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PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

President's Criteria Used by Councils In Making Grants

Measures to ensure compliance with President Eisenhower's criteria for research grants were employed during the latest series of National Advisory Council meetings which ended November 25.

The new administrative procedures were developed by DHEW Secretary Flemming and Surgeon General Burney, with the assistance of an inter-Council Committee appointed by the Councils.

Will Test Procedures

The new procedures will guide administration of the grants programs throughout fiscal year 1960. Modifications, if necessary, will depend upon how the new procedures work out in the remainder of the fiscal year.

The President, in expressing concern over the fourfold increase in NIH funds during the last six years, called for continued high standards of review for each new research and training application. He enumerated a three-point criterion for review when signing the DHEW appropriations bill for this fiscal year:

Projects should be of high priority.
(See CRITERIA, Page 2)

Judson Hardy Named Public Affairs Officer For New BSS Division

Judson Hardy, Clinical Center Information Officer, has accepted an appointment as Public Affairs Officer of the Division of Radiological Health, Bureau of State Services, PHS. He assumed his new duties November 27.

Mr. Hardy has been well known on the NIH reservation since 1942. During World War II, when he was Chief of Technical Aids for the VD Division of PHS, he was stationed in T-6, one of the few buildings on the reservation at that time. He became acquainted with NIH and its work, which then consisted principally of infectious disease, nutritional, and pathophysiology research, and the just-established Cancer Institute.

In 1948 he transferred to NIH as Information Officer and developed an information and public relations program which anticipated

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Mr. Hardy

U.S.A., Soviet Agree on Expansion Of Medical Exchange Program; NIH Plans to Participate

An agreement signed November 23 between the Ministry of Health, U.S.S.R., and the U. S. Public Health Service provides for an expansion of the medical exchange program between the two nations.

During the recent visit of Premier Khrushchev to the U. S., proposals for the new agreement were discussed by

Dr. Leroy E. Burney, PHS Surgeon General, members of his staff and of the Department of State; and Dr. A. M. Markov, Professor and Member of the Collegium of the Ministry of Health, and Dr. V. M. Butrov, Ministry of Foreign Affairs, both of the U.S.S.R.

This meeting was a part of the general discussions on exchange missions undertaken between G. A. Zhukov, Chairman of the Soviet State Committee for Cultural Relations with Foreign Countries, and William S. B. Lacy, Special Assistant, East-West Exchange, U. S. Department of State.

NIH Is Included

A number of groups of scientists have already been exchanged between the U. S. and the U.S.S.R. under the January 27, 1959 (Lacy-Zaroubin) agreement.

The new agreement provides for cooperation between various Soviet and American scientific institutions, including NCI, NHI, and DBS, on studies of the problems of cancer, cardiovascular illnesses, poliomyelitis, and other important problems of medicine.

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CP Review Goes to DRG

The Cerebral Palsy Review Committee, formerly of NINDB, has been abolished.

The responsibility for review of the collaborative projects has been transferred to DRG's Human Embryology and Development Study Section, headed by Dr. Samuel Moss.

He's Universal Type

Cedric the Boxer Wins Fame

Not all the claimants to fame at NIH are of the genus *Homo sapiens*. Now comes Cedric, of the taxonomic category *Canis familiaris*—and only six years old, at that.

Cedric, in common parlance, is a boxer dog—one of the many dogs and other varieties of animals that play an important part in medical research conducted at NIH.

But even in such distinguished company Cedric is outstanding. Nominated by NIH as its candidate for the "research dog hero of the year" award, Cedric is one of eight throughout the country to receive a certificate of honorable

mention. First prize went to a Brooklyn dog reportedly named Ruff.

The awards were established by the National Society for Medical Research, Chicago, as a part of its program to explain animal research and promote understanding of professional ethics governing the care of animals in most research institutions today.

Cedric's award was based upon

(See CEDRIC, Page 2)

The organizations are encouraged to exchange plans of scientific research work and information about research conducted, to organize joint scientific studies, to exchange specialists, and to participate in yearly joint scientific meetings alternately in the U. S. and the U.S.S.R.

In 1960 such meetings will be held at NIH, the Sloan-Kettering

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the NIH Record

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CEDRIC

(Continued from Page 1)

his record as a canine blood donor. One of several at NIH, he is considered to be "head and tail," one might say, above his fellows.

Cedric's blood is of the canine universal type, A-negative. And as with humans, the universal-type donor is much in demand. During his three years at NIH, Cedric has donated dozens of pints of blood to other dogs undergoing experimental surgery, and is none the worse.

From the point of view of boxer breeders, Cedric is unfortunate because he is white rather than tan. But within the Animal Hospital, Lab Aids Branch, DRS, he is rated tops.

"Cedric is also quite a ham," says Dr. William Gay, Chief of the Animal Hospital, "and he shares with a cat named Thomas the honor of being the hospital mascot."

CEDRIC and FRIEND



Tiny has reason to feel indebted to Cedric. She is one of the many dogs in the NIH Animal Hospital whose blood has been replenished by Cedric's donations of A-negative, the canine universal type.

HARDY

(Continued from Page 1)

the rapid expansion of the Institutes. His plans also set the patterns of organization and general policy for the present NIH information programs.

In the spring of 1953 Mr. Hardy became Information Officer for the Clinical Center during final stages of the building's construction.

In his new position, he will work with other Federal agencies, State governments, industries, and civic organizations to disseminate information and gain public awareness and acceptance of the newest of the public health problems, that of radiological health.

Since many of the research aspects of radiological health will be carried out by NIH or through the NIH grants procedures, Mr. Hardy expects to maintain close relationship with the staff here.

Prior to his departure from NIH, Mr. Hardy was feted at parties in Top Cottage and in the Officers Club, NNMC.

HAPPY BIRTHDAY, DOCTOR VAN!



