor Toru Tsumita: biochemistry of cyclitols in animal tissues; cell surface changes and host responses; chemistry of mycobacterial antigens; chemistry of brain myelin with reference to experimental allergic encephalomyelitis.

- Chemistry - Professor Yoshito Kaziro: mechanisms of polypeptide chain elongation by bacterial and mammalian elongation factors; characterization of elongation factors; role of co-factors in chain elongation; mechanism of calcium transport, mechanism of stringency regulation in bacteria.

- Clinical Oncology - Professor Genshichiro Fujii: establishment of cell cultures of human tumors; cytotoxicity studies of human leukocytes for autologous tumors; monitoring of immune function of cancer patients on immunotherapy in cancer; testing of immunostimulants in animals; mixed leukocyte cultures.

- Fine Morphology - Professor Kiyoshi Hama: fine structure of the nervous system, including synapses, membranes, and sensory organs; vitamin A metabolism (by autoradiography).

- Genetics - Professor Takeshi Odaka: genetic resistance to leukemia viruses in mice; replication of murine oncornaviruses; interaction between mouse hepatitis virus and leukemia virus; immune response genes in mice.

- Immunology - Professor Akiyoshi Kawamura - seroepidemiology of EB virus-associated tumors; isolation of tumor-specific antigens; studies of lymphocyte receptors; mechanisms of induction of immunologic tolerance; standardization of immunofluorescence techniques; pathogenesis of *Rickettsia tsutsugamushi* infections.

- Infectious Disease - Professor Sugishi Otani: pathogenesis of rabies using immunologic probes; pathogenesis of post-rabies vaccination encephalitis; normal and pathologic porphyrin metabolism in liver; non A-non B hepatitis pathology; mechanisms of action of new antibacterial drugs.

- Molecular Biology - Professor Hisao Uchida: control of DNA synthesis; mechanism of recombinant formation; control of ribosome synthesis; mutagenesis mechanisms.

- Molecular Oncology - Professor Taijiro Matsushima: relationship between mutagenesis and carcinogenesis; mechanism of comutagenic action; metabolic activation of muta-carcinogens; screening of environmental muta-carcinogens; changes in gastric mucosa induced by nitrosamines; suppression of metastasis by protease inhibitors; relationship of antibody formation against poly (ADP-ribose) and systemic lupus erythematosus.

- Oncology - Professor Tadashi Yamamoto: establishment of Rous sarcoma virus tumors in mice and study of virus masking; induction of endogenous tumor viruses with gonadotropic steroids; study of immunopotentiating drugs in the Rous system.

- Organ Transplantation and Physiology - Professor Tsunamasa Inou: experimental organ transplantation; physiology and pathology of tissue rejection; chemotherapy of transplant recipients; histocompatibility testing; organ preservation; artificial organs.

- Parasitology - Professor Hiroshi Tanaka: epidemiology, immunodiagnosis and pathogenesis of filariasis in the cotton rat; epidemiology, immunodiagnosis and intermediate host biology of schistosomiasis; epidemiology, diagnosis and biology of hookworms; experimental chemotherapy of filariasis and schistosomiasis; biology and control of mosquito vectors of filariasis; biology of trombiculid mites and acaroid mites.

- Pathological Pharmacology - Professor Keimei Mashimo: pharmacokinetics and tissue distribution of antibiotics; pharmacometabolism of antibiotics in liver-damaged animals; combined therapy of pseudomonas infections with antibiotics and specific antibody.

- Pathology - Professor Yuzo Aoyama: differentiation of smallpox and chicken pox by electronmicroscopy; pathogenesis of vaccinia in rabbits, including postvaccinal encephalitis; detection of adenovirus in association with epidemic keratoconjunctivitis; distribution of viral antigens in herpes simplex virus and varicella zoster infections of humans.

- Tumor Virus Research - Professor Hiroto Shimojo: genetic analysis of viral oncogenesis with mutants of SV 40 and adenovirus; virological and molecular analysis of malignant transformation with SV 40 and adenovirus; tumor virus effects on macromolecular synthesis of cells.

- Viral Infection - Professor Seijiro Uchida: oncogenicity of BK virus; biology of parainfluenza viruses; immunologic analysis of structural polypeptides of mammalian C-type RNA viruses.

- Virology - Professor Kamesaburo Yoshino: mechanism of virus neutralization: tumorigenicity and teratogenicity of herpes simplex virus; purification of rabies vaccine; mechanism of interferon production; carcinogen-mutagen interactions with DNA.

- Amami Laboratory of Injurious Animals (near Kagoshima) - Professor Hiroshi Tanaka: studies of venomous animals (the habu snake, *Trimeresurus flavoviridis*), endemic diseases (filariasis, strongyloidiasis), and disease vectors in the Amami Islands (southern Kyushu).

- Laboratory of Biological Products - Professor Iwao Kato: products of staphylococcal toxoid; protein A; restriction endonucleases; immunoregulatory alphaglobulin; antibodies to mouse immunoglobulins.

My host at the Institute was Dr. Masanosuke Yoshikawa, a bacterial geneticist working under Professor Iwao Kato. Dr. Yoshikawa's specific work is on R plasmids in enterobacteria, the extrachromasomal genetic material which carries genes for antibiotic resistance. In addition to investigating mechanisms of plasmid intergration, Dr. Yoshikawa is also seeking drugs which "cure" plasmids or uniquely affect plasmid-bearing bacteria; an example is the antibiotic kasugamycin from Dr. Umezawa's Institute of Microbial Chemistry. A recent observation from Dr. Yoshikawa's group is that the organism causing whooping cough, *Bordetella pertussis*, readily mutates to *B. parapertussis* when subjected to antibiotic selective pressure. Immunization against *B. pertussis* offers little protection against *B. parapertussis*, so that the mutant can cause epidemics among vaccinated populations. A recent publication from Dr. Yoshikawa's laboratory, of which he is justly proud, is a simplified method for classifying plasmids based on integrative incompatibility. This uses the principle that related plasmids are not comaintained by a bacterium, and utilizes a special strain of *E. coli* with defined integrated plasmids.

In the Department of Immunology I met with Associate Professor Michio Fujiwara, who is studying immune tolerance in inbred mice. Specifically, he is investigating the source of resistance to tolerance to human gamma globulin (HGG) in the Japanese mouse strain DDD. He has shown that the resistance is mediated by a T cell which lodges preferentially in the spleen and increases in number with age. It is not due to a loss of suppressor T cells, as is the case with the NZB-mouse strain which similarly resists tolerance induction by HGG. DDD mice also differ from NZB mice in their failure to develop autoimmune disease. Dr. Fujiwara has also shown that stimulation of B cells of NZB mice with endotoxin will accelerate the development of their autoimmune anemia.

In the Department of Cell Chemistry, Associate Professor Kohji Egawa discussed a macroglobulin isolated from sera of certain tumor-bearing animals which binds to the terminal galactose on the tumor antigen and makes the tumor antigen immunogenic. A very small inoculum of the macroglobulin-tumor antigen complex protects animals from challenge with that tumor. He also showed that tumor antigen from older tumor cells has a terminal sialic acid residue which makes it nonimmunogenic.

Associate Professor Hiroshi Shibuta of the Department of Viral Infection is studying the biology of parainfluenza viruses. Different strains cause radically different pathology in experimental animals. The host range *in vitro* is altered by adding the protease trypsin to the medium. A recent observation reveals that Sendai-infected cells will activate complement by the alternative pathway in the absence of antibody to the virus. Professor Seijiro Uchida in the same department is studying the molecular aspects of the oncogenic virus BK, looking at deletion mutants involved in different tumor types.

Professor Tyoku Matsuhashi in the Department of Allergology is examining the selective adjuvanticity of the glucose polymer pullulan. This substance, when conjugated with antigen, will selectively block the IgE response in mice while potentiating other classes of antibody. Its mechanism of action is being sought.

KYOTO UNIVERSITY

INTRODUCTION

Kyoto University is the second oldest (founded 1897) national university, located in the most historic of Japan's cities and the seat of its capital for over a thousand years. Approximately 15,000 students are enrolled at its five campuses. Its Faculty of Medicine was founded in 1899 and retains the classic structure, containing 27 departments and a growing number of subdepartments.

Historic contributions of the Department of Microbiology are vital staining of the reticuloendothelial system (K. Kiyono), introduction of tissue culture and the electron microscope to Japan, and discovery of vitamin B-decomposing bacteria (R. Kimura).

The Department of Microbiology recently underwent fission, to yield an Institute of Immunology. Although the younger faculty in this Institute are established and are working in the areas of cellular immunobiology and immunogenetics, a Professor of Immunology has not yet been appointed to replace the famed allergist Dr. Kimishige Ishizaka, who has moved permanently to the U.S. (John Hopkins). The Institute is currently directed by my host, Dr. Yohei Ito, Professor of Microbiology.

