

# the

# Record

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## Dr. Kety Chosen To Give Lecture Here May 18

Dr. Seymour S. Kety, Chief, Laboratory of Clinical Science, NIMH, will deliver the next in the series of NIH lectures on Wednesday, May 18, at 8:15 p.m. in the CC auditorium.

He is the second NIH scientist so honored since the lecture series was broadened to include NIH staff. Dr. Harry Eagle, Chief of the Laboratory of Cell Biology, NIAID, delivered one of the lecture series last February.

In his forthcoming lecture, "The Biologist Examines the Mind and Behavior," Dr. Kety will discuss achievements in the application of chemistry and physics to the definition, elucidation, and control of mechanisms which determine health and disease, and the relationship of mental and behavioral phenomena to these disciplines.

A native of Philadelphia, Dr. Kety received his medical degree (See DR. KETY, Page 2)



Dr. Kety

## Fletcher to Leave NIH; Will Be 'PR' Director For Division of Merck

John E. Fletcher, Chief, Office of Research Information, OD, and staff assistant to Dr. Shannon, has accepted the position of Director of Public Relations for the Merck Sharp & Dohme Division of Merck & Co., Inc. He will assume his new duties on July 1 in West Point, Pa.

Mr. Fletcher came to NIH in April 1949 as staff consultant to the National Heart Institute. In 1950 he was named Assistant Chief of the Scientific Reports Branch and in 1953 he became chief of that branch. He served in that capacity until 1956 when he was appointed to his present position.

Dr. Shannon says of him, "Important contributions have been made by Mr. Fletcher to the development of better public understanding of medical research and to improved communications among the scientific professions, universities, voluntary health organiza-

(See FLETCHER, Page 2)



Mr. Fletcher

## NIH Director's Office Reorganized; Staff Increased, Scope Broadened

A reorganization of the Office of the Director, NIH, has been approved by Surgeon General Leroy E. Burney.

The announcement explained that the reorganization is designed to provide the added staff capacity required for dealing effectively with the increasing number of complex

problems associated with the administration of NIH program today and in the years immediately ahead.

## Dr. Huebner Elected To Science Academy

Dr. Robert J. Huebner, Chief, Laboratory of Infectious Diseases, NIAID, was one of 35 scientists elected to the National Academy of Sciences at its annual meeting in Washington, D.C., on April 26. He is the seventh from NIH to be so honored.

Dr. Huebner's election to the Academy is in recognition of distinguished and continuing achievement in original research in the field of virology.

Dr. Huebner is widely known for his contributions to the understanding of viruses and their relationship to diseases, and is con-



Dr. Huebner

(See DR. HUEBNER, Page 2)

## NEW EMERGENCY EQUIPMENT, PROCEDURES RECOMMENDED

Following the electrical power failure in this area of Montgomery County on March 29, the NIH Disaster Control Group met to review emergency procedures and make recommendations for more efficient handling of possible future emergencies on the NIH reservation.

The Group, established by the NIH Director in 1956, has the responsibility of developing plans for managing extensive emergencies, including Civil Defense action, taking place at NIH. George P. Morse, Chief, Plant Safety Branch, OAM, is coordinator of the Group.

Although NIH is supplied with two relatively independent sources of PEPCO power, it was apparent on March 29 that they were not true emergency sources. A

minor fault in an up-county power station put too much demand on the remainder of the complex network of power stations, and the alternate feeder lines to NIH were unable to supply the reservation with power.

As a result, critical power was cut off in the CC surgical suite, elevators were stopped between floors, and lights, fire pumps, chemical hood exhaust fans, and many other essential operations were inactivated throughout the reservation.

Although the emergency generator in Bldg. 11 was started immediately, 45 minutes to one hour is required for the necessary warming-up and switching before it becomes operative.

Following a survey made March 31 of conditions existing at the time of the emergency, an ad hoc committee of the group made the following recommendations:

To offset the effect of possible future electrical power shortages, new equipment should be provided in order to maintain the continuity of essential operations.

A 40 kilowatt generator with automatic starting facilities is needed to supply power to the present surgical suite in the CC for essential equipment such as suction, cautery, and extra-corporeal circulation.

The contract for a separate electrical circuit with manual switch-over to be installed in the new

(See EMERGENCY, Page 8)

1. Establish a position of Deputy Director, NIH, with special responsibility for the coordination of policy for extramural programs.

2. Broaden the scope of the Associate Director for Intramural Research and change the title of that position to Director of Laboratories and Clinics.

3. Provide for five top-level staff positions with titles of "Associate Director"—four covering extramural activities (research grants, training, institutional relations, and collaborative research) and working primarily with and through the new Deputy Director; and one for the intramural area of clinical care administration and similarly linked with the Director of Laboratories and Clinics.

Under the reorganization plan, four present offices—Office of Administrative Management, Office of Program Planning, Office of Re-

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# the NIH Record

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## NEWS from PERSONNEL

#### Scientist Administrators

The Recruitment and Placement Section has received and distributed copies of the new Civil Service Examination Announcement for Scientist Administrators. The announcement will be used to fill positions in the extramural programs of the NIH. The grades range from GS-11 through GS-15.

NIH employees who do not have competitive Civil Service status and who are serving in "Executive Secretary" and similar type positions in the programs concerned with research and training grants, awards, and contracts, should consult their personnel assistants for details concerning this announcement. Additional information may be obtained from the Recruitment and Placement Section, Bldg. 1, Rm. 21.

Pamphlets outlining the announcement have been distributed to the Institutes and Divisions, and have also been posted on all official bulletin boards.

#### DR. HUEBNER

(Continued from Page 1)

sultant to the World Health Organization Expert Committee on Virus Research.

A graduate of St. Louis University, Dr. Huebner has been with the Public Health Service since 1942. In addition to his duties at NIH, he is Clinical Assistant Professor in Infectious Diseases in Pediatrics at the Georgetown University School of Medicine and a Visiting Lecturer in Microbiology at Harvard University.

Other NAS members now on the staff at NIH are Drs. Joseph E. Smadel, Charles Armstrong, and Kenneth S. Cole.