December 1 was Dr. Van's Day, as Dr. C. J. Van Slyke, NIH Deputy Director, was guest of honor on his 59th birthday at a party in Wilson Hall, attended by his many friends from within DHEW and its Bureaus. Posed here with Dr. Van Slyke (left) are Dr. James A. Shannon, NIH Director (right), and Dr. Rolla E. Dyer, former NIH Director and long-time friend and associate of Dr. Van Slyke, who later that evening attended the ninth of the Annual Dyer Lectures, established in his honor. Later that evening, also, Dr. Van's daughter, Beverly (Mrs. Charles Mitchell), presented him with a granddaughter, her first-born.

EXCHANGE

(Continued from Page 1)

Institute, and the Institute for the Study of Poliomyelitis, AMS, U.S.S.R.

Provisions are made for the exchange of high-level specialists and junior scientific workers to conduct research or to exchange experience. In addition, five delegations will be exchanged for a period of 3-4 weeks each to study a variety of subjects.

Each country will facilitate the publication of research findings by scientists of the other country, and develop an exchange of medical journals, books, and medical films between Soviet and American libraries and institutions.

It is further agreed that the World Health Organization will be informed of the activities carried out under this Agreement.

The program was negotiated in Moscow by a committee directed by Dr. Fred Merrill, Chief of East-West Contacts, U. S. Department of State. As a member of this team, Dr. Van Zyle Hyde, Assistant to the Surgeon General for International Health, PHS, arranged details of the medical exchange programs.

Dr. James M. Hundley, Special Assistant on International Affairs, and Dr. Michael B. Shimkin, Chief, Biometry Branch, NCI, participated in the meetings with Drs. Markov and Butrov.

Prior to Dr. Hyde's trip to Mos-

CRITERIA

(Continued from Page 1)

ority and promise, should not harmfully divert manpower and resources from teaching and medical care, and should not bring about substitution of Federal for non-Federal sources of support of medical research and training.

Among the new measures undertaken to assure compliance with the President's directive were:

- Study Sections and staffs of NIH identified certain projects to receive special attention of the Advisory Councils over and above the review normally given.

- Each institution receiving NIH funds was asked to assess the effect of these funds on the availability and distribution of manpower and other resources.

- Individual scientists who received grants in 1950, 1954, 1958, and 1960 are to be asked to supply detailed information on the use of their time before and after receiving a grant.

- Institutions will be encouraged to make an assessment of the effect of NIH funds on the availability of private support for their teaching, research, medical care, and other responsibilities.

cow, further details of the proposals were worked out with him by Dr. James A. Shannon, NIH Director, and members of his staff.

Science Section

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

Committee on Primates Replaces and Expands One on Rhesus Monkeys

The National Advisory Committee on Primates, now formally established in the Division of Research Grants, replaces and expands the functions of the National Advisory Committee on Rhesus Monkey Requirements.

The renamed Committee functions as a study section to review and evaluate applications for research grants in which the use and care of primates are important. It continues to evaluate the requirements for the importation of rhesus monkeys from India.

The Committee on Primates will review a dozen applications for the establishment of two primate centers, and will make recommendations to the National Advisory Heart Council as to scientific merit and priority consideration. Committee members will visit all sites under consideration.

These centers will be supported from the \$2,000,000 made available by the Congress to the National Heart Institute this year.

Under the sponsorship of the Committee, a study of the diseases of Indian rhesus monkeys was begun October 31, 1959, and 600 monkeys were imported for this purpose. One objective of this study is to define the causes of death of untreated rhesus monkeys imported from India. Another is to evaluate the effectiveness of different caging and treatment procedures. NIH is participating in the study with Parke, Davis, and Company, the Christ Hospital for Medical Research, the University of Pittsburgh, and the PHS Communicable Disease Center.

Blood cultures and fecal specimens were taken in India before the monkeys left New Delhi, and this procedure is being repeated during the two months of the study. Bacteriologic and viral studies will require several months to complete, and then the accumulated data will be published.

Scientists in India have expressed keen interest in the study, realizing that it will enable them to learn more about the viral and bacterial infections to which monkeys are susceptible even in their

natural habitat. Some of these infections could be transmitted to man.

Committee members include Chairman Dr. K. F. Meyer, University of California; Executive Secretary Katharine A. Parent, DRG; Dr. Jack Ralph Andy, The George Williams Hooper Foundation, University of California; Dr. Willard H. Eyestone, NIH; Dr. Harry Harlow, University of Wisconsin; Dr. Donald E. Pickering, University of Oregon Medical School; Dr. Arthur J. Riopelle, Yerkes Laboratories of Primate Biology, Inc.; Dr. Fredrick J. Stare, Harvard University School of Public Health.

Develop Rapid Blood Test to Detect PKU In Infant at Birth

A simple and rapid blood test for diagnosing the metabolic disease known as phenylketonuria (PKU) has been developed by Dr. Bert N. La Du and P. J. Michael, of the Arthritis and Rheumatism Branch, National Institute of Arthritis and Metabolic Diseases. The test makes practical the diagnosis of the disease within a day after birth and will aid physicians in controlling the special diet vitally needed by PKU patients.

Phenylketonuria is an "inborn error of metabolism" whose most disastrous consequence is severe mental retardation; the majority of affected individuals require institutional care. The retardation is believed to be a result of the abnormally high level of phenylalanine in the patients' blood.

In normal persons this amino

acid when absorbed from the intestine is immediately metabolized to tyrosine, another amino acid, but in patients with this disease the metabolic step has been blocked. One specific enzyme needed for the conversion is lacking. Consequently, toxic amounts of phenylalanine accumulate in the blood and spill over in the urine as phenylpyruvic acid.