The Graduate School of Medicine consists of all the departments in the Faculty of Medicine and, in addition, the Institute for Virus Research, the Chest Disease Research Institute, and the Radiation Biology Research Center. In addition to the Department of Microbiology, I also visited the Institute for Virus Research, which contains nine departments. Founded in 1956, it is the only virus research institute in Japan other than one for plant viruses. I spoke with Dr. Seiichi Matsumoto, Professor of Tumor Virology, who provided me with the Institute's Annual Reports for 1978 and 1979. These reports print about 50 articles or abstracts (in English) out of the approximate 100 annual publications generated by the Institute.

Separate from the Graduate School of Medicine and the medical campus is the Primate Research Institute, a central facility for all of Japan established in 1967. It is located in Inuyama City (150 km from Kyoto) and has a field laboratory on a small island in Kyushu. It contains 11 departments covering physiology, behavior, and physical anthropology as well as small primate production and maintenance. Japanese and other Asiatic macaques are featured.

This report will cover my discussions in the Department of Microbiology and the Institute for Virus Research.

DEPARTMENT OF MICROBIOLOGY

Dr. Ito has rather diverse research interests in tumor virology. He works both with the Shope papilloma virus in rabbits and with the Epstein-Barr (EB) herpes virus of humans.

Currently, he is using the Shope papilloma system for evaluating synthetic retinoids (related to vitamin A) as antitumor drugs. He has found that susceptible tumor cells contain a small glycoprotein (14,000 d) which binds the retinoid and carries it to the nucleus, where it appears to serve a growth regulation function. Resistant tumors lack this retinoid binding protein.

Dr. Ito's interest in EB virus is in the virus induction mechanism. EB virus is one of

the most interesting of the human herpes viruses, known to cause the Burkitt's lymphoma of African children (and thus is the only defined human tumor virus), and the relatively mild disease of infectious mononucleosis in young adults. It is also closely associated in some way with nasopharyngeal carcinoma of older adults. It is known to integrate its genetic material into B lymphocytes, where it can be activated to a productive infection by such agents as bromodeoxyuridine and a variety of compounds known as tumor promoter factors. All known continuous lines of B lymphocytes have integrated EB virus, which appears to be required for lymphoblastic grown in culture.

The variety of diseases caused by EB virus is certainly one of its most interesting features. The age at which it is contracted appears important; in countries where it is endemic, including most of Africa and Asia, antibodies appear almost universally before the age of eight, associated with no clinically defined disease. In Western countries infection is often delayed to age 16 or beyond, and causes the infectious mono syndrome. However, many as yet undefined factors determine if a tumor is induced. One which has been proposed by Dr. Ito is that certain microbial flora may influence virus activation. It was recently observed that n-butyrate will induce EB virus synthesis in cells normally resistant to induction. The phenomenon is quite specific for n-butyrate and does not result from treatment with closely related compounds, such as isobutyrate. Dr. Ito has found that n-butyrate is produced in large quantities by oral bacteria of the fusobacteria group. It is tempting to speculate that the tumors of the oral cavity associated with EB virus (including the Burkitt's lymphoma which begins in the jaw) may be influenced by such microbial factors.

Another way in which microflora might influence tumor development is demonstrated in the plant world. There a form of cancer in plants is known to be induced by a plasmid carried in a common bacterium. Dr. Ito has examined stomach carcinomas (the most common form of cancer in Japan) for associated bacteria. He has found a consistent association (in 22 cases) of a hemolytic group C streptococcus with these tumors, and is now examining the plasmids of these bacteria.

INSTITUTE FOR VIRUS RESEARCH

Dr. Seiichi Matsumoto, although designated as Professor of Tumor Virology, actually works on rabies virus and other CNS associated agents. He heads the Japanese side of the U.S.-Japan Medical Research Cooperation Group for rabies. Although rabies has been absent from Japan for 25 years, and dog quarantine is strictly enforced in Japan as in England, the growing incidence of so-called sylvan rabies (that found in wild animals other than dogs) throughout the world could eventually affect Japan.

Dr. Matsumoto was kind enough to elucidate the SMON syndrome frequently discussed in the Japanese press. Recently a large pharmaceutical house which produced the drug Clioquinol was held liable for the victims of SMON, or sub-acute myelo-optico neuropathy. The drug was used to treat diarrhea, and is still being so used in Europe. Although the mechanism of the disease, which results in blindness and paralysis, is not known, similar neurological lesions can be produced in dogs by the drug given for a prolonged period. A herpes virus, called Inoue virus, was isolated from human victims at the Institute for Virus Research, but its association with the disease is uncertain. Dr. Matsumoto feels that the main problem with the drug in Japan is that it is prescribed to excess and the victims take much more of the drug than is needed, resulting in the severe reaction.

Dr. Matsumoto's recent work with rabies revealed a form of the virus, called

"spikeless," which is produced in cell culture at low pH. The spikeless virion lacks the surface spikes which bind to new host cells, and thus is noninfectious. The spikes appear to be lost by enzymatic mechanisms, perhaps due to insufficient glycosylation. This is the first demonstration of a complete virus made noninfectious by such an environmental factor.

Dr. Toshiki Inada of the Department of Serology and Immunology has made the interesting observation that mouse adenovirus selectively kills or inhibits suppressor T cells. He first realized this when he found that adenovirus-infected mice produce 3 times the number of antibody-forming cells to red cell antigens as normal controls. Subsequently, he observed the mice which recover from adenovirus infections develop autoimmune diseases such as hemolytic anemia. This observation is consistent with the concept of autoimmune diseases in NZB mice being caused by a loss of suppressor T cells, presumably by genetic mechanisms.

Other viruses being studied at the Institute include mouse tumor viruses, influenza virus, measles virus, and bacterial viruses. A small diagnostic center is used for exotic agents that cannot be identified in clinical laboratories, or by the National Institute of Health laboratory. No highly pathogenic agents are used, and there are no facilities above the level of P2 for such studies.

KYUSHU UNIVERSITY

INTRODUCTION

Kyushu University is the third oldest (founded 1911) national university in Japan. It is located in Fukuoka, the largest city on Kyushu, the southernmost of the three main islands. Fukuoka is an industrial city of about one million which offers few tourist attractions other than its elegant new art museum.

The Faculty of Medicine was also established in 1911, incorporating Fukuoka Medical College founded in 1903. Kyushu University also has separate Faculties of Pharmaceutical Science and Dentistry. Biological institutes include the Research Institute of Balneotherapeutics (natural hot spring therapy), located in the spa town of Beppu, and the new Institute for Animal Experiments adjacent to the Medical School.

My visit to the Medical School campus was hosted by Professor Kenji Takeya of the Bacteriology Department and Professor Ryoichi Mori of the Virology Department. In addition, I met briefly with Professor Kikuo Nomoto, head of the new Immunology Department (previously with Professor Takeya), and was shown the very impressive Institute for Animal Experiments. Assistant Professor Masao Mitsuyama acted as a most gracious guide throughout my visit.

DEPARTMENT OF MICROBIOLOGY, SUBDEPARTMENT BACTERIOLOGY

Professor Takeya has a wide range of interests which are directed primarily at understanding nonspecific as well as immune mechanisms which act to control infections. His work on pathogenic intracellular bacteria such as *Mycobacteria* and *Listeria* has led to studies of macrophage function, regulation of hypersensitivity responses, and differential pathogenesis of intracellular parasites in various immunodeficiency states such as nude mice and germ-free mice.

DEPARTMENT OF MICROBIOLOGY, SUBDEPARTMENT VIROLOGY

Professor Mori is interested in viruses associated with neurological diseases such as measles. He currently is studying some unusual membranous structures which develop in cells infected with herpes simplex type 2 (but not type 1) when the cells are treated with inhibitors such as 2-deoxy-D-glucose. He proposes this as a method for distinguishing these 2 virus types, which are difficult to distinguish by other means. Another interesting observation in his laboratory is that low doses of bacterial endotoxin will inhibit the induction of allergic encephalomyelitis in guinea pigs. He has a general interest in the role of cellular immunity and humoral immunity in protection/pathogenesis in viral infections.

DEPARTMENT OF IMMUNOLOGY

Professor Nomoto has not really completed the organization of this new department started this year. His primary interests are in transplantation immunity and immunopotentiating drugs. He is apparently screening a number of derivatives of the immunopotentiator muramic acid dipeptide for a pharmaceutical house in order to find an improved form for therapy of cancer.

INSTITUTE FOR ANIMAL EXPERIMENT

This Institute houses a wide variety of experimental animals and experimental facilities, including germ-free isolators for maintaining genetically nude mice (which also lack the thymus gland) and a small P2 facility for infectious disease work . An extensive facility for specific pathogen-free animals is available as well as facilities for large animals. Few primates are maintained at this facility.