Dr. Shannon (right) officially launches this year's U.S. Savings Bond Drive with Dr. F. A. Arnold, Jr., Director, NIDR, Chairman of the 1960 drive. Dr. Arnold urges all employees to give serious thought to bond investment through the payroll-deduction plan.

#### FLETCHER

(Continued from Page 1)

tions, industry and government. The interchange of personnel among these agencies of medical research aids in its advancement and is a long-practiced principle. Mr. Fletcher will undoubtedly make further contributions to this field in his new post."

Mr. Fletcher was born in Takoma Park, Md., but spent most of his early life in State College, Pa. He received his B.A. and M.A. degrees in English literature at Pennsylvania State University.

Prior to his association with NIH, Mr. Fletcher was production manager of Eddie Albert Productions, makers of educational motion pictures. During World War II he served with the Navy as a gunnery and amphibious officer in the Pacific Theatre, participating in numerous assault landings from Tarawa to Okinawa.

Mr. Fletcher plans to leave NIH at the end of May.

## Pakistan Cholera Project Established With NIH Aid

Ten tons of supplies and equipment for a cholera research laboratory were shipped from NIH late in April. The recipient is the Institute of Hygiene at Dacca, East Pakistan.

Establishment of this laboratory is one phase of the cholera research project undertaken by NIH with \$400,000 voted by the SEATO Council for this purpose. The funds come from the President's Fund for Asian Economic Development, a part of Mutual Security Program Appropriations.

The laboratory supplies were selected by DBS personnel. They were crated here, with the equip-

ment, and numbered for proper order of transshipping in Pakistan and installation there. The shipment left New York May 10 on the *SS Explorer*.

James E. Moynihan, Office of the Director, NIAID, will receive the shipment in Chittagong, East Pakistan, and supervise its transportation to Dacca. George R. Elmore, Jr., Sanitary Engineering Branch, DRS, will arrive in Dacca about the time the equipment reaches there and will remain for several months as resident engineer to supervise its installation.

#### Result of Recommendation

Establishment of this project was recommended by a cholera research advisory group headed by Dr. Joseph E. Smadel, NIH Associate Director for Intramural Research. The group, which included five other U.S. scientists, visited the Far East and South Asia last August to develop the project and determine the most effective location.

The project is designed to bring American research scientists into working cooperation in this field with their Asian counterparts. As a result of a series of studies carried out by U.S. scientists the whole concept of how cholera damages and kills has been revolutionized. (See Page 3.)



Dr. Felix

#### DR. KETY

(Continued from Page 1)

at the University of Pennsylvania in 1940 and studied at Harvard University under a National Research Council Fellowship in 1942 and 1943.

He came to NIH in 1951 as Associate Director in Charge of Research, NIMH and NINDB, and was appointed to his present position in 1957. Prior to his association with NIH, he was Professor of Clinical Physiology at the Graduate School of Medicine, University of Pennsylvania.

Dr. Kety's major fields of research interest are cerebral circulation and metabolism, the theory and application of inert gas exchange, and the biological aspects of mental disease.

Among the many honors received by Dr. Kety are the Theobald Smith Award, the Max Weinstein Award, and the DHEW Distinguished Service Award.

Dr. Kety is also a special lecturer at the Department of Neurology, George Washington University Medical School, and is editor-in-chief of the *Journal of Psychiatric Research*.

# Science Section

This four-page section, devoted chiefly to summaries of research findings that have been reported by scientists of the National Institutes of Health, is prepared with the cooperation of the Information Offices of the Institutes and Divisions of the National Institutes of Health.

## U.S.-Thai Research Project Aids Cholera Victims in East

The research that saved lives of cholera victims in Thailand and led to the SEATO (South East Asia Treaty Organization) Cholera Research Project was carried on by scientists of the Army (Walter Reed Army Institute for Research), the Navy (NAMRU 2 in Taiwan), the National Institutes of Health, and Jefferson Medical College, Philadelphia, in collaboration with Thai scientists. This is what they did:

1. Obtained the first detailed quantitative information on water and electrolyte loss in cholera, and developed a simple method for evaluating the degree of dehydration. On the basis of this information, it was possible to determine precisely how much fluid and how much of which electrolytes—sodium, potassium, chloride, bicarbonate—should be given each patient. Heretofore it was known that replacement of fluid and electrolytes was necessary but opinions varied on how to do this most effectively. These findings by Capt. R. R. Phillips, U.S.N., and his associates of the U.S. Naval Medical Research Unit No. 2, with headquarters at Taipei, Taiwan, and their Thai associates, are reported in two NAMRU TWO bulletins and in the *Journal of Clinical Investigation*.

2. Made extensive bacteriologic studies in order to improve laboratory diagnostic tests for use under field conditions and studied various cholera vaccines. This research, by Dr. Ralph Freter and associates of Jefferson Medical College, is continuing and results have not yet been published.

3. Used the Crosby Biopsy Capsule (a device developed at Walter Reed Army Institute of Research by Col. W. L. Crosby, MC) to take tissue from the intestinal tract of living cholera patients for the first time. Studies of the tissue so obtained showed that, contrary to theories held for 50 years or more, there was no sloughing off of the mucous lining of the intestine, but that this lining, although intact, was inflamed. The previous belief that cholera denuded the intestine of its mucous lining is considered due, in part at least, to postmortem changes, since previous studies had been made on autopsy material. The studies with the Crosby capsule were made in Thailand by Capt. E. J. Gangarosa, MC, U.S.A., and associates of Walter Reed Army Institute of Research in collaboration with Thai physicians, and were reported at the meeting

last fall of the American Society of Tropical Medicine and Hygiene.

4. Applied a new test for possible loss of blood plasma proteins from the gastrointestinal tract. This test was devised by Dr. Robert S. Gordon, Jr., of the National Heart Institute. The test is made by injecting into a vein radioactive polyvinylpyrrolidone (PVP), a plasma protein analogue introduced as a blood plasma extender during World War II. The large molecules of this synthetic chemical imitate the natural large molecules of plasma protein. If the lining of the gastrointestinal tract is abnormally permeable to large molecules, as is the case in certain diseases, the molecules will be excreted in abnormal amount. With Dr. Gordon's test, the radioactivity of the feces gives a measure of the amount of large molecules being lost.