No Cure for Basic Defect

Although there is no cure for the basic defect, recent studies by several groups of investigators have shown that if PKU patients are placed on a special low-phenylalanine diet soon after birth, much if not all of the retardation may be prevented. Rapid diagnosis is crucial, for the earlier the diet is started—within days or weeks after birth—the better the chances for normal mental development.

The diagnostic test developed by Dr. La Du uses an enzyme obtained from snake venom to measure the level of phenylalanine in the blood sample, and can be performed in ten minutes.

In addition to its speed and simplicity, the spectrophotometric test has several advantages over a more complex one that was developed by investigators of the National Heart Institute in 1953. One advantage is that with a slight modification the new test can be done on a microscale—that is, with finger-prick samples of blood instead of the two milliliters required by the older method. (This is of great value in an infant where venipuncture is always a formidable task.)

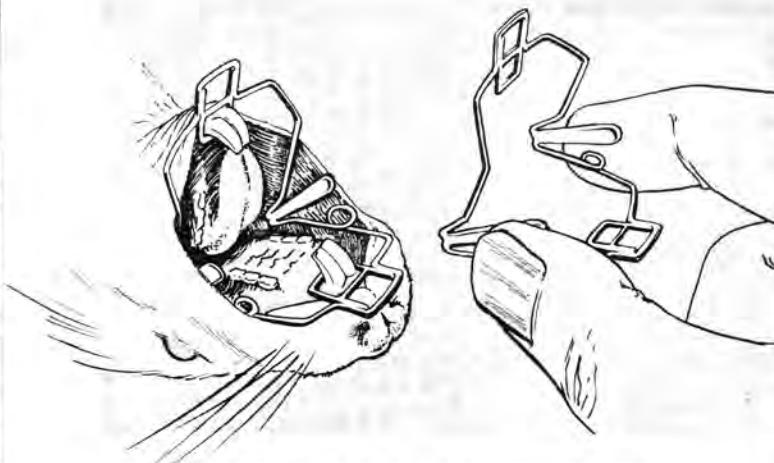
Further Advantages

Another advantage is that the new test not only measures phenylalanine, but also measures the level of the amino acids tyrosine and tryptophan in the serum. This is important during treatment with the PKU diet, for tyrosine must be added in the correct amounts to supply what normally would be produced by phenylalanine metabolism.

Dr. La Du's test will be most valuable in newborn infants from families with known PKU. At present PKU is first suspected when abnormally high levels of phenylpyruvic acid appears in the urine, but it may be several weeks after birth before this happens. These are weeks in which a low-phenylalanine diet is vital.

An editorial by Dr. La Du on the importance of early diagnosis and treatment of PKU will appear in the *Annals of Internal Medicine* (December). He reported on the new spectrophotometric test and its applications at a meeting of the American Society for Pharmacology and Experimental Therapeutics in September.

New Device for Rodent Oral Work



New device for rodent oral work developed at NIDR.

A National Institute of Dental Research scientist has developed a new mouth prop to facilitate oral examinations and operations in live rats and other rodents. Its special advantages allow the displacement of oral tissues in the horizontal as well as the vertical plane, thus spreading both cheeks and jaws to leave all oral structures directly accessible. In addition, it involves no extra-oral components which might obstruct light and interfere with operative manipulations.

The device, developed by Dr. A. A. Rizzo, NIDR Microbiology Laboratory, requires methods and materials used in the average orthodontic laboratory. Round, stainless steel orthodontic wire, 0.025 inch in diameter, seems to offer the best combination of strength and resiliency for appliances to be used in young adult rats. Since head size varies much

less than body size, an appliance with two incisor loops at each end (see drawing) permits an accurate fit in rats varying widely in weight. However, for rats of fairly constant size, an opener with only one upper and one incisor loop is adequate and can be made with a single length of wire and one soldered joint.

With slight modifications, devices of the same basic design can be used successfully in other rodents. Such appliances have been used successfully to examine more than 100 rats weighing from 70 to 600 grams, a number of hamsters and guinea pigs, and a few mice. A similar prop has been made for rabbits.

These devices have been useful in studies in which it has been necessary to apply drugs to specific oral sites, obtain bacteriologic specimens, and perform surgical procedures.

WORLD EPIDEMIOLOGY OFFERS HOPE FOR DISEASE CONTROL

Excerpt from "Patterns of Incidence of Certain Diseases Throughout the World — Opportunities for Research Through Epidemiology," a Committee Print submitted to the Committee on Government Operations, U. S. Senate, by its Subcommittee on Reorganization and International Organizations (Government Printing Office, 1959).

EACH civilization, it has been said, makes its own diseases.

The first half of the 20th century, with its many social, industrial, and economic changes, confirms that present civilization follows the time-tried pattern. A list of significant changes in the 20th century might include:

Newly discovered and improved types of transportation;

Increasing use of radioactive sources of energy;

Development of new knowledge for infectious disease control;

Steadily increasing world population;

Increasing numbers of older people; and

Emerging importance of chronic disease as a health factor.

These changing patterns of living are universal. They contribute to the worldwide problem of disease in a wide variety of ways. The network of sources, causes, and carriers of disease is so intricate that it suggests the need for a special effort (a) aimed at defining the questions and (b) pinpointing the answers to diseases and disabling conditions that occur on a worldwide basis.

One of the most interesting and hopeful avenues of approach to the control and eradication of today's major diseases is through world epidemiology.

Epidemiology Defined

Epidemiology has been defined as a science of mass phenomena of diseases and human defects. Other terms frequently used to denote this general discipline, but implying somewhat differing meanings, are *medical geography* and *ecology*. Epidemiology describes significant varieties of these phenomena in time and place. It draws upon statistical methods and theory, all phases of medicine, and the natural sciences to give a true picture of the occurrence, distribution, and types of diseases or defects.