OSAKA UNIVERSITY

INTRODUCTION

The Osaka Medical School was founded in 1869, well before the establishment of the Osaka National University in 1931. Indeed, Osaka was the original site for establishment of Western medical training in Japan in 1838, with assistance of Dutch physicians. The current Faculty of Medicine has three affiliated institutes: Cancer Research, Molecular Genetics, and Higher Nervous Activity. Administratively separate are the Research Institute for Microbial Diseases, established in 1934, and the Institute for Protein Research, established in 1958. Another biological research resource in Osaka is the Faculty of Dentistry, established in 1951, which contains eight departments of basic science research. My visit included the Research Institute for Microbial Diseases, hosted by Dr. Tsunehisa Amano, Professor of Bacteriology at the Medical School and Immunology at the Research Institute, and a meeting with Professor Shozo Kotani, Dean of the Division of Dentistry Research and famed in the world of immunopharmacology for his discovery of muramic acid dipeptide independently of French workers. Dr. Kotani's work will be discussed in a separate article on "Immunopharmacology in Japan."

Included in this report is a description of the Institute for Protein Research, which I was unable to visit.

RESEARCH INSTITUTE FOR MICROBIAL DISEASES

Thirteen basic science departments and one department of clinical research comprise the research section of the Institute. Affiliated are a hospital, infected animal facilities, a culture collection, and a human cell collection of hereditary diseases. The Institute has a total staff of 150, and is located in Suita (a suburb of Osaka near the airport) since it was moved in 1967. The Institute publishes the *Biken (Bacteriology) Journal*, a very prestigious publication.

Following is a summary of research activities in each department (as of 1977, the date of publication of the last brochure):

- Bacteriology and Serology - Professor Toshio Miwatani: *Vibrio parahaemolyticus* toxin; enterotoxins; bacterial cardiotoxins; colonization mechanisms of enteropathogens; rapid clinical diagnosis; role of polyamines in cell growth.

- Immunology - Professor Tsunehisa Amano: structure of antigenic determinants of lyzozyme; O-antigens of *V. parahaemolyticus*, role of antibody in allergy; mechanism of complement lysis of bacteria; *Clostridia* toxinology.

- Preventive Medicine - Professor Konosuke Fukai: architecture of paramyxoviruses and togaviruses, mechanism of dengue haemorrhagic fever; role of cell mediated immunity in myxovirus infections; togavirus infection in mammalian and mosquito cells; high voltage electron microscopy of hydrated biological specimens.

- Experimental Chemotherapy - Professor Junichi Kawamata: antitumor action of interferon and antibiotics; molecular regulation of genetic expression.

- Parasitology and Protozoology - Professor T. Nakabayashi: fine structure of pathogenic protozoa; drug resistance in *Trypanosoma*; antigenic variation in *Trypanosoma*; immune mechanisms in toxoplasmosis and malaria; epidemiology of parasitic diseases imported to Japan, especially malaria.

- Pathology - Professor Shiro Kato: Marek's disease lymphoma cell lines: EB virus-associated human tumors in nude mice; immunoelectronmicroscopy of herpes viruses and pox viruses; morphology of cells chronically infected with herpes viruses.

- Virology - Professor Michiaki Takahashi: live attenuated vaccines of measles virus, rubella virus, mumps virus, influenza virus, and varicella virus; immune mechanisms in varicella; anticancer therapy with mumps virus; mechanisms of tumor induction with adeno viruses and herpes viruses.

- Tumor Viruses - Professor Kumao Toyoshima: mechanisms of malignant transformation with Rous virus and polyoma virus; molecular regulation of retro viruses and papova viruses; genetic control of endogenous virus replication

- Microbial Genetics - Professor Aizo Matsushiro: genetics of phage 80; regulation of genetic transcription and RNA degradation; regulation of testicular germ cell differentiation.

- Animal Virology - Professor Yoshio Okada: mechanism of cell fusion by Sendai virus (discovered by Dr. Okada in 1957); analysis of DNA repair defects in xeroderma pigmentosa cells using cell fusion; cell receptor transfer by fusion methods; use of cell fusion to transfer genes to mammalian cells.

- Tuberculosis I - Professor Junichi Kawamata: isolation of protective components of BCG vaccine; antigenic relationships of mycobacteria; genetic control of diphtheria toxin and tetanus toxin formation; essential structure of tetanus neurotoxin; improvement of tetanus vaccine.

- Tuberculosis II - Professor Mitsuo Hori: new chemotherapy of tuberculosis (streptomyces products); mechanism of drug resistance in mycobacteria; mechanism of immunopotentiation by cord factor glycolipids; identification and classification of mycobacteria.

- Leprology - Professor Tonetaro Ito: methods for cultivation of *Mycobacterium leprae* ; passage of *M. leprae* in nude mice; chemotherapy and chemoprophylaxis of leprosy in nude mice; immunology of leprosy in nude mice.

Perhaps the most exciting discovery at the Institute in recent years[3] is the development of a live attenuated varicella virus vaccine. Varicella, or chicken pox, represents the last major childhood viral disease to be subjected to immunoprophylaxis. Most virologists (including the writer) have assumed that it would be impossible to develop a live vaccine for a herpes virus which would be safe for human use, especially the virus responsible for herpes zoster. (Herpes zoster, the very painful neuritis experienced by adults immunosuppressed by drugs or natural means, is a result of activation of latent varicella virus established in neurones during a childhood episode of chicken pox.) The temperature-sensitive vaccine strain developed by Dr. Takahashi has been under testing since 1972. Initially, it was tested in 74 normal children. When no problems occurred it was tried in steroid-treated (immunosuppressed) nephrotic syndrome patients with no complications. Subsequently, it has been used in over 100 leukemic children in remission (not being treated with cytotoxic drugs and expressing skin test responses to common antigens) with no complications. It should be noted that immunosuppressed children often develop very severe and occasionally lethal varicella infections after contact exposures in hospitals. Testing of the vaccine in the U.S. by the Merck Company may begin soon.

Dr. Takahashi has also developed a varicella skin test antigen which is highly reliable for demonstrating immunity to the virus.

Varicella is a poorly studied virus, and techniques for investigation of chronic latent infections initiated by the wild type or the vaccine strains have yet to be worked out.

Another area of great interest is determining if the use of the vaccine can prevent or ameliorate zoster disease. Dr. Takahashi has had good support from pediatricians in his work, but as yet no oncologists or gerontologists have expressed interest in doing clinical trials with zoster patients.

Another live viral vaccine being studied at the Institute is that for Japanese encephalitis virus vaccine. This vaccine, prepared from neonatal mouse brain, has been in use in Japan for many years. Workers at the Institute have recently developed methods to reduce

[3] It should be noted that Professor Okada's discovery of cell fusion in 1957 has led to the current technology of the hybridoma, permitting large scale production of monoclonal antibodies with numerous research and clinical applications.

the contamination of the vaccine with brain basic protein, the antigen used to induce experimental allergic encephalitis. More stable forms of the vaccine, such as lyophilized preparations which withstand 37°C for 14 weeks, are also being investigated.

INSTITUTE FOR PROTEIN RESEARCH

Although I was unable to visit this Institute, I did acquire a comprehensive brochure describing it. This large, well-equipped Institute was established in 1956, long before the future of proteins in industry was realized. It is currently supported by a fund contributed by industry in addition to funds from the Ministry of Education.

A new eight-storied building (7,873 m) was constructed in Suita City in 1971. There are 41 permanent professional staff, 20 visiting scientists, 15 technical assistants and some 40 graduate students working on various aspects of protein chemistry. Some 40 foreign scientists have been included in the visiting category, approximately half from the U.S.S.R.

The sketches below of the 12 research divisions are abstracted from the 1978 brochure:

- Molecular Biophysics - Professor Y. Kyogoku: infrared spectroscopy, Raman spectroscopy, and nuclear magnetic resonance spectroscopy of protein and protein models; resonance Raman spectra of hemoproteins; structure and properties of phospholipids and biomembranes; specific interactions in nucleic acid bases and nucleic acid-protein systems.

- Protein Crystallography - Professor Masao Kakudo: x-ray analysis of Taka-amylase A, lipase, ferredoxin, etc.; computerization of crystal structure analysis; development of a protein structure data base.

- Organic Chemistry - Professor Yoshiharu Izumi: asymmetric hydrogenation with modified Raney-nickel; catalysis of amino acid racemization; synthesis of biochemical reagents.

- Physical Chemistry - Assistant Professor Toshio Takagi: protein-surfactant interactions; physical characterization of membrane proteins; hydrodynamic properties of model polypeptides; determination of molecular size and shape of proteins; stability of protein configuration.

- Enzymology - Professor Takekazu Horio: functions of chromatin-bound proteins; coupling of electron and proton transport with phosphorylation; methodology of enzyme preparation and activity assay.