Dr. Gordon and two Thai physicians applied this test to cholera patients in Bangkok. The results of the test were essentially normal. This, the scientists believe, indicates that cholera patients do not lose appreciable quantities of

## Behavior Changes Found Following Neonatal Asphyxia

Behavioral changes that may result from lack of oxygen at birth have been described for the first time in a controlled group of young rhesus monkeys. Psychological tests of monkeys partially asphyxiated at birth, and of control animals delivered in a similar manner, indicate that normal animals are more emotional and more responsive to their immediate environment than are asphyxial animals.

The studies were conducted by Miss Sue V. Saxon of the National Institute of Neurological Diseases and Blindness Laboratory of Neuroanatomical Sciences, and the Field Station of Perinatal Physiology, University of Puerto Rico School of Medicine, and reported at a recent meeting of the United Cerebral Palsy Association, San Juan.

Since asphyxiation of newborn monkeys has been shown to produce neurological deficits similar to those found in some human infants, the effects of partial asphyxia on behavior and learning is currently of great interest. Pre-

plasma protein into the stool. Replacing protein is therefore not a necessary part of the treatment of cholera patients.

The results of the test also indicate that there is no extensive destruction of the intestinal lining in cholera. Dr. Gordon and associates are reporting their findings in the *Journal of the Siamese Medical Society*. Development of the test and its clinical application in conditions other than cholera were previously reported by Dr. Gordon in *The Lancet*.



In the shipping and receiving area of Bldg. 13, NIH personnel check a portion of the 10 tons of cholera research lab equipment in preparation for shipment to Dacca, East Pakistan, via New York.

vious studies of guinea pigs, conducted in the NINDB Laboratory of Neuroanatomical Sciences, indicate that nervous system damage can be directly correlated with behavioral changes.

Subjects for the primate study were six rhesus monkeys, asphyxiated by clamping of the placental cord before Caesarian delivery, and five normal controls. The range of asphyxiation times in the experimental group was from 11 to 16 minutes, with a mean time of 14 minutes. When the studies were initiated, all monkeys were between six and ten months of age.

### Behavior Recorded

In the first series of experiments, animals were placed individually in a soundproof chamber for ten minute periods weekly for 15 weeks. Behavior was recorded at ten second intervals and scores were based on the number of times the animal displayed emotionality, locomotion, or contact with any of the five stimulus objects in the chamber. The emotionality score was based on previously determined criteria of emotional behavior such as sucking, convulsive jerking, rocking, and crouching.

Results of this study indicated that the asphyxial subjects locomoted significantly more, tended to contact objects more, and were significantly less emotional than the normal subjects. However, near the end of the series, locomotion scores in normal monkeys increased, and contact scores in the normal group exceeded the experimental. According to the investigator, the greater emotionality in the normal group accounted for these differences, which tended to level off as normal monkeys became adapted to the observational situation.

### Study Followed Up

A follow-up study of the same monkeys at ages 10 to 14 months partially confirmed these assumptions, since no statistically significant differences between groups in frequency of locomotion or in stimulus contact were found. Surprisingly, however, normal animals continued to be more emotional than were the asphyxial animals. In this study, each animal was observed for three minutes four times a day for eight days.

The use of four stimulus conditions, ranging from an empty chamber to a complex condition (a toy bug) did not influence behavior patterns. For all of the conditions, it was found that normal animals locomoted slightly less and contacted the stimulus more often. No one emotional behavior was characteristic of any one animal or group.

In general, Miss Saxon con-

(See ASPHYXIA, Page 4)

# Intensive Cancer Detection Program in Progress Here

Early detection of cancer is of crucial and often vital importance, since the earlier treatment is begun, the greater is the opportunity for cure. The National Cancer Institute has in progress a program of intensive research in cancer diagnosis, with the objective of devising procedures that will reveal the presence of unsuspected early cancers.

On the basis of a combination of ideas and recommendations on this program from the scientific advisors and the staff, it was decided that the areas of research which held the greatest potential for improvement in cancer diagnosis were clinical enzymology, clinical chemistry and biochemistry, clinical immunology, clinical pathology, endocrinology, steroid chemistry, fluorescent microscopy, protein chemistry, tissue culture, and clinical cytology particularly as it related to cellular blood elements.

Enzymes govern the activities of cells and under special circumstances, usually injury or disease, they escape from the cell into the blood stream. In recent years investigators have shown that detection and measurement of characteristic enzymes in the blood may lead to diagnosis of cancer invading bone and of liver cancer. A broad program to identify and measure enzymes in the blood and to correlate the results with cancer growth within the body could form the basis for a useful diagnostic test. Studies are being encouraged along this line in the diagnostic program.

In a like manner the identification, measurement and study of blood proteins and hormone excretion patterns in cancerous and non-

cancerous individuals may provide a basis for improved diagnostic methods. Here again additional research is being encouraged.

It is now becoming quite clear that cancer growth may be profoundly influenced by many factors within the body of the host. Does the body, as it does in bacterial and virus diseases, have natural defenses against cancer? Can these be used to identify and diagnose the disease? Antigen-antibody studies of cancer by means of tissue culture, fluorescent microscopy, and immunologic techniques may reveal whether or not cancer cells have a common antigen not shared by normal cells. If such a cancer specific antigen could be demonstrated the validity of an immunologic approach to cancer diagnosis would be established. More studies of this nature are needed.

Cancer cells can be found circulating in the blood in many cases of the disease. If the true significance of these cells can be determined and understood it may contribute a great deal to many facets of the cancer problem including diagnosis.