As an illustration, the epidemiological study of hypertension (high blood pressure) seeks—as in similar studies—to evaluate the influence of diverse genetic and environmental factors upon the occurrence and severity of the disease. No one has succeeded in demonstrating specifically what causes high blood pressure. Yet



The National Institute of Mental Health conducts epidemiological studies to learn how quality of housing, population density, and social conditions affect occurrence of mental illness in the community.

marked differences in the incidence and severity of the disease in different population groups support the hope that epidemiological studies may succeed in defining the causative factors.

Methods of Epidemiology

By contrast with clinical medicine, the unit of study in epidemiology is the population or group, not the individual. Deaths, or any other event, are studied only if information can be obtained or inferred about the population in which the events occurred. The population may be a small and well-defined group in a municipality, may include a whole country or even an entire continent. The epidemiologist, therefore, as opposed to the clinician who deals in cases, is concerned with cases as they occur in their population. He may start with a population and find the cases in it, or he may start with a number of cases and refer them to a population or group that can be taken to represent a population. In addition to observing the occurrence of cases, the epidemiologist must be keenly aware of the importance of variations in human traits and must understand what effect environmental factors might have on individuals under his observation.

Epidemiology was originally the

study of epidemics—usually of one particular disease. From those early studies it is possible to establish a framework of questions to seek out the characteristics of the disease: where and when it occurs, the frequency and intensity of the occurrences, the persons most likely to be affected, and whether such conditions as climate or weather are a factor. Armed with the answers to these and other questions, which together describe the pattern of the disease, it is then possible to advance theories about the source and mode of spread of the disease and to put these theories to the test by clinical, field, or laboratory study. Finally, it may be possible to establish a logical plan for the control of the disease under study.

One of the principal uses of epidemiology is to discover populations or groups with high and low rates of disease, in the hope that causes of disease and of freedom from disease can be found. The epidemiological approach to a search for the cause of a disease may often suggest steps that may be taken for prevention and control. Thus, it is possible to reduce the impact of a major disease before the exact nature of the disease is understood.

Examples of Historical Contributions: Cholera

John Snow established an important landmark in epidemiological research with his conclusions about the source of cholera. Long before bacteria were discovered, the features of cholera epidemics had been explored thoroughly, and the existence of minute living causative organisms had been theorized. In 1854, Snow, through masterly detective work in the Broad Street pump epidemic in London, held that a contaminated water source was responsible for the outbreak. Later, the well-known Hamburg-Altona epidemic of 1892 indisputably established the theory of waterborne disease.

Smallpox

Edward Jenner, an English physician, observed that milkmaids throughout the countryside who contracted cowpox while milking were subsequently immune to smallpox. In 1796, he vaccinated against smallpox by transferring material from a cowpox pustule on the hand of a milkmaid to the arm of a small boy. Six weeks later the boy was inoculated with smallpox and failed to develop the disease. Although it was to be many years until the virus of smallpox was discovered and the exact nature of this highly infectious disease understood, the epidemiological method pointed to an effective means for curbing the spread of smallpox. By 1800 the scientific basis of this method, still in use today, was firmly established.

Breast Cancer Rate Of Survival Remains Stable for 20 Years

The survival rate for patients with breast cancer, the leading cause of death due to cancer among women, has remained stable for a quarter of a century. This conclusion is confirmed by a statistical study of data obtained in the State of Connecticut, in which the 10-year survival rate was 38 percent for cases diagnosed during 1935-44 and 39 percent during 1945-54.

The survival experience for some 10,000 patients with primary cancer of the breast diagnosed in Connecticut in the 20-year period from 1935 to 1954 was studied in detail by scientists of the National Cancer Institute in collaboration with those of the Connecticut State Department of Health. Survival data on patients was compared with the expected survival experience for a group of women from the general population, and relative survival rates computed as the ratio of observed to expected survival rates.

The relative survival rate for the first 5 years during both periods, 1935-44 and 1945-54, was approximately 50 percent. This indicates that one-half of the patients expected to survive to the end of the fifth year were alive. Furthermore, patients alive 10 years after diagnosis of cancer were not free of an excessive mortality risk, and even after 20 years of follow-up, the rate of mortality in the population of breast-cancer patients exceeded the rate in the general population.

Other results showed that 1) of patients with localized tumors alive at the end of the tenth year, only 82 percent of the expected number of survivors were actually alive at the end of the twentieth year; and 2) the most favorable survival experience was observed among patients with localized tumors treated by surgery only. Yet, in this group, mortality was greater than expected for 15 years after diagnosis of the disease.

The results obtained in Connecticut were comparable with those reported from leading treatment centers, such as the Mayo Clinic and Johns Hopkins Hospital. Since incidence, mortality, and survival rates have been stable for a good many years, the investigators conclude that "future improvement is more likely to result from the development of new therapeutic techniques rather than from further refinement of current methods."

The work is reported in the current issue of the *Journal of the National Cancer Institute*.