- Regulation of Macromolecular Function - Professor Setsuro Fujii: Function and control of serum proteins; biochemistry of tumors and tumor-bearing animals; control of lipid metabolism; roles of tissue proteases in normal and pathological conditions.

- Protein Chemistry - Professor Kozo Narita: structure-function relationships in Taka-amylase A and neurotoxins; ozone modification of tryptophane in proteins; semisynthesis of active enzyme derivatives from chemically modified lysozyme and ribonuclease T_1; analysis of the microenvironment around histidine residues in proteins; posttranslational modifications of proteins.

- Physiology - Professor Ryo Sato: studies on the electron transfer systems of microsomes, structure of microsomal membranes; mechanism of virus-induced cell fusion; role of intracellular filamentous structures in phagocytosis.

- Protein Biosynthesis - Professor Kiyoshi Kurahashi: biosynthesis of oligopeptides; carbohydrate metabolism enzymes; regulation of sporulation and antibiotic production; reaction mechanism of ribosomal GTPase.

- Protein Metabolism - Professor Hachiro Nakagawa: physiological significance of the circadian rhythm of gluconeogenesis in the liver and kidney; sex-linked development of receptors for sex steroids; cooperation of the liver and kidney in nitrogen metabolism; molecular interaction between nucleotide-forming enzymes and contractile proteins.

In addition to these research divisions are two service divisions concerned with improving general protein chemistry methodology and synthesizing biologically active peptides.

NAGOYA UNIVERSITY

Like Osaka University, Nagoya University was established in 1939, long after the founding of its medical school (1871). The School of Medicine has three small associated institutes: closely affiliated are the Cancer Research Institute (1962) and the Research Institute for Germ Free Life (1959). Administratively separate is the Research Institute of Environmental Medicine (1946) which absorbed the Institute of Aviation Medicine (1943). The Environmental Medicine Institute was reported on previously in the ONR Tokyo *Scientific Bulletin 1* (1), (1976).

I attempted to visit the Germ Free Life Institute (established 1959) in addition to the Department of Pathology and Bacteriology, but it was closed due to the retirement of the former Director, Dr. Miyakawa, and the move of the Acting Director, Dr. Iijima, to the post of Dean of the Medical School. However, a colleague of Dr. Iijima's, Dr. Junpei Asai, gave me some indication of previous work in the Institute. He also mentioned that Dr. Miyakawa is directing a large germ free life facility at a pharmaceutical firm in Gifu for studies of carcinogenesis in germ free rats.

DEPARTMENT OF PATHOLOGY

Formerly headed by Dr. Iijima, and now awaiting the appointment of a new chairman, this Department is primarily concerned with comparative aspects of the morphology of the immune system. Dr. Asai has done extensive work in conventional and germ free rodents and chickens, studying spleen and lymph node structure in serial sections and building elegant plastic models of these complex organs. Comparison of the hypoplastic lymphoid organs of germ free animals before and after immunization or endotoxin administration has permitted a good understanding of the ontogenesis of germinal zones, etc. They are now beginning to look at the immune system components of the salamander.

Another area of investigation, by Dr. Hiroshi Nagura, is the relationship of surface charge on particles to phagocytosis. Using elicited peritoneal macrophages and glutaraldehyde-fixed sheep red blood cells, the effect of reduced ionic strength or treatment with polyelectrolytes was observed. Medium of 0.015 ionic strength (10% of

physiologic ionic strength) greatly reduced phagocytosis. Adding a polycation (protamine sulfate) increased phagocytosis, while adding a polyanion (chondroitin sulfate) inhibited phagocytosis. Macrophages naturally demonstrate a lower electrophoretic mobility than nonphagocytic cells, suggesting a lower negative charge density than is present on nonphagocytic cells. Presumably this property promotes attachment of negatively-charged particles to the macrophage surface, helping to overcome electrostatic forces.

DEPARTMENT OF BACTERIOLOGY

Professor Nobuo Kato heads this vigorous group, which might better be termed the Department of Immunology.

Dr. Kato's interest is the immunobiology of the capsular polysaccharide from the bacterium *Klebsiella pneumoniae*, type 1, Kasuya strain. This material, which is now available in a highly purified form, is termed CPS-K. It is a high molecular weight polymannose, linked alpha 1-2. The substance is highly effective as an adjuvant, acting as a polyclonal activator of B lymphocytes. It is also highly effective in the induction of autoimmune disease of all kinds, even in resistant species like the mouse. While it exhibits antiviral activity (presumably as a result of interferon stimulation) it potentiates infections with such intracellular pathogens as salmonella. This is a result of reduced antimicrobial function in macrophages of animals treated with CPS-K. Dr. Kato's laboratory has worked intensively on the immunologic action of this substance for nearly ten years, and they have a great wealth of information; it will be reviewed in depth in a separate report on "Immunopharmacology in Japan," to appear in the ONR Tokyo *Scientific Bulletin*.

Another project in Dr. Kato's laboratory is a study of the frequency of leukocytes in different lymphoid organs which will induce an immune response to histocompatibility antigens. Macrophages and B cells are not immunogenic whereas T lymphocytes are, higher-density T cells being more immunogenic than low-density T cells.

CHIBA UNIVERSITY

Chiba University was founded in 1949, incorporating a number of small local institutions including the Chiba Medical College. Since Chiba is essentially a suburb of Tokyo at this time, the university sits in the shadow of the illustrious Tokyo University. In fact, the famed immunologist Professor Tomio Tada, who "put Chiba on the map," recently transferred to Tokyo University.

Attached to the School of Medicine are the Institute of Pulmonary Cancer Research, the Institute of Epidemiology, and the Brain Research Institute. Administered separately is the Research Institute for Chemobiodynamics. The latter, which pursues enzymology, toxicology, and natural product chemistry, is of substantial size. Unfortunately, my schedule did not permit me to extend my visit beyond the Department of Microbiology.

DEPARTMENT OF MICROBIOLOGY

Professor Tsugio Kuwata was my host. His interests are in the effects of human interferon on tumor cells. He has developed lines of Rous sarcoma virus transformed human embryonic fibroblasts with varying sensitivity to interferon, as well as human cancer-derived cell lines characterized as to interferon sensitivity. He has used these lines to study combined action of anticancer drugs and leukocyte interferon (the same kind used

in U.S. clinical trials from Finland), and has shown additive anticellular effects even with drugs which inhibit the antiviral action of interferon. He also has compared the anticellular effects of fibroblast and leukocyte interferons, and shown more anticellular activity in the fibroblast type. Another interest is the effect of interferons on natural killer cells activity of human blood cells, demonstrating that killer cell activity was enhanced by both types of interferons—in infants and aged persons as well as in normal adults.

Dr. Masaru Taniguchi (along with Dr. Tada) has characterized the suppressor T cell factor with specific suppressor activity obtained from a hybridoma line comprised of a myeloma fused with suppressor-enriched spleen cells. This factor binds to the inducing antigen (KLH) and has I-J determinants. It is a 70,000 dalton protein composed of two chains with a sulfhydryl bond; one chain is coded by immunoglobulin heavy chain genes and the other by I-J region genes. Other classes of T lymphocytes are also being characterized as to surface antigens and secretory products by members of this group. They have all the necessary antisera and equipment including a fluorescent cell sorter.

HOKKAIDO UNIVERSITY

Hokkaido Island's oldest, and most distinguished, university was founded in 1876 in Sapporo as the Sapporo Agricultural College, headed by an American missionary/botanist, Dr. W.S. Clark. It was attached to Tohoku Imperial University as its Agricultural School in 1907, but became an autonomous Imperial university in 1918. The School of Medicine was established the next year, and the affiliated hospital was established in 1921. The affiliated Research Institute for Tuberculosis was established in 1950 and was converted to the Research Institute of Immunological Science in 1974. Schools of Pharmaceutical Sciences and Dentistry were added in 1958 and 1967, respectively. The campus of Hokkaido University is spacious and graced with ancient trees imported from many countries by Dr. Clark.

Professor Hiroo Iida of the Department of Microbiology hosted my visit. A tour of the Institute of Immunological Science was hosted by Professor Kenichi Yamamoto.

DEPARTMENT OF MICROBIOLOGY

Dr. Iida is widely known for his work on botulinus toxin. Surprisingly little is known about this most toxic of bacterial products, produced by the obligate anaerobe *Clostridium botulinum* in food. Recently type E botulism has been observed to be a serious threat to infants, and the reduced use of nitrates in meats may lead to more incidents of botulism.