The exfoliative cytology technique, which is one of the best detection aids for early cancer in general, has been most widely ap-

## Baby Mice Susceptible To Carcinogenic Stimuli

Increasing realization of the extraordinary susceptibility of baby mice to carcinogenic stimuli is afforded by recent work at the National Cancer Institute. Dr. Roger W. O'Gara, Laboratory of Pathology, and Dr. Margaret G. Kelly, General Medicine Branch, have reported microgram quantities of carcinogenic hydrocarbons introduced subcutaneously into newborn randomly bred Swiss mice produce pulmonary tumors in all of them within 16 weeks.

Similar results have been obtained in two inbred strains of mice with low spontaneous incidence of pulmonary tumors. The number of pulmonary tumors obtained from exposure to the carcinogen on the first day of life is substantially greater than that from the same dose injected at 1, 3, or 6 weeks of age.

In addition to the pulmonary tumors, some mice develop subcutaneous fibrosarcomas. Tumors of the sebaceous glands, adrenal cortex, and liver have appeared, as well as leukemias and lymphosarcomas.

The authors reported their findings to the recent meeting of the American Association for Cancer Research in Chicago.

plied to detection of cervical cancer. Its potential in regard to detection of cancer of other sites, for example, lung, gastric, prostate, etc., has not been completely explored to date. It is now being investigated under the diagnostic research program.

One of the limiting factors to many of the investigations in these proposed areas of research is the time required by present techniques to carry out enzyme determinations, hormone assays, protein determinations, cytologic interpretations, etc. Techniques which will speed up such determinations through automation, electric devices and computers are being developed and supported under the program in order to speed up the search for improved diagnostic methods and procedures.

Diagnostic test development research is complex and difficult and any significant results are likely to take many years to accomplish.

## ASPHYXIA

(Continued from Page 3)

cludes, the activity most characteristic of the animals deprived of oxygen was random or undirected locomotion. In addition, these animals did not appear to be as responsive to or directed by their immediate surroundings as were the normal monkeys.

## Cellular Repolarization Is Believed Caused by Electrical Discharges

Repetitive, self-sustained electrical discharges from brain cells, very similar to those taking place during human epileptic seizures, may be caused by a slow process of cellular repolarization, which occurs after the cell membrane has been excessively depolarized by repeated electrical stimulation.

In an experimental approach to the problem of epilepsy, Dr. Paul Gerin, former guest worker in the Electroencephalography Branch, National Institute of Neurological Diseases and Blindness, systematically analyzed spike patterns elicited by repeated electric stimulation of brain cells. An interpretation of the mechanisms which may cause afterdischarge, that is, self-sustained activity which follows repetitive electrical stimulation, has been published in the *Arch. Ital. Biol.* "Afterdischarge" is very similar to spontaneous seizures recorded from the exposed cortex of epileptic patients, and is often used as a tool for experimental study of epileptic activity.

### Cell Activity Recorded

Electrical stimulation of varying strength, frequency, and duration was applied to the cerebral cortex of adult cats with bipolar silver electrodes. The activity of single cells during and after stimulation was recorded by means of tungsten microelectrodes and by larger electrodes on the surface of the cortex. Of a total of 2,500 afterdischarges elicited, 600 were accompanied by visible spike activity and were recorded on film. Detailed analysis was made of activity in 80 different cortical cells.

Repeated stimulation, Dr. Gerin found, was usually accompanied by progressive and characteristic changes in the size and frequency of spike activity elicited by each electric pulse. When these changes did not occur, the phenomenon of afterdischarge rarely developed. Changes included a tendency for units to discharge repetitively and progressive decreases in the amplitude of spikes until activity sometimes ceased entirely.

When the spike firing ceased entirely, self-sustained electrical activity (afterdischarge) usually occurred, characterized by small, high frequency spikes, which progressively increased in amplitude and decreased in their rate of firing. The self-sustained activity eventually ceased when the spikes returned to the pre-stimulation level of amplitude.

According to Dr. Gerin, spike (See REPOLARIZATION, Page 6)

## CYTOLOGIC TEST FOR UTERINE CANCER Results in Memphis

### Diagnosis

Intraepithelial carcinoma of cervix

	First screening	Second screening
	393 (3.6) 3/	72 (2.2) 3/

Invasive uterine cancer

	373 (3.4) 3/	11 (0.3) 3/
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✓ First screening - 108,000 women  
 3/ Second screening - 33,000 women  
 3/ Case finding rate per 1,000 women

One of the best detection aids for early cancer in general is the exfoliative cytology technique. The chart shows results from the large scale study in Memphis of use of the technique in detecting uterine cancer.



## Carotid Reflexes Control Vigor Of Heart Action

Reflexes originating in the carotid sinus have been shown by National Heart scientists to control the vigor with which the heart's receiving chambers (atria) pump blood into the ventricles. This, in turn, importantly affects ventricular performance and cardiac output.

The carotid sinus has long been known to be sensitive to changes in blood pressure and to initiate nervous reflexes to compensate those changes. However, it was formerly thought that this was accomplished primarily by bringing about changes in peripheral resistance to blood flow and by reflexly changing heart rate. Now studies at the NIH Laboratory of Cardiovascular Physiology have revealed that when arterial pressure falls, the carotid sinus, in addition to reflexly increasing peripheral arteriolar and venous tone and heart rate, also increases the force of atrial contraction.

This is done by diminishing the activity of the vagus nerve (which normally restrains the atrial pulse) while simultaneously increasing the activity of the cardiac sympathetic nerves. Sympathetic stimulation increases the vigor of atrial contraction, presumably by increasing heart levels of catechol amines. These increase the excitability of the atrial muscle fibers and also the synchronization with which they contract.

The increased vigor of atrial contraction pumps more blood into the ventricle, distending it and elongating its muscle fibers more than usual. Since muscle fibers contract more forcefully from longer fiber lengths than from shorter ones (provided that the chemical environment of the fibers is not altered), the result is a more vigorous contraction of the ventricle and hence increased heart output.

The opposite takes place when arterial pressure is high. The carotid sinus reflexly increases vagus activity while decreasing sympathetic activity. This suppresses the atrial pulse, reducing ventricular filling pressure and decreasing heart output.