DISEASE MAY LINK ALS TO INHERITED NEUROLOGIC ILLS

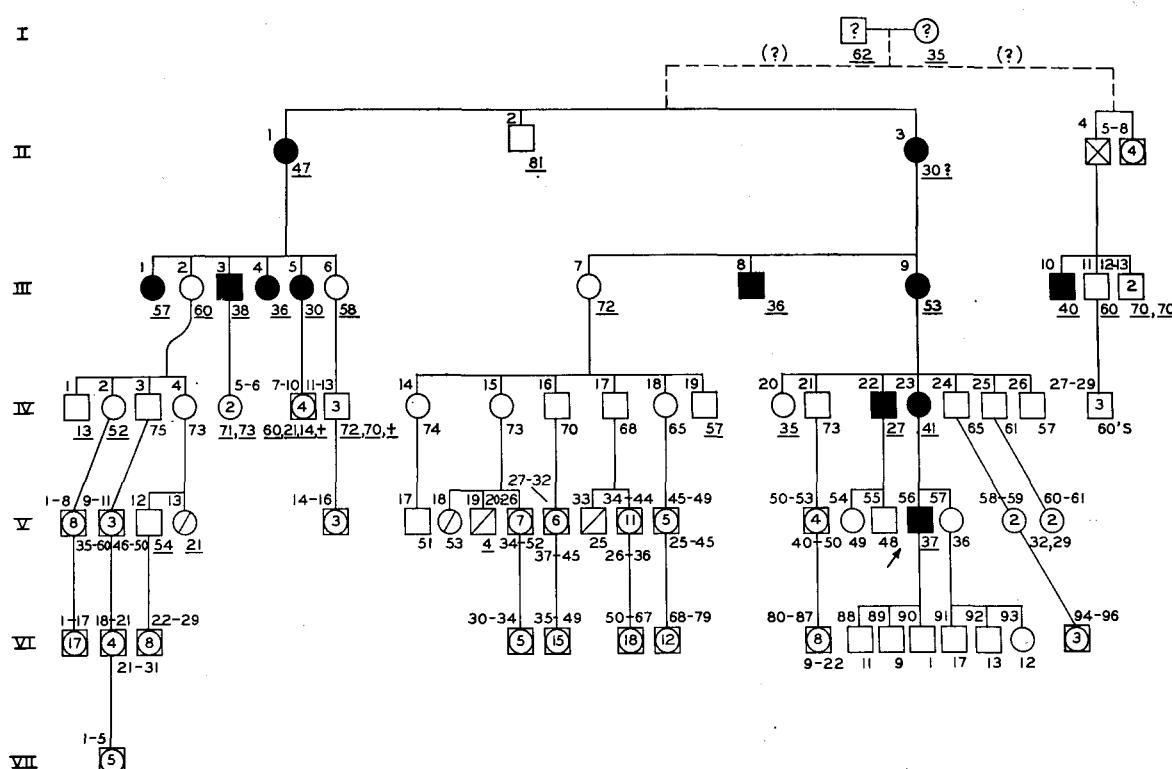
An inherited neurological disorder clinically indistinguishable from amyotrophic lateral sclerosis (ALS) has been observed in several generations of two families. Pathologically, similarities between the cases and disorders such as hereditary ataxias indicate that this disease may represent part of a continuum linking ALS to these inherited neurological conditions.

The disease was described by Drs. W. King Engel and Igor Klatzo of the National Institute of Neurological Diseases and Blindness's Surgical Neurology Branch and Dr. Leonard T. Kurland of the NINDB Epidemiology Branch in *Brain*.

In the first family studied, at least 11 persons representing four generations were affected; in the second, three persons in two generations were afflicted. The genetic pattern of both families indicates that the disorder is probably a dominantly inherited metabolic failure, affecting the neurone cell body and its processes.

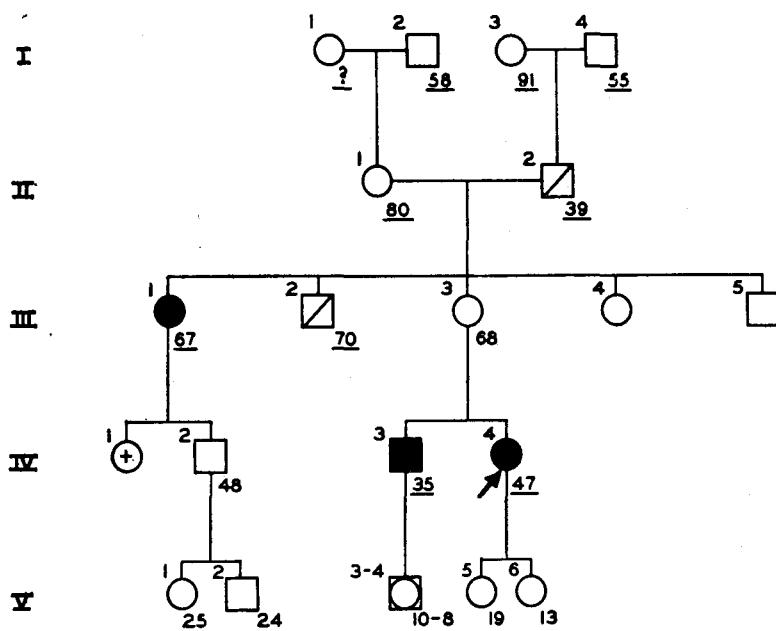
The disorder was clinically similar to ALS in that both conditions usually begin in adult life, terminate fatally within one to four years, and show both upper and lower motor neurone involvement. In addition, the majority of neuropathologic findings were compatible with ALS.

However, evidence of features not occurring in ALS, but present in other conditions, indicates that these cases may be variations caused by modifying genetic fac-



1. Inheritance pattern of "The Family Disease" in family A. This is a "Pennsylvania Dutch" family that has resided in north-central Pennsylvania for at least 100

years. Nearly all the living descendants of III-9, most of the children of III-7 and many of their descendants, and IV-3 were personally examined.



2. Inheritance pattern in family B, all members of which were born and raised in Louisiana. Autopsy studies of two persons dying of the familial disease were available.

tors. In addition to genetic patterns which are usually absent in ALS, pathological examination of three cases revealed an unexpected pattern of posterior spinal cord demyelination, especially in the middle root zones. The middle root zones are also selectively involved in other inherited neurological conditions such as subacute combined degeneration, a deficiency disease, and the hereditary ataxias, or idiopathic spinocerebel-

lar degenerations. These diseases may have, at the biochemical level, a similar pathogenesis.

On the basis of this evidence, the authors conclude that the cases studied probably represent a variant of ALS. However, further study of the underlying abnormalities of ALS and its variations are necessary to determine if the disorder is a true example of an intermediate form in the continuum of these diseases.