The toxin is a protein dimer weighing 150,000d. Antiserum to the heavy chain is protective. The toxin kills by blocking neural transmission—sialic acid and a ganglioside is involved in its receptor. Dr. Iida has demonstrated the protective value of antitoxin serum in animals, and his current interests involve the role of phages in toxin production as well as the structure of the toxic moiety. His group has shown that types C and D toxin producers have pseudolysogenic phages of an unusually large size which are responsible for toxin production. The phage DNA can be eliminated easily with many chemicals binding to DNA. Recipients must be free of the phage to become infected. He is planning structural analysis with the aid of monoclonal antibodies which have neutralizing activity.

Dr. Kimura is investigating the properties of *Vibrio haemolyticus* toxins, another cause of food poisoning associated with sea food. There was no opportunity to discuss work in the Bacteriology Department on the antitumor activities of macrophages, lipids of tubercle bacilli, structure of tubercle antigens.

- Serology - Professor Kenichi Yamamoto: mechanism of immunological tolerance induction using intrathymic antigen; genetic analysis of susceptibility to lung granulomas induced by BCG in mice.

- Chemistry - Professor Ichiro Azuma: purification of bacterial constituents with adjuvant and antitumor activity; development of new variants of the synthetic adjuvant MDP, muramic acid dipeptide.

- Biochemistry - Professor Shuichiro Kubo: antigenic structure of phosphorylating enzymes such as adenylate kinase and creatine kinase; structure of trypanosome coat proteins.

- Pathology - Professor Kazuo Morikawa: primary structure of L chains in pathologic human immunoglobulins; function of epithelioid cells; mechanism of contact sensitivity responses; immune responses of allogeneic chimeric mice.

The Institute has the best animal facility for work with specific pathogen free and infectious animals that I encountered in Japan, another inheritance from their previous tuberculosis research. Another feature of the laboratory is its impressive collection of equipment for biochemical analysis.

Starting with 1980, the collected papers from the Institut : (mostly in English) will be published annually. Volume 1, recently printed, contains representative papers from 1974-1978.

TOHOKU UNIVERSITY

Founded in 1907, Tohoku University was the northernmost Imperial university until Hokkaido University was established. Tohoku means northeast in Japanese, and is used to designate that portion of Honshu. The university is located in the bustling city of Sendai, near the Pacific coast. Its College of Medicine was established in 1915. The Research Institute for Tuberculosis and Leprosy was started in 1941. A Dental School was added in 1965. An Institute of Brain Research is another recent addition.

At Tohoku University, I visited the Bacteriology Department of the School of Medicine. My host was Professor Nakao Ishida, who runs the largest (30 professional staff—mostly postgraduate students) and perhaps the most productive of such "one-man" departments I visited. Dr. Ishida is famed in the world of virology for his discovery of the Sendai virus. His career started just after the War with investigations of antibiotics from bacteria, but his interests now span basic and epidemiological aspects of virology, immunology, and cell biology. A testimony to his energy is that during a recent four-year tenure as Dean of Medicine, he built four new large research buildings and continued his research activities.

DEPARTMENT OF BACTERIOLOGY

Sendai virus was discovered by Dr. Ishida in 1952. Initially considered the etiologic agent of a severe infant pneumonitis, it is now recognized as a common contaminant of laboratory mice which may be used for virus isolations (as in the case of the 1952 pneumonitis epidemic). Another name for Sendai virus is hemagglutinating virus of Japan or HVJ--it is often considered the prototype of the paramyxoviruses. Its use for creating hybrid cells via its membrane fusion protein was discovered elsewhere in Japan (see Osaka University Research Institute for Microbial Diseases, Animal Virology Department).

Follow-up on Dr. Ishida's early career in antibiotics is under the direction of Instructor Tokusaburo Ebina. Dr. Ishida isolated the drug neocarzinostatin, an antitumor agent, from *Streptomyces carzinostaticus* in 1965. Because it inhibits DNA synthesis it was originally thought to exert its antitumor action by that means. However, Dr. Ebina has shown the drug inhibits the protein kinase required for phosphorylation of microtubules and share some properties of colchicine. Dr. Ebina had earlier observed that vinblastin induces large "paracrystals" in cells visible in the phase microscope--this vinblastin effect is blocked by neocarzinostatin and colchicine. Neocarzinostatin also inhibits membrane antigen capping induced by hypertonic solutions, a property shared with cytochalasin B. The drug is active on microtubules at very low concentrations (0.02 micrograms/ml) and may prove a useful tool in cell biology.

Recently Dr. Ebina has turned to the study of viral effects on the cytoskeleton, observing that adenovirus and herpes virus will inhibit paracrystal formation.

Assistant Professor Yasushi Ono has recently developed EB virus-induced human lymphoblastoid lines which produce antibody with known activity. Among those he has defined are diphtheria antitoxin and antibody directed to hepatitis type B. This approach to producing immunoglobulins for passive therapy, although not monoclonal, has great clinical potential.

Other virological studies in Professor Ishida's laboratory include epidemiology of parainfluenza viruses (in humans), Japanese encephalitis virus (swine, mosquitoes and humans), and influenza viruses (birds, swine and humans). He has also worked on the agent of Korean hemorrhagic fever (following outbreaks in his laboratory in 1974 and 1978 affecting 13 personnel) and shown that it was established in certain stocks of laboratory rats in Japan (now eliminated) as well as in Japanese wild rodents of the genus *Apodemus*. A disturbing outcome of his recent follow-up on the affected laboratory personnel is that the viremia persists in humans for at least two years. His group has also defined an antibody which detects an antigen associated with non A-non B hepatitis. This antiserum may be used to define the agent of that disease, and is already being used to identify the agent in donated blood. Non A-non B hepatitis is now responsible for hepatitis in about 10% of blood product recipients.

SECTION II

PRIVATE MEDICAL SCHOOLS

KEIO UNIVERSITY

Keio University began in 1858 as a Dutch language school for young men of a noble clan in Edo. Its founder was Yukichi Fukuzawa, who studied Dutch in Nagasaki and Osaka. (Fukuzawa went on to teach himself English and travel to the United States, writing books about his travels describing Western ways.) Keio achieved true university status in 1890. As mentioned in the Introduction, the School of Medicine was established in Tokyo in 1917 by the great microbiologist, Dr. Kitasato. It is the most prestigious private medical school in Japan, and turns away 40 applicants for every one accepted.

Professor Kazuhisa Saito, Chairman of the Department of Microbiology, discussed the research activities of his group.

Lecturer Takushi Tadakuma is looking at triggering of B lymphocytes by haptens conjugated to phospholipids. These materials are tested for their immunogenicity *in vitro*. A hapten density such that the hapten molecules are 35 Å apart gives optimal immune responses, implying that this is the distance between two adjacent receptors or two sites on the same receptor. A fatty acid chain length of 16 on the phospholipid is optimal for immunogenicity. If lipid A (from bacterial endotoxin) is incorporated in the liposomes, the response is greatly amplified (5 to 10 times) *in vitro* and *in vivo*. Another variable affecting immunogenicity of the liposomes is the membrane fluidity, which can be regulated by modulating cholesterol content.

Assistant Professor Hisashi Narimatsu is studying T cell growth factor, a 30,000 d protein produced by T cells, which induces T cell blasts to grow indefinitely in culture. This factor will permit cloning of T cells such that cytotoxic T cells directed against a specific antigen can be produced in large quantities.

Assistant Professor Hiromichi Ishikawa is studying the genetics of hybrid resistance in mouse bone marrow. This phenomenon, where a hybrid rejects cells from the parental line, is thought to be mediated by natural killer cells.

JUNTENDO UNIVERSITY SCHOOL OF MEDICINE

Juntendo is representative of the wave of new private medical schools which have rapidly expanded medical training in Japan in the last 20 years. It is located in central Tokyo (near Tokyo University) in a very modern physical plant.

My host was Dr. Takeshi Yokota, Professor of Bacteriology. Dr. Yokota is well known for his work in cholera, and has recently done definitive studies of bacterial nucleotide cyclases (begun while at the U.S. National Institutes of Health in 1968).

In *Vibrio cholera* he observed that adenyl cyclase deficient mutants were incapable of synthesizing flagellae and lacked adaptive enzymes of various types.

He also studies plasmids in *E. coli* as to their role in enterotoxin synthesis.

Another area under investigation in his laboratory is the role of glucocorticoids and adenyl cyclase in macrophage function. This work is being done by Assistant Professor Ryushi Nozawa.

Dr. Yokota serves as a consultant for a pharmaceutical house in Tokyo which is developing a number of immunomodulatory drugs. He is also personally synthesizing and screening drugs which simulate cyclic AMP as potential antitumor agents.

KITASATO UNIVERSITY SCHOOL OF MEDICINE

This newly established medical school is located in a suburb of Tokyo. It is affiliated with the Kitasato Research Institute in Tokyo, as described in Section III.