These reflexes, called the carotid-sympatho-atrial and carotid-vago-atrial reflexes, are held to be of substantial importance in the regulation of the circulation in changing states. They are particularly important at high heart rates, which give the ventricles less time to relax and the atria less time to fill them adequately between pumping strokes. By

## Decay Reduced by Mineral Phosphates

Convincing evidence that dental decay in experimental animals is dramatically reduced by adding certain mineral phosphates to the diet has been accumulated in recent years. This evidence provided a firm foundation for current National Institute of Dental Research clinical studies to assess the inhibitory effects of dicalcium phosphate on human caries. Concurrent with these laboratory and field trials are studies by Dr. F. J. McClure, Chief, Laboratory of Biochemistry, to identify the mode of inhibitory action associated with mineral phosphates.

Reporting in the *Journal of the Indiana State Dental Association*, Dr. McClure has discussed areas of major interest in his studies, particularly the evidence that cariostatic effects of the phosphate minerals occur primarily within the oral cavity rather than via an indirect systemic route. For example, there is evidence that the relative solubility of phosphates is an important factor, i.e., highly insoluble phosphates are consistently noncariostatic, whereas the very soluble forms, particularly sodium and ammonium phosphate are extremely effective.

Further support of this hypothesis was recorded when insoluble dicalcium phosphate proved to be effective only if sodium chloride was present in the diet to serve as a solubilizing agent. In addition, when  $\text{Na}_2\text{HPO}_4$  was given by stomach tube, thereby bypassing the oral cavity, it was not as cariostatic as when consumed as part of the diet.

Just how the cariostatic effects of the phosphate minerals occur remains speculative. However, data gathered to date suggest a direct action of this mineral on oral enamel surfaces and focus increased attention on the chemical reactivity of tooth surfaces. Thus, enamel maturation, brought about through surface mineralization, may alter the caries decalcification process. Paralleling these considerations is the nutrition of the oral flora and their metabolic products which may undergo significant change in the presence of freely available phosphate ions.

causing the atria to deliver more blood to the ventricles more rapidly under these conditions, these reflexes help to maintain the heart output at appropriate levels at high heart rates.

The work leading to the discovery of the carotid-atrial reflexes was done by Drs. Stanley J. Sarnoff, J. P. Gilmore, and J. H. Mitchell. Their findings were reported at the Federation Meetings held at Chicago.

## Greenhouse Provides Stage For Enzyme Action Studies

Utilization of plant materials to elucidate the biosynthetic pathways of various compounds has brought new information about transmethylation, a process which now appears to be important for all forms of life. The study from which this finding resulted is part of a program of research being conducted by National Institute of Mental Health's Laboratory of Cellular Pharmacology, in the greenhouse facility opened on the grounds at NIH in the spring of 1959.

Data reported by Dr. S. Harvey Mudd have established that in the biosynthesis of the alkaloids N-methyltyramine, hordenine, and gramine by cell-free extracts of barley or millet, the methyl group of these compounds is donated by S-adenosylmethionine. Several other compounds which have been suggested in the literature as possible methyl donors are inactive in this system.

These findings were extended in a series of experiments in which it was shown that barley can synthesize S-adenosylmethionine identical to that found in vertebrates, even to the extent of having the same stereochemical configuration about the asymmetric sulfur and  $\alpha$ -carbon atoms. Together, these facts indicate that the predominant pathway of plant transmethylation may lie through S-adenosylmethionine just as it does in vertebrates and microorganisms.

These findings illustrate once again the value of studying fundamental enzymatic mechanisms in

whatever biological material is most convenient, with the assurance that the facts in a given form may well apply to widely divergent species. Although transmethylation is apparently very important for all forms of life, the enzymatic mechanisms at work here are imperfectly understood, and it is hoped that further work with botanical systems may clarify details of the process.

A matter which requires further exploration is suggested by the structural resemblance of two of the particular plant alkaloids studied to the adrenal hormones of mammals and of a third to mammalian serotonin. If the role, as yet unknown, of these compounds in plant metabolism can be elucidated, we may gain thereby an important lead to discovering the role of these neurohormones and of chemically related hallucinogenic materials.

The formation of the alkaloids now being studied is known to be under not only genetic control but under other controls as well, so that the formation occurs in a dramatic outburst at a specific stage of ontogenesis and in restricted types of tissues.

It seems not unlikely that a study of the interplay of the control mechanisms which are at work here will give insight into the important question of how enzyme formation and activity is governed in higher organisms. The genetic, environmental, tissue-spe-

(See GREENHOUSE, Page 6)



Dr. Harvey Mudd (right), Chief, Section on Alkaloid Biosynthesis and Plant Metabolism, and Larry Brown, Biologist, both of NIMH, inspect growth of cacti plants in the NIH greenhouse. The cacti are being raised for a future study.

## Antibody Development Found Allied To Rare Form of Blood Platelets

From studies of a surgical patient of the National Heart Institute who developed a severe bleeding tendency one week after operation, hematologists of the National Institute of Arthritis and Metabolic Diseases have found that there are two distinctly different types of human blood platelets, a common type and a rarer form.

Individuals with the rarer form may develop antibodies against the common type following transfusion, and under certain circumstances as a result of this antibody a patient may destroy his own platelets. The study also provides a clear demonstration that different platelet types exist which are unrelated to red cell types. The significance of this finding with respect to the safety of blood transfusion is not yet fully known.

The discovery of the unusual type of antibody was made by Dr. Raphael Shulman and associates of NIAMD's Metabolic Diseases Branch, and stemmed from blood studies of a patient who developed uncontrollable internal and external bleeding one week after successful heart surgery at the National Heart Institute.

### Blood Platelets Gone

At the time she was bleeding, blood studies revealed that all her blood platelets were gone, and on further study it was found that her blood contained an extremely high level of a circulating antibody which reacted with normal platelets and had presumably destroyed all the platelets in her blood. Because her condition was critical an exchange transfusion was carried out to remove the antiplatelet antibody. Within a 16 hour period, during which 90 percent of the patient's blood volume was replaced, all hemorrhage was stopped, and within several days thereafter her platelet count had returned to normal.