	MALE, APPARENTLY UNAFFECTED, AGE 49
	FEMALE, APPARENTLY UNAFFECTED, DIED AGE 49
	EXAMINED AND AFFECTED OR GOOD HISTORY OF AFFECTION
	POSSIBLY AFFECTED
	OTHER NEUROLOGIC DISEASE
	DIED IN CHILDHOOD
	PROPOSITUS
	NO INFORMATION

3. Key to inheritance pattern charts.

Single Psychological Score Detects Physical Ills

Analysis of psychological measurements made on a group of relatively healthy elderly men has made possible the construction of a single critical score which can be used to distinguish individuals without physical disease from those with some non-interfering disease such as a mild vascular problem.

This study, conducted by investigators in the National Institute of Mental Health's Laboratory of Psychology, utilized some 150-200 psychological measurements that had been made during a large NIMH interdisciplinary study of aging involving contributions from the biological, the psychological, and the social sciences.

Using data from tests which measured, among other factors, reaction time, perception, and verbal and motor learning of the group of elderly subjects (normal

volunteers, aged 65 years and over) under a variety of conditions, the investigators made a series of inter-correlations from which 32 independent scores were extracted. These 32 scores were subjected to an analysis to extract the "principal components" that were measured by the scores.

As a result of this analysis, each subject was given over-all scores on four or five major components, and these scores were combined into a single score for each person. The resultant score proved to be effective in distinguishing between subjects with no physical disease and those with disease, even though both groups were above average in health.

The study was reported by Dr. James E. Birren, Dr. Jack Botwinick, Dr. Alfred D. Weiss, and Donald F. Morrison to the American Psychological Association.

Perinatal Project Fully Under Way

The Collaborative Project on Cerebral Palsy, Mental Retardation, and Other Neurological and Sensory Disorders of Infancy and Childhood, Sponsored by NINDB.

It is now believed that a major source of the tragic problem of cerebral palsy, mental retardation, and other neurological and sensory disorders lies in the time span from conception to about one month after birth. An estimated 4½ million persons are mentally retarded, and ½ to ¾ million have cerebral palsy. Mental retardation alone afflicts approximately 3 percent of the 4,200,000 children born annually.

Many research studies have been conducted on disorders of the so-called perinatal period of life. Most of these, however, have involved small numbers of persons or have been done on a "retrospective" basis. In other words, when cerebral palsy has been discovered in a child (sometimes as late as two years of age), attempts have been made to review the medical records of the child and the pregnancy records of the mother to determine the cause of the disorder. It has been difficult to establish relationships between cause and effect through this approach.

The Program

To evaluate causes of neurological and sensory disorders arising during pregnancy and the early newborn period, a broad program has been developed by the National Institute of Neurological Diseases and Blindness. As one phase, 16 medical centers across the Nation are making detailed investigations of 40,000 mothers and their offspring. The children will be followed until they are six years of age. This phase of the study, referred to as the "intensive" phase or central core study, envisages an intensive investigation covering every detail of pregnancy and labor. All unusual events during pregnancy are being carefully documented. Should a neurological disorder develop in the infant, an attempt will be made to correlate it with events and conditions of pregnancy, birth, or infancy which might possibly have caused brain damage.

Another phase, known as the "extensive" phase or community study, parallels these intensive investigations. It is designed to obtain less detailed information regarding certain special groups of children known to be suffering from cerebral palsy, mental retardation, and other neurological and sensory disorders. This information will be compared with that obtained from the group more intensively studied. As causes are discovered, it is hoped that such

disorders as cerebral palsy, mental retardation, blindness, and deafness will be prevented.

To support this vast undertaking within the cooperating institutions, and the laboratories and coordinating offices of the NINDB, more than \$4 million was allocated for fiscal year 1959 and more than \$5 million for 1960. Of the latter sum, \$3,804,000 has been allocated for grants to the 16 collaborating institutions and \$1,354,000 for the NINDB program of coordination.

The Program in 1958

During 1958, some 3600 cases (i.e., 3600 women plus approximately 2000 children) were subjected to partial study in order to pretest protocols for the central core study and to develop a method for data collection.

As of December 31, 1958, collaborators had completed their preparation for the study and were ready to begin processing their share of the 40,000 cases over a five-year period.

This processing will be done according to protocols which include detailed interviews on socio-economic-genetic data, past medical history, repeated prenatal obstetrical examinations, observations throughout labor and delivery, observations of the neonate in the delivery room and in the nursery, pediatric examination of the infant at four months, psychological examination at eight months, and neurological examination at twelve months.

Followup protocols for the children from one to six years of age are still in the process of development.

Accomplishments to Date

It is obvious that this vast project is in its infancy. The complete study of the first child to be enrolled in the study will not be finished for at least six years. The project, however, is already paying important dividends in terms of increased knowledge of the early period of life and an understanding of some of its hazards to normal development.

Specifically, investigators have discovered that a previously disregarded lowering of the blood sugar, occurring during the neonatal period of the children of toxemic mothers, may account for some cases of permanent brain damage. This tragedy is preventable by the appropriate administration of sugar. Similarly, intensive observation of infants within the collaborating institutions has

Biochemical Factors Important in Drug Activation and Effects

In a paper read before the German Pharmacological Society in Basle, Switzerland, Dr. Julius Axelrod, Chief of the Section on Pharmacology in the National Institute of Mental Health's Laboratory of Clinical Science, summarized current knowledge about the biochemical factors involved in the metabolism and pharmacological activity of drugs.

Knowledge concerning the biochemical changes that a pharmaceutical agent undergoes *in vivo* and the factors influencing these changes may be of considerable importance in the understanding of drug action, the elucidation of new biochemical phenomena, and the synthesis of more effective and safe drugs.