My host was Professor Masaya Kawakami of the Molecular Biology Laboratory. He is interested in immunopotentiating components of *Salmonella*, although his main interest is RNA processing in myeloma cells. Together with Assistant Professor Kunie Nakamura, he has developed methods of isolating newly-synthesized RNAs from malignant plasma cells. They have also isolated a factor from myeloma nuclei which stimulates the activity of RNA polymerase II. They hope eventually to isolate messenger RNA specific for mouse IgG in this system.

JIKEI UNIVERSITY SCHOOL OF MEDICINE

Located in central Tokyo, Jikei is among the older private medical schools established well before World War II in its current physical plant.

Professor Isamu Kondo's Department of Microbiology is devoted to the study of the staphylococci. Professor Kondo is particularly interested in the mechanism of action of the exfoliative toxin of *S. aureus*, which causes impetigo in children. Using inbred mice which show a similar response as humans, i.e., demonstrating massive skin necrosis in neonates while developing protective immunity in adults, he has shown that susceptible mouse strains have toxin receptors in the granular layer of the skin. He has also examined relative pathogenicity of several hundred strains of staphylococci for mice by the intravenous route. A curious finding is that mice which recover express no immunity to subsequent challenge with the same or different strains. This observation is intriguing in view of the fact that humans demonstrate a comparable lack of protective immunity following a staph infection.

NIHON UNIVERSITY SCHOOL OF MEDICINE

The Nihon University (sometimes referred to as Nippon University) is among the oldest private universities in Japan, being established in 1889. It is also the largest, I was told, although I was unable to obtain precise figures. The School of Medicine in an outlying district of Tokyo, founded in 1925, is located in modern and elegant facilities, among the best I saw in Japan. My host, Assistant Professor Akira Ishibashi, was justifiably proud of their magnificent new medical library.

The Department of Microbiology is strongly oriented toward nonspecific defense mechanisms in bacterial infections. In particular, they have studied beta-lysin, a serum component lethal for Gram-positive bacteria, and microbicidal action of activated macrophages. Dr. Ishibashi recently purified rabbit Beta-lysin.

Assistant Professor Yamamura is undertaking an elegant study of parenteral infusion of interferon on mouse tumor metastasis. C57BL/6 mice are injected with Lewis lung carcinoma cells and after two weeks, subcutaneous infusion of 80,000 units of L-cell mouse interferon per day is accomplished with the Takezawa catheter, an ingenious device which permits the animal to be unrestrained during treatment. This therapy has no perceptible effect on the primary tumor, but greatly restricts metastasis (nine metastases in the treated vs. over 100 in controls). Unfortunately, the stress of the catherization process is great and has been demonstrated to suppress cell mediated immunity. Dr. Yamamura is looking for a better system.

SECTION III

RESEARCH INSTITUTES

THE NATIONAL INSTITUTE OF HEALTH

The National Institute of Health was founded in 1947 and is supported by the Ministry of Health and Welfare. Established to cope with public health problems after the war, the Institute has concentrated on research on communicable diseases and on assay of biological products and antibiotics. Originally, the Institute was also responsible for research on atomic bomb casualties in Hiroshima and Nagasaki, but that function was abolished in 1975 and transferred to the Radiation Effects Research Foundation. The Central Virus Diagnostic Laboratory and National Serum Reference Bank, under the Institute's Department of Virus Diagnosis and Epidemiology, are located in Murayama about 40 km from Tokyo. A number of viral vaccines are produced in the Murayama facilities. Also attached to the Institute is the Tsukuba Primate Center for Medical Sciences in Tsukuba Science City, Ibaraki Prefecture.

The Institute is charged with: conduct and coordination of research on the causative agents of infectious diseases, their prophylaxis and therapy; control, assay, and testing of vaccines, sera and other biologicals, antibiotics, disinfectants, insecticides, and rodenticides; and production of significant vaccines and sera which are unsuited to commercial-scale production. It is also responsible for coordinating international programs with the World Health Organization.

The Institute publishes *The Japanese Journal of Medical Science and Biology* in English on a bimonthly basis and an annual report in Japanese. The professional staff numbers about 500, over half of whom have doctoral degrees.

My host was Director General Dr. Akira Shishido, formerly head of the Department of Measles Virus. He discussed some aspects of the Japanese immunization programs which I outlined in the Introduction to this monograph.

The Institute is broken down into 17 departments, some of which are mainly concerned with quality control of biologicals:

- Bacteriology I - Dr. Koomi Kanai, Director: Services - identification of enteric bacteria; potency assay of cholera vaccine, typhoid vaccine, and pertussis vaccines; production of plague vaccine; phage typing of typhoid and paratyphoid bacilli; Research projects - mechanisms of shigellosis; *V. cholerae* genetics; group A hemolytic streptococci epidemiology and mechanisms of associated rheumatic fever; pertussis immunogens.

- Bacteriology II - Dr. Tyoko Matsuhashi, Director: Services - purification and mode of action of bacterial and animal toxins; production and control of toxoids, antitoxins and antivenins; serodiagnosis of syphilis and some allergic diseases; control and production of leptospirosis vaccine and antiserum; Research projects - clostridial toxins; principles of toxicology of bacterial toxins and snake venoms; *Treponema pallidum* enzymes and antigens; improvement of leptospirosis vaccine.

- Virology and Rickettsiology - Dr. Akira Oya, Director: Services - scrub typhus: herpesviruses; rabies and other rhabdoviruses, respiratory viruses; arboviruses; Research projects - interaction between Japanese *encephalitis virus and host cells*: JEV epidemiology; rabies subunit structure; influenza epidemiology; biological studies of varicella zoster; development of human diploid cell lines.

- Central Virus Diagnostic Laboratory (Murayama) - Dr. Reisaku Kono, Director: Services - virus reference laboratory for prefectural health institutes and hospital laboratories; preparation and supply of viral antigens and antisera; National and WHO Serum Reference Bank; Research projects - epidemiology of echo virus, coxsackie A virus and rubella virus; intestinal immune mechanisms toward enteroviruses; vertical transmission of rubella in rabbits; studies on acute hemorrhagic conjunctivitis virus (discovered in this laboratory); interferon purification.

- Enteroviruses (Murayama) - No appointed Director: Services - polio vaccine control and safety testing; smallpox vaccine control; Research projects - study of SV 40, BK and oncogenic human adenoviruses; genetics of enteroviruses; molecular aspects of pox viruses; hepatitis viruses; epidemiology of nonbacterial acute gastroenteritis in children.

- Measles - Dr. Akira Shishido, Director: Services - measles vaccine control and safety testing; rubella vaccine control and safety testing; Research projects - studies of neurotropic properties of measles virus; antigenic relatedness of measles, distemper and rinderpest; immunology of mumps virus; mechanism of interferon induction; experimental studies of congenital rubella.

- Tuberculosis - Dr. Tooru Tokunaga, Director: Services - BCG Vaccine control; tuberculin control; identification and classification of mycobacteria; chemotheraphy of tuberculosis; Research projects - mechanism of delayed-type hypersensitivity in tuberculosis; mechanism of cellular immunity in tuberculosis; immunotherapy of cancer with BCG; comparative efficacy of BCG substrains; drug resistance of tubercle bacilli; cultivation of *M. leprae* and *M. lepraemurium* in cell-free culture; pathogenicity of atypical mycobacteria; phage typing of mycobacteria; definition of the active principle of tuberculin; studies on sarcoidosis and Kveim antigen preparation.

- Blood Products - Dr. Junichi Yasuda, Director: Services - testing for biological activity and safety of immunoglobulins; assay of blood products and typing reagents; evaluate heptitis antigen tests; quality assurance for blood and blood products.

- General Biologics Control - Dr. Kiyoto Akama, Director: Services - pyrogen testing; sterility testing; statistical procedures for biological assays; Research projects - Mycoplasma contamination testing; testing of pertussis vaccine and influenza vaccine toxicity; lysozyme as an antigen; bacterial *endotoxins*; histamine-sensitizing action of pertussis vaccines; alumina adjuvants.

- Antibiotics - Dr. Suyehiko Okamoto, Director: Services - screening of antibiotics; chemistry of antibiotics; mycology of antibiotic producing microorganisms; Research projects - isolation of new antibiotics; streptomyces genetics; mode of action of antibiotics; anticancer drug screening; mechanisms of antibiotic synthesis.

- Parasitology - Dr. Shigeo Hayashi, Director: Services - parasite identification; helminth antigen preparation; testing of new antihelmintics and molluscicides; Research projects - fine structure and cytochemistry of *Toxoplasma gondii* and other protozoa; taxonomy of *Anisakidae* and other helminths; epidemiology of clonorchiasis and paragonimiasis; ecology of avian schistosomes; epidemiology and control of filariasis and onchocerciasis; immunodiagnosis of human schistosomiasis.