It was after the patient recovered, however, that Dr. Shulman made the peculiar finding which suggested that the woman might have an unusual type of platelet. He took a fresh sample of blood from the patient (a sample containing her newly restored platelets) and mixed it with some of the antibody-containing blood that had been flushed out during the exchange transfusion. Since the antibody was active against normal platelets, it was assumed that it would also be active against the patient's platelets, but no reaction took place.

This finding was corroborated in a second patient (hospitalized at Faulkner Hospital in Boston) with

the same clinical history of hemorrhage one week after transfusion; that is, the platelets of both patients after recovery would not react with the antibody which was present in their blood at the time they were bleeding. This could have been due to some agent in the patients' blood which blocked the attachment of antibody or to the fact that the patients' platelets were different from usual normal platelets.

### Genealogic Studies Made

Genealogic studies by the NIAMD investigators of platelet type in 35 members (covering 4 generations) of the family of one of the patients as well as a general population survey of platelets from 100 randomly selected individuals indicated that the patients indeed had an unusual form of platelets and that this form of platelet is inherited as a recessive trait. Platelet typing was done using the original antibody from the patients.

The unusual form of platelet was not as rare as had been expected for two percent of the population studied proved to have it, indicating that the chances of the usual form of platelets being transfused into an individual with the unusual form is approximately 1 in 50. It is evident that reactions are not caused every time this is done, for it was found that a patient with the rare type could receive as many as 17 transfusions with the common type without provoking antibody. In addition, there are only two other cases in the medical literature which might have had the same complication.

### Donor Also Unusual

The NIAMD hematologic studies suggest that in order to develop an antibody and have the antibody destroy an individual's own platelets, the donor of the common type of platelets might have to be unusual also. It appears that some individuals with the common type platelet may very rarely have some of the antigen substance from their platelets free in their blood. This free substance transferred into a patient with the uncommon form of platelet may not only be necessary in order to provoke antibodies in the recipient but also may be necessary to coat the recipient's platelets and thus permit antibody to react, leading to lysis of platelets and possible severe hemorrhage.

The studies were reported to the American Society for Clinical Investigation at Atlantic City by Drs. N. R. Shulman, R. Aster, A. Leitner, and M. Hiller.

## Triglyceride Synthesis Mechanisms Similar In Adipose Tissue, Liver

Recent studies by the Section on Metabolism of the Laboratory of Cellular Physiology and Metabolism, National Heart Institute, have explored the mechanisms whereby fatty acids are stored in the body's lipid depot as triglyceride esters (neutral fat) or are released from these depots as unesterified fatty acids (UFA) to meet the body's energy requirements. The studies revealed that the metabolic pathway for triglyceride synthesis in adipose tissue is similar to that previously reported by others for triglyceride synthesis in liver. The studies also suggested that UFA release from adipose tissue may be importantly influenced by factors affecting the rate of triglyceride synthesis, and that hormonal control of UFA release may be exerted at some stage of esterification process.

### Palmitic Acid Used

In these studies Drs. Daniel Steinberg, Martha Vaughan, and Simeon Margolis, of the Laboratory of Cellular Physiology and Metabolism, and Dr. Arthur Karmen, of the Laboratory of Technical Development, used palmitic acid tagged with radioactive carbon to measure the incorporation of this fatty acid into triglyceride and other neutral fat in rat epididymal bodies. These fat bodies from the rat testis were ground up and the homogenized extract divided into two portions. One portion was then fortified with substrates known to favor triglyceride synthesis; the other, unfortified, served as the control. The incorporation of the radioactive palmitic acid into neutral fat esters was found to occur only in the fortified extracts, and was almost exclusively in the form of diglycerides and triglycerides. This indicated that diglyceride formation was an intermediate step in triglyceride synthesis. Having started with known substrates in the fortified tissue, the scientists were also able to determine the probable biochemical steps of the esterification process. The mechanism was found to be very similar to that previously reported by others to operate in triglyceride synthesis in liver.

Triglycerides, the form in which most fats are stored in the body, are neutral esters formed by the combination of three molecules of fatty acid with one molecule of glycerol. However, under the biochemical conditions of the body, this combination cannot occur directly. Instead, the fatty acid is first combined with an enzyme

## REPOLARIZATION

(Continued from Page 4)

changes during and after stimulation may be ascribed to changes in polarization levels in the cell membrane. Thus, during repeated stimulation, recovery of the resting polarity level cannot occur, and a progressive depolarization of the membrane results. When this depolarization exceeds a critical level, firing stops, and during the process of cell repolarization self-sustained activity develops. Although conducted on an experimental level, these studies suggest that this unusually slow process of repolarization might be the characteristic feature of "epileptic" neurons.

Dr. Gerin is now working in the Laboratory of Electroencephalography, Hôpital Ed. Herriot, Lyon, France.

## GREENHOUSE

(Continued from Page 5)

cific, and hormonal factors cooperating in this system are undoubtedly complex, but it is hoped that the relative ease of experimental control of the plant will aid considerably in work on this question. Dr. Mudd's findings are reported in *Biochimica et Biophysica Acta*.

(coenzyme A); two of these combined molecules (fatty acyl-CoA) can then react with one molecule of the glycerol phosphate, yielding a diglyceride and regenerating coenzyme A. The third molecule of fatty acid is then combined with the diglyceride to yield the triglyceride, coenzyme A once again serving as the "carrier." The energy required to make these reactions go is afforded by ATP, a high energy phosphate compound which drives most of the body's energy-requiring processes. The triglyceride thus formed can in turn be broken down to yield three molecules of unesterified fatty acid, a major metabolic fuel during the fasting state.

Studying the effects of triglyceride synthesis of UFA release, the scientists found that under biochemical conditions favoring triglyceride synthesis (e.g., in the fortified extract), there was a net uptake of UFA by the system. In the unfortified extract, however, there was a net release of UFA. This suggests that UFA release may be strongly affected by the rate of triglyceride synthesis, perhaps even dependent upon it; thus hormonal control over UFA release may be exerted over one or more of the steps of the esterification process.