Most drugs undergo chemical change in the body to either pharmacologically active or inactive products. A wide variety of biochemical changes, including decarboxylation, acetylation, reduction, oxidation, N- and O-dealkylation, and N- and O-methylation can form active metabolic products. However, depending on the structure of the drug, these reactions may also form inactive metabolites. Other metabolic changes which generally produce inactive metabolic products include deamination, hydrolysis, and conjugation reactions.

Dr. Axelrod, while he was with the National Heart Institute, was the first to describe a family of

revealed that many cases of neonatal jaundice have previously been unrecognized. It is known that such bile intoxications may produce permanent brain damage. New discoveries are making it possible for these cases to be recognized and for the damage to be prevented.

Another cause of perinatal mortality, whose importance is being demonstrated by the study, involves the existence of abnormal forms of hemoglobin in the pregnant woman. In one series of 16 women having this condition, four died during pregnancy. The way is now open for early recognition.

Investigations within the collaborating institutions have revealed that the presence of bacterial infection in the newborn can be reliably detected through the study of frozen sections of the placental membranes and umbilical cord at birth. This technique is now being widely applied as a guide to treatment of the neonate. A large number of other investigations, ancillary to the collaborative project, are still in their "probing" stages within the collaborating institutions.

enzymes, localized in the microsomes of the liver, which are responsible for metabolizing a wide variety of drugs. Dr. Schmid (formerly of the National Institute of Arthritis and Metabolic diseases) and Dr. Axelrod, in their work on glucuronides (an important means by which the body inactivates drugs), discovered that a defect in the enzyme which forms glucuronic acid is the cause of the disease congenital non-hemolytic, non-obstructive jaundice. This is an example of how the study of drug metabolism can help in uncovering the cause of disease.

Although compounds are ultimately transformed by enzymes, there are many factors that modify enzyme activity such as inhibitors, activators, tissue localization, vitamins and hormones. Many drugs owe their longlasting action to storage in certain tissues; this protects the drug from enzymatic destruction.

The action of many drugs can also be prolonged by substances which block the enzymes from acting. Other substances, which increase enzyme activity, can speed up the metabolism of many drugs. There are considerable species differences in the metabolism and action of drugs, owing primarily to species differences in enzyme activity. Many hormones, vitamins, and other foreign compounds affect drug metabolism by enhancing or inhibiting enzyme activity.

Repeated administration may result in the inactivation of certain drugs, notably narcotic drugs. This phenomenon is known as tolerance. Dr. Axelrod found striking similarities between the "analgesic" receptors for narcotic drugs and the enzymes that N-demethylate these compounds. This parallelism suggests a mechanism for the development of tolerance to narcotics.

Ills of GI Tract Are Major Health Problem

Gastrointestinal ailments are poorly understood, yet are among the most common serious illnesses in this country. They rank second only to diseases of the heart and circulation in the number requiring attendance by a physician. Peptic ulcer alone, it has been estimated, strikes more than 10 percent of all adults in the United States at some time in their lives. Diseases of the stomach and intestines may strike persons of any age, but usually affect those in the younger and middle-aged groups at the peaks of their most vigorous and productive periods, often causing prolonged and expensive hospitalization and countless social and emotional problems.

Publication Preview

The following manuscripts were received by the SRB Editorial Section between June 16 and June 26.

DBS

Kauffmann, F.; Lund, E.; and Eddy, B. E. Proposal for a change in the nomenclature of *Diplococcus pneumoniae* and a comparison of the Danish and American type designations.

NCI

Bases, R. E. Modification of the radiation response determined by single cell techniques: Actinomycin D.

Boggs, D. R. and Frei, E., III Clinical studies of fever and infection in malignant neoplastic disease.

Burmester, B. R.; Fontes, A. K.; Waters, N. F.; Bryan, W. R.; and Groupe, V. The response of several inbred lines of white Leghorns to inoculation with the viruses of strain RPL 12 visceral lymphomatosis-erythroblastosis and of Rous sarcoma.

DeWitt, S. H.; Rabson, A. S.; Legallais, F. Y.; Del Vecchio, P. R.; and Malmgren, R. A. Chromocenters resembling sex chromatin in human tissue culture cell lines.

Heller, J. R. Cancer control in the United States.

Heller, J. R. Cancer research in the United States.

Hertz, R. Choriocarcinoma of women maintained in serial passage in the hamster and rat.

Peterson, E. A. and Sober, H. A. The plasma proteins.

Rosen, F. R. and Landy, M. Inactivation of endotoxin by a humoral component V. EDC activity during gram-negative infection and shock.

Rowe, W. P. and Brodsky, I. A graded response assay for the Friend mouse leukemia virus.

Sanford, K. K.; Merwin, R. M.; Hobbs, G. L.; Young, J. M.; and Earle, W. R. A clonal analysis of variant cell lines transformed to malignant cells in tissue culture.

Sanford, K. K.; Merwin, R. M.; Hobbs, G. L.; and Earle, W. R. The influence of animal passage on a line of tissue culture cells.

Shimkin, M. B. Epidemiology of cancer. Stewart, S. E.; Eddy, B. E.; Irwin, M.; and Lee, S. The development of resistance in mice to tumor induction by S. E. polyoma virus.

Vlahakis, G. and Heston, W. E. Relationship between recessive obesity and susceptibility to induced pulmonary tumors in mice.

NHI

Baker, S. P.; Landowne, M.; and Gaffney, G. W. Electrocardiographic changes following the administration of thyroid stimulating hormone (thyrotropin: TSH). Despopoulos, A. Renal excretory transport of organic acids.

Eden, M. A note on error detection in noisy logical computers.

Flavin, M. and Slaughter, C. Rapid and specific determination of threonine.

Goldsmit, R. S. and Bartter, F. C. Prominent peripheral edema associated with primary aldosteronism due to an adrenal cortical adenoma.