- Medical Entomology - Dr. Ryosuke Murata, Director: Services - bioassay of insecticides of public health value; distribution of mosquito vectors; Research projects - mechanisms of insecticide resistance; taxonomy of cockroaches and chironomid midges; epidemiology of Japanese encephalitis virus; studies of biologically active substances produced by insects; ecological consequences of pesticide use.

- Veterinary Science - Dr. Kiyoshi Imaizumi, Director: Services - investigations of zoonoses; supervision of vivarium of Institute; testing smallpox vaccine for *Bacillus anthracis*; serodiagnosis of human brucellosis; serotyping of *Listeria monocytogenes*; Research projects - disease control in animal colonies; breeding of experimental animals; guinea pig genetics.

- Biomedical Research on Foods - Dr. Kageaki Aibara: Services - food microbiology; food toxicology: associations of chronic diseases and foods; epidemiology of acute food poisoning; Research projects - metabolism of aflatoxins; assay for N-nitrosamines; toxic products of UV irradiation of oils; microbial testing of gamma-irradiated foods; effect of food on intestinal flora.

- Pathology - Dr. Yasuyuki Egashira, Director: Services - histopathology of vaccine test animals; Research projects - pathogenesis of viral diseases; pathology of allergic and viral encephalitides; pathology of immunological adjuvants; correlation of humoral and cellular immunity.

- Chemistry - Dr. Yuzuru Akamatsu, Director: Services - control of chemical ingredients in vaccines and antibiotics; Research projects - relation between structure and function of biological membranes; enzymatic transformation of biological membranes; regulation of biosynthyesis and assembly of membrane proteins; replication of bacterial chromosomes.

- Dental Research - Dr. Shimpei Araya, Director: Services - epidemiology of dental caries and periodontal disease; Research projects - chemical nature of tooth enamel; characterization of human salivary proteins and their reactions with enamel; remineralization mechanisms; interaction of plaque with enamel; modifications of sucrose as a means of caries prevention.

- Technology Laboratory - Dr. Ryosuke Murata, Director: Services - control of radioisotopes, analytical instruments, and culture media in support of the Institute; Research projects - tritium labeling techniques; heavy metal accumulations in deciduous teeth; chemistry of the mycotoxin fusarenon; EM of phage P22 DNA; gene expression in cell differentiation; standardization of animal sera.

THE NATIONAL CANCER CENTER RESEARCH INSTITUTE

I visited only a very small segment of this large Institute, located in Tokyo, for the

purpose of discussion of the use of immunomodulators in cancer therapy. The details of this discussion, with Dr. Kazuo Nitta, will appear in another report. Here, I would like to mention that the high level of interest in immunopharmacology of cancer that I observed elsewhere in Japan is also found at the Natonal Cancer Center Research Institute. I have the impression that most of the clinical trials of immunomodulators are conducted in the adjacent Clinics. (The overall structure and function of the National Cancer Center of Japan resembles that of the National Cancer Institute in the U.S.).

NATIONAL CENTER FOR BIOLOGICAL SCIENCES

The National Center for Biological Sciences is a facility unique in Japan. Established and primarily supported by the Ministry of Education, Science and Culture, its closest equivalent in the U.S. is the intramural NIH laboratories in Bethesda, Maryland. When completed, the Center will consist of two Institutes: Physiological Sciences and Basic Biology. These two Institutes are administratively separate but physically adjacent to the Institute of Molecular Science, a center for chemistry research. All are located in the small town of Okazaki, essentially a suburb of Nagoya, near the center of Honshu Island. The campus is quite elegant and pleasantly free of the urban congestion which marks so much of modern Japan. Begun in 1977, the Institute for Physiological Sciences is completed, and the Institute for Basic Biology is near completion. While many of the professional staff have permanent appointments, temporary appointments of individuals from Japanese universities and from abroad are common. Dormitory-type housing is available on the campus for temporary staff.

I was graciously received by the President of the Center, Dr. Yasuji Katsuki. His associates showed me around the facilities, which due to construction and rain proved to be quite a muddy operation. The tour permitted little detailed analysis of scientific activities, and I shall simply outline the ongoing programs below. In addition, I might add my overall impressions which are certainly good ones: the laboratories are well designed and supplied with state-of-the-art (and beyond) equipment. Among the facilities are the world's largest visible light spectrometer (a room about 30 feet square), a superconducting magnet-equipped nuclear magnetic resonance spectrometer, and a high voltage electron microscope. The Center is intended to serve the needs of the country with respect to major equipment, serving as a centralized NIH Division of Research Resources.

The Institute for Physiological Sciences (Professor Koji Uchizono, Director General) is composed of five Departments:

- Molecular Physiology, incorporating Laboratories of Ultrastructure Research (Professor Hiroshi Watari) and Cellular Metabolism (adjunct head).

- Cellular Physiology, incorporating Laboratories of Membrane Biology (Professor Shunichi Yamagishi), Correlative Physiology (adjunct head), and Active Transport (adjunct head).

- Information Physiology, incorporating Laboratories of Neural Information (Professor Akimichi Kaneko) and Higher Nervous System (Nakaakira Tsukahara).

- Biological Control Systems, incorporating Laboratories of Neural Control (Professor Hiroshi Irisawa), Humoral Control (adjunct head), and Biomedical Engineering (adjunct head).

- Research Facilities, incorporating Laboratories of Tissue Culture and Histology, Computers, Biofunctions, and High Voltage Electron Microscopy.

The Institute for Basic Biology, still under construction, is composed of three Departments:

- Cell Biology, incorporating Laboratories of Cellular Mechanisms, Cell Reproduction, Cellular Information, Cellular Energetics and Cell Engineering.

- Developmental Biology, incorporating Reproductive Biology, Cell Differentiation, and Morphogenesis.

- Biological Regulation, incorporating Neurobiology, Biological Rhythms, Regulatory Mechanisms, and Neuroethology.

Questions regarding the Basic Biology Institute are best directed to the President of the Center, Dr. Yasuji Katsuki.

INSTITUTE OF MICROBIAL CHEMISTRY

This Institute has the unique quality of being owned by a private individual, Professor Hamao Umezawa. Formerly with Tokyo University, Professor Umezawa (now in his 80s) was the discoverer of such antibiotics as kanamycin, neomycin, and kasugamycin. Over his extraordinarily productive career he has turned from antimicrobials to carcinostatic compounds and now to immunostimulants. His Institute is supported primarily by royalties derived from his many discoveries. Approximately a third of the Institute's activities are currently devoted to isolating yet more antibiotics from streptomyces strains occupying large fermenters in the basement. It would appear from the elegant physical plant and the excellent research facilities for the 30-40 professionals in the Institute that the royalty income is quite adequate.

My visit was hosted by Dr. Masaaki Ishizuka, Senior Researcher in a laboratory investigating the immunostimulatory action of low-molecular weight microbially-derived compounds. These compounds, about 40 in number, have been selected based on their capacity to inhibit proteinases. They are being screened for their antitumor activity; this appears to fall into three distinct classes:

- glyoxalase inhibitors which increase endogenous levels of the growth inhibitor methylglyoxal,

- protease inhibitors which in some way induce resistance to chemical carcinogenesis and metastasis, and

- compounds which inhibit surface proteases potentially involved in immune function.

This latter group is considered to be a category of immunopotentiating compounds which exert anticancer activity by enhancing host defense mechanisms. Two compounds in the immunopotentiating category are diketocoriolin B, a mushroom-derived sesquiterpene which enhances antibody formation, and bestatin, a leucine derivative which enhances delayed hypersensitivity responses and T cell mitogenesis. These drugs have limited antitumor activity when used alone, but appear very promising when used in combination

with carcinostatic drugs like adriamycin. Much enthusiasm was envinced by numerous researchers in Japan about this combined carcinostatic-immunotherapeutic approach to cancer therapy, and immunotherapy in general is considered the wave of the future for cancer treatment.

MITSUBISHI-KASEI INSTITUTE OF LIFE SCIENCES

Located in a suburb of Tokyo, this large, well-appointed Institute is supported entirely by the industrial giant Mitsubishi Chemical Industries Ltd. It is devoted to basic research in a wide range of biological sciences, and I was assured by the Director and my host, Dr. Fujio Egami, that the researchers have a completely free hand as to the direction of their work. The Biosciences Division of the Central Research Laboratories of Mitsubishi Chemical Industries, near Yokohama, is charged with technology transfer of findings made at the Institute of Life Sciences. The Life Sciences Institute was founded in 1971 and completed in 1977. The professional staff numbers about 175. An annual scientific report is published in English.

The basic research arm of the Institute is the Department of General Sciences. Its eleven divisions are as follows:

- Biophysics - Dr. S. Fujima, Director: Study of muscle cells, muscle proteins, and cultured cell membranes by means of photon fluctuation and fluorescence correlation spectroscopy.