These findings were presented at the meeting of the Federation of American Societies for Experimental Biology.

# FROM '35 TO '38

## How "The Reservation" Came to Be

### Part II of Two Parts

The initial installment of this two-part feature appeared in the preceding (April 26) issue. Chief source of information was a copy of the authentic report written in May of 1938 by Dr. L. R. Thompson who was Director of NIH when it transferred to its present location. Dr. Thompson's historical narrative is among the documents sealed in the cornerstone of the NIH Administration Building.

**DR. THOMPSON** notes that, "After Mr. Wilson made his decision to give the property to the National Institute of Health, he and Mrs. Wilson and their son Luke became intensely interested in the project and the general scientific work of the Institute."

It was then, as news of the proposed gift became known, that local opposition developed. "The Bethesda Chamber of Commerce passed resolutions against it, the County Commissioners did the same, and finally the Maryland Park and Planning Commission voiced its disapproval."

#### Residents Opposed

A number of residents and a few business men were also opposed, but "a few influential men were friends of the project." Among these were "Canon Peter who lived directly to the south of the land, and Mr. Gilbert Grosvenor, the editor of the National Geographic Magazine," whose property lay to the north.

At this juncture the Social Security Act was passed by Congress, providing a sudden increase in funds for research. As a result, Dr. Thompson "conceived the idea of rebuilding the National Institute of Health at Bethesda." He observes that, "The idea came at a fortunate time as the Navy Hospital was considering a great expansion of their hospital and Medical Center, and our new buildings at 25th and E Streets fitted nicely into their plans."

#### Appropriation Authorized

This proposal was quickly approved by the President and other Administration officials, and an appropriation was authorized for "the construction of three new buildings which were to house the new work of the National Institute of Health."

But the sailing was not yet smooth. "Although the authorization had been obtained, there seemed little chance of obtaining the funds, as Dr. Cumming, the Surgeon General, considered other building programs of the Service of more importance."

Soon afterward, however, Dr. Cumming retired. Fortunately for the success of the project he was succeeded by Dr. Thomas Parran. Dr. Thompson's narrative continues:

"Dr. Parran was greatly interested in the research work of the Service and immediately placed the building program of the National



The portrait of Luke I. Wilson, reproduced here, was painted some years before his death in 1937. Owned by the late Mrs. Wilson, the oil painting occupied a place of prominence in the living room of her home on the NIH reservation.

Institute of Health at the head of the Service construction program. As he was a personal friend of the President and of the Secretary of the Treasury, he prevailed on them to have funds made available in the sum of \$1,363,000 to begin construction. On January 1, 1938, he dug the first shovel-full of earth for the three authorized buildings."

This marked the beginning of construction for the new home of NIH. Even then, however, events moved swiftly, pointing toward the tremendous expansion yet to come.

#### Cancer Program Studied

Dr. Thompson reports that Congress meanwhile had become interested in the possibility of a national program looking toward the control of cancer and had made inquiries of the Surgeon General concerning the essentials of such a program.

Following a series of conferences with outstanding authorities in this field, a program was formulated and presented to Congress by the Surgeon General.

A bill authorizing \$750,000 for the construction of the National Cancer Institute and \$700,000 annually for the work of the Institute was then introduced in both the House and the Senate.

Dr. Thompson comments: "It



Dr. Lewis R. Thompson, Director of NIH from February 1937 to January 1942, was subsequently the first Chief of the Bureau of State Services, PHS. He served in that capacity until retirement in 1947 at the age of 71. Dr. Thompson died in 1954. This is a photograph of his portrait, which hangs in Wilson Hall.

was my privilege, under the direction of the Surgeon General, to have written the bill and also the report of the House committee on the bill."

He also calls attention to the interesting fact that, "The Senate bill when introduced had the names of every one of the 96 Senators as co-authors," and adds, "So far as I know, this is the only bill up to this date that has had such an honor."

The bill was passed in both Houses of Congress by unanimous vote. As soon as it had been signed into law, Dr. Parran called on the President "and by rearranging the building program of the Service secured the necessary funds for the building of the Cancer Institute."

This development was eminently appropriate and most gratifying to Mr. Wilson and the members of

## Tissue Disease Theme Of Dr. Black's Talk

Dr. Roger L. Black, Assistant Chief of the Arthritis and Rheumatism Branch, NIAMD, was selected to speak on "Connective Tissue Diseases: Current Concepts and Treatments," at the 11th annual meeting of the Northern Virginia Clinical Assembly. The assembly was held at the Wakefield High School auditorium, Arlington, Va., on April 3.

his family, for, "Early in 1937," the Thompson narrative states, "Mr. Wilson was found to be suffering from cancer of the bladder, and he died in June of that year, just three days before the Cancer Institute bill was passed by Congress. Knowing his condition, he was greatly interested in my reports to him on the progress of the bill."

Dr. Thompson records that on the Sunday following Mr. Wilson's death, "Mrs. Wilson and Luke W. Wilson, his son, offered me, as the Director of the National Institute of Health, additional ground on their property at Bethesda as a site for the Cancer Institute, with other land which could eventually be used as quarters for officers stationed at the Institute. The deed for this land is being signed by Mrs. Wilson during this month of May 1938."—E. K. S.



On June 30, 1938, Secretary of the Treasury Henry Morgenthau laid the cornerstone of Building 1. Looking on were Mrs. Luke I. Wilson and PHS Surgeon General Thomas Parran.

## REORGANIZATION

(Continued from Page 1)

search Information, and Office of International Medical Research Activities—will continue as component parts of the Office of the Director NIH.

The new positions, titles, and relationships are indicated in the accompanying chart.

The Deputy Director will serve as the NIH Director's principal assistant and advisor for the extramural programs of NIH. These programs are of major policy concern to the Surgeon General, the Secretary, and the Congress, representing some 80 percent of NIH's total annual appropriations. The Deputy Director will also act for the Director, NIH, in the Director's absence.

### To Advise on Policy

The Director of Laboratories and Clinics will be the NIH Director's principal policy assistant and advisor on all intramural programs, including certain direct operations in field installations not previously receiving policy and program review by the Associate Director for Intramural Research.

With regard to these two positions, Dr. Shannon points out that although Directors of Institutes and Divisions will normally consult with and work through the Deputy Director and the Director of Laboratories and Clinics, they will continue to have direct access to the NIH Director on questions of over-all or basic policy.

Each of the five Associate Directors will have staff responsibility for discrete functional areas as indicated by their titles.

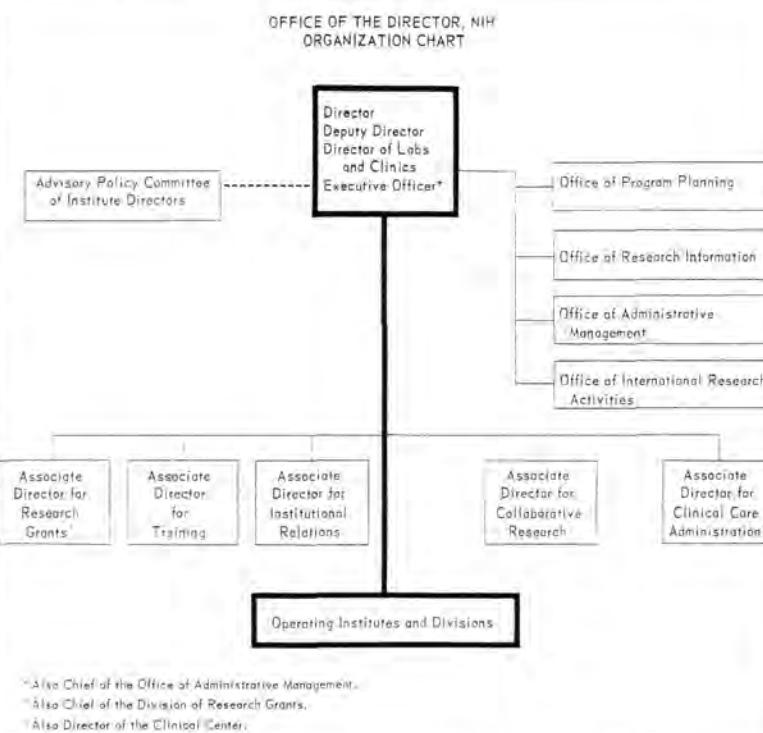
### Assume New Titles

In the case of two of these—the Associate Director for Research Grants and the Associate Director for Clinical Care Administration—the incumbents of the present positions of Chief, DRG (Dr. Ernest M. Allen), and Clinical Center Director (Dr. Jack Masur), will succeed to the new titles.

Both Dr. Allen and Dr. Masur will continue to have operating responsibility for the divisions they head, as well as staff responsibility within the Office of the Director, NIH.

The three other Associate Director positions will involve new appointments.

The Associate Director for Training will have staff responsibilities for a segment of the NIH extramural program which this year reached a level of \$90 million and, in Dr. Shannon's words, "represents, from a policy point of view, one of the most significant aspects of NIH activity in terms of the future capacity of the United States to broaden and in-



tensify its medical research efforts."

The Associate Director for Institutional Relations will assist in the evolution of policy in NIH's relationships with educational and research institutions as such (as distinguished from individual investigators or departments) and recognizes the impact of the extensive development of NIH programs on such institutions.

The Associate Director for Collaborative Research will serve in the program areas represented by the cancer chemotherapy, psychopharmacology, and perinatal studies—fields which constitute a major segment of the total NIH research support and represent some of NIH's most sensitive problems in outside relationships.

Commenting to a *Record* reporter on the new plan of organization for his immediate office, Dr. Shannon said, "We are indeed fortunate to have Dr. David E. Price return to us after an absence of eight years, during which time he has served as Assistant Surgeon General in the Office of the Surgeon General and, more recently, as Chief of the Bureau of State Services.

"Dr. Price, as Deputy Director, will be a tremendous asset to my office. I am delighted, too, to recognize the contributions of Dr. Masur and Dr. Allen by according them the new title of Associate Director.

"I am sure that as the remaining staff vacancies in my office are filled and become operative and as the top staffs of the Institutes and Divisions are similarly strengthened, the result will be the more effective total functioning of NIH as we face the challenging years ahead."

## Dr. Freund Dies Here; Famed Immunologist

Dr. Jules Freund, 69, Chief of the Laboratory of Immunology, NIAID, died of cancer April 22 in the Clinical Center.

An internationally known immunologist, he won the Albert Lasker award last year for his achievements in medical research. (See *NIH Record*, Vol. XI, No. 22, pp. 4 and 7.)

Dr. Freund was a pioneer in modern immunology research and was noted for his work on adjuvants increasing the protective value of vaccines.

He also made significant contributions concerning the little-understood mechanisms of allergy. His work has provided methods used routinely in basic laboratory research by immunologists throughout the world today.

Hungarian born, Dr. Freund received his M.D. degree and Certificate of Public Health from the Royal University Medical School in Budapest.

### Was in Austrian Army

After service as a medical officer in the Austrian army during World War I, he was a faculty member of the Royal University Medical School. In 1923 he came to the United States where he continued his research and taught at the Henry Phipps Institute in Philadelphia and at Cornell University.

Before joining NIH in 1957, he was Chief of the Division of Applied Immunology of the Public Health Research Institute in New York City.

Dr. Freund was Vice-President of the American Association of Immunology in 1954, and President in 1955. He was Chairman of the Federation of American Societies for Experimental Biology in 1956 and 1957.

He is survived by his wife, Elizabeth; a son, Dr. Thomas Freund, a physicist, of La Jolla, Calif.; and two grandchildren.

train the staff and familiarize employees with procedures. Building and floor wardens are instructed and empowered to assume control of hazardous situations of any kind until the arrival of emergency personnel.

New instructions for employee action in the case of an electrical failure emergency will be issued shortly. Each employee should retain a copy and familiarize himself with the directions.

Drills are held at intervals to