- Biological Activities of Biopolymers - Dr. M. Kageyama, Director: Analysis of *Pseudomonas aeruginosa* bacteriocins (proteins which are specifically toxic for other pseudomonas strains) as to structure and mechanism of toxic action.

- Biochemical Reactions and Biocatalysts - Dr. T. Oshima, Director: Study of biochemical adaptation mechanisms of bacteria inhabiting extreme environments, such as thermophiles, psychrophiles and acidophiles.

- Microbiological Chemistry - Dr. K. Sakaguchi, Director: Analysis of *Bacillus subtilis* plasmids and RNA phages; genetic engineering.

- Cell Biology - Dr. T. Miyake, Director: Study of the structure and function of phage nucleic acids; similar study of temperature-sensitive Chinese hamster cell lines; study of *Drosophila melanogaster* cells in culture; study of genetic control of differentiation using T-locus mutants of the mouse.

- Developmental Biology - Dr. Y. Kato, Director: Developmental and biochemical analysis of cell and tissue interactions in echinoderms; control of the cell cycle and cell population kinetics in embryogenesis; molecular biological approaches to the problems of the regulation of expression, maintenance and loss of differentiated traits of animal cells *in vitro* and during development.

- Neurophysiology - Dr. H. Kawamura, Director: Study of the neuronal mechanism of the operant conditioning of vertical eye movements using the intracranial self-stimulation technique; analysis of circadian rhythms and ultradian rhythms sleep-wakefulness rhythms and the role of the suprachiasmatic nucleus; miniature endplate potentials in cockroach muscle fibers; cockroach pheromones.

- Physiological Psychology - Dr. H. Kawamura, Director: An offshoot of the Neurophysiology Laboratory, this group also studies the midpontine pretrigeminal cat preparation; punishment areas in the cat brain; sleep mechanisms in mutant mice with perturbed sleep-waking rhythms.

- Neurochemistry - Dr. T. Amano, Director: Studies of neurotransmitter receptors for acetylcholine, catecholamines, gamma-amino butyric acid and glutamate at the biochemical and biophysical levels; excitable membrane physiology in cultural neuronal and myogenic cells; study of neuromuscular junction formation *in vitro*.

- Pharmacology - to be appointed: Studies of drug action in hypertension, arteriosclerosis and heart failure; drugs from marine sources; excitation and contraction of smooth muscle; prostaglandins and polypetide hormones.

- Biogeochemistry and Sociogeochemistry - Dr. E. Wade, Director: Studies of the distribution of nitrogen and carbon isotopes and their regulating factors in soil, organisms, and fresh water; contributions to soil and water by metabolic processes of microorganisms; chemical ecology.

The Special Research Department has five laboratories with diverse functions:

- Biochemical Preparation - Dr. T. Uchida, Director: Studies of the primary structure of RNase U and superoxide dismutase; enzymatic synthesis of oligonucleotides; search for DNA-degrading enzymes with defined specificities; enzymes secreted by cultured plant callus.

- Organochemical Preparation - Dr. U. Nagai, Director: Studies of the role of D-amino acids in bacterial peptides (Gramicidin S); micromethods for amino acid configuration; peptide conformation analysis via chiroptical properties of their DNP derivatives; stereoselective deuteration of amino acids; structural analysis of insect pheromones and traditional Japanese drugs.

- Social Life Science - Dr. K. Nakamura, Director: Studies of the social and ethical aspects of genetic engineering; the relationship between science and technology and Japanese culture.

- Director's Group - Dr. F. Egami, Director: Studies of chemical evolution in hypothetical primeval sea water; polyamine analogs; selective DNases; asparagusate dehydrogenase.

- Nakashibetsu Serum Preparation Center - Dr. T. Miyake, Director: A support facility located in rural Hokkaido for harvesting and analyzing cell growth factors in fetal calf serum.

KITASATO INSTITUTE

Established in 1914 by the great microbiologist, Professor Shibasaburo Kitasato, the Kitasato Institute in Tokyo is a not-for-profit institution supported by income from its manufacture of drugs and biologicals. Associated with it is a private medical school, Kitasato University (cf. Section II), outside of Tokyo, and paramedical schools of Hygienic Sciences and Nursing. Adjacent to the Institute is the Kitasato Hospital (Western-style), and Research Centers for Oriental Medicine (with clinical facilities) and Veterinary

Science. The Institute consists of a Research Laboratory and a Production Laboratory for biologicals. Kitasato Pharmaceuticals Industry Company, Ltd. was established in 1955 to market the Institute's products.

The research arm of the Institute has a professional staff of about 35 in seven divisions:

- Bacteriology - Cellular immunity of tuberculosis, including transfer factor studies; protective antigen of tubercle bacillus; local immune mechanisms of the intestines; endotoxins; streptococcal mutation mechanisms; Bordatella bacterin in swine atopic rhinitis.

- Virology - Cell origins of interferons; interferon inducers; diagnosis of Epstein-Barr virus induced tumors; EM of viral synthesis; Japanese encephalitis virus markers; characterization of Ibaraki virus; protective antigens of measles virus and rubella virus; influenza subunit vaccines.

- Cancer and Antibiotics - Screening of new antibiotics; biosynthesis of leucomycin and cerulenin; anticancer substances isolated from *Staph. aureus* ; screening of new antifungal agents; classification of the *Actinomycetales*; antibiotic sensitivity of thermophiles, taxonomy of water molds.

- Biochemistry - Mode of action of antibacterial and antitumor agents; peptides and petidases; immunological study of lipids; liposomes in the study of hemolysis; therapeutically effective components of human placentae.

- Serology - Chemical and physical characterization of hepatitis B antigen.

- Pathology - Immunohistological studies on experimental whooping cough; cyto-histological studies on the mode of action of anti-tumor drugs.

- Veterinary Science - Cell mediated immunity in chickens; Newcastle disease virus and avian leukosis agent; rabies vaccines; avian vaccines; fish diseases.

I was unable to acquire information as to individual division heads, but the reader is referred to my host, Dr. Satoshi Makino, Vice President and Chief of the Virology Department as a source of specific contacts.

Dr. Makino discussed some interesting findings on Epstein-Barr virus in Japan. This agent rarely causes clinical infectious mononucleosis or nasopharyngeal cancer in Japan or Taiwan, although over 80% of individuals seroconvert between one-three years of age. An acute exanthematous disease called Isumi disease, resembling measles, occurs in Japanese children, and is thought to be caused by Epstein-Barr. This observation raises some interesting points regarding herpes virus pathogenesis and human genetics.

APPENDIX I

ADDRESSES OF INSTITUTIONS AND PERSONNEL IN THIS REPORT

I. NATIONAL UNIVERSITIES

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APPENDIX II

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IN THE BIOMEDICAL SCIENCES

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ACKNOWLEDGEMENTS

This tour was initiated at the invitation of Dr. Rudolph J. Marcus, Scientific Director of ONR Tokyo at the time of my visit. It was generously supported by funds provided by Dr. Arthur B. Callahan of ONR Headquarters. My Commanding Officer, Commander James Wheeler, and my Director for Science, Dr. George Sandoz, graciously released me from my duties at ONR Chicago for the duration, and the ONR Chicago staff held the fort in my absence.

My stay at ONR Tokyo was made most pleasant and productive by the hospitality and wise counsel of Dr. and Mrs. Marcus, Dr. and Mrs. Leon Fisher, and Ms. Eunice Mohri. Mr. Seikoh Sakiyama arranged my many visits and made it possible to cope with the often inscrutable Japanese train system. The manuscript preparation was borne by Ms. Mayumi Shirakawa and final editing provided by Ms. Mary Lou Moore. Dr. Young B. Kim, Scientific Director of ONR Tokyo at this writing, inspired the completion of the task. Finally, Professor Tadayo Hashimoto, my colleague at Loyola University School of Medicine, guided me in my choice of institutions to be visited and graciously provided me with letters of introduction to most of the department heads I met during the trip.

No acknowledgements can be complete without recognition of the remarkable hospitality of the Japanese people. My numerous hosts, identified herein, always made me feel welcome and gave generously of their time. Even more heartwarming, however, was the kindness of the dozens of people on the streets who guided me gently to my destinations. I am certain that without their help I would still be lost in Tokyo Station.

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Dr. Jeannine A. Majde was born in 1940, received her B.S. degree in zoology from the University of Chicago in 1964 and her Ph.D. degree in microbiology from Notre Dame University in 1970. Postdoctoral training in immunology was undertaken at the University of Chicago from 1970 to 1972. She then joined the Office of Naval Research, Chicago Branch, in 1972 as a contract monitor in the biomedical and oceanic biology areas. She currently consults for numerous ONR program managers in the microbiological and biochemical sciences and serves as Project Officer for Immunology for the ONR Biophysics Program.

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* U. S. GOVERNMENT PRINTING OFFICE : 1981 731-328/2417


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