Pisano, J. J.; Abraham, D.; and Udenfriend, S. Conversion of gamma-amino-butyric acid to gamma-guanidobutyric acid by transamidination in mammalian tissues.

Shore, P. A.; Burkhalter, A.; and Cohn, V. H., Jr. A method for the fluorometric assay of histamine in tissues.

NIAD

Brennan, J. M. *Ectonyx*, a new neotropical genus of chiggers (Acarina: Trombiculidae).

Habel, K. and Atanasiu, P. Transplantation of polyoma virus induced tumor in the hamster.

Ribi, E.; Brown, W.; and Goode, C. Preparation of microorganisms for electron microscopy.

NIAMD

Donaldson, K. O. and Keresztesy, J. C. Naturally occurring forms of folic acid. I. "Prefolic A", preparation of concentrate and enzymatic conversion to citrovorum factor.

Kirkman, H. N. Primaquine sensitivity. Murayama, M. On the nature of the mercapto-mercapto interaction in normal human hemoglobin.

Simon, E. R.; Pesch, L. A.; and Topper, Y. J. Further observations on the steroid hormone stimulation on the conversion of (¹⁴C) galactose to (¹⁴C) CO₂.

Spicer, S. S.; Burtner, H. J.; and Swarm, R. L. Comparison of basophilic with S³⁵ label in normal and methylated mucopolysaccharides.

Stetten, DeW., Jr. The place of science in the baccalaureate program of the student preparing for a career in medicine.

Thomas, E. D.; Loche, H. L., Jr.; and Stohlmeyer, F., Jr. Attempts to develop an *in vitro* system for the assay of erythropoietin.

Thompson, M. J.; Mosettig, E.; and von Brand, T. The unsaponifiable lipids of *Taenia taeniaformis* and *Moniezia* sp.

NIDR

Baer, P. N. and Newton, W. L. The occurrence of periodontal disease in germ-free mice.

Hamp, E. G.; Mergenhagen, S. E.; and Omata, R. R. Studies on mucopolysaccharide activity of oral spirochetes.

Keyes, P. H. The infectious and transmissible nature of experimental dental caries. Findings and implications.

NIMH

Brown, D. D. and Kies, M. W. The mammalian metabolism of L-histidine. I. The enzymatic formation of L-hydantoin-5-propionic acid.

Brown, D. D. and Kies, M. W. The mammalian metabolism of L-histidine. II. The enzymatic formation, stabilization, purification and properties of 4(5)-imidazolone-5(4)-propionic acid, the product of urocanase activity.

Isbell, H. and Fraser, H. F. Addiction liabilities of dl-2'-hydroxy-5,9-dimethyl-2-(2-phenethyl)-6,7-benzomorphan HBr (NIH-7519) and 1-hydroxy-N-phenacylmorphinan methane sulfonate (NIH-7525).

Streicher, E. Age and calcium deposition in rat brain.

NINDB

Ajmon Marsan, C. and Abraham, K. A seizure atlas.

Baldwin, M. The history of American military neurosurgery. II. Section on injuries of the spinal cord.

Baldwin, M.; Bach, S. A.; and Lewis, S. A. The effects of certain radio-frequency energy on primate cerebral activity.

Dekaban, A. S. The outcome of pregnancy in diabetic women. Part II. Analysis of clinical abnormalities and pathological lesions in offspring of diabetic mothers.

Dekaban, A. S. and Baird, R. The outcome of pregnancy in diabetic women. Part I. Fetal wastage, mortality and morbidity in the offspring of diabetic and normal control mothers.

Fuortes, M. G. F. Inhibition in limulus eye.

Kauffmann, H. E. and Thomas, L. B. The vitreous opacities diagnostic of familial primary amyloidosis.

Myrianthopoulos, N. C. and Rowley, P. T. Monozygotic twins concordant for Huntington's chorea, in a family with chorea and mental illness.

Trams, E. G. Neurochemistry of adenine nucleotides.

von Sallmann, L. and Paton, D. Familial dyskeratosis of the perilimbal conjunctiva.

Seven NIH Employees Receive Incentive Award Checks

Incentive awards were made to seven NIH employees at the end of November. The checks totalled \$25.

In a Thanksgiving Eve ceremony, Donald Riggs, Laboratory of Bacterial Products, DBS, received a \$200 award for unusual production, valuable suggestions which have increased both the quality and quantity of experimental results, and sustained superior performance through his 17 years of employment here. He was also cited last year by Dr. Sara E. Branham, just before her retirement from NIH, for his abilities, reliability, and loyalty.

Another sustained superior performance award was given to Doris Marshall, SRB Medical Arts Section, DRS, for her outstanding spirit of cooperation and her ability and willingness to participate in every difficult, emergency

project during her seven years in the position from which she resigned in October to accompany her family to Hawaii.

Donald Allnutt, Office Services Branch, OAM, received \$75 for installing an oil line by-pass on one of the NIH trucks.

For inventing a device which ensures safer and quicker catching and transfer of wild mice, John W. Jones, Laboratory of Infectious Diseases, NIAID, received \$35.

Checks for \$25 were given to Ruth Scott, Information Section, NINDB, for suggesting changes in the NIH bus schedules; Herbert Wright, Laboratory of Viral Products, DBS, for his invention of a money-saving syringe drive for a filter; and Leonard Coombs, Office Services Branch, OAM, for suggesting the installation of new directional signs for the NIH buses.



In an awards ceremony held by the Laboratory of Bacterial Products, DBS, Donald Riggs (third from left) reads his superior performance award citation. He is congratulated by (from left) Drs. Roderick Murray, DBS Director; Michael F. Barile, LBP; and Margaret Pittman, Chief, LBP.

OBITUARY

W. Brooke Cunningham, 59, died in Mt. Alto Hospital, October 23 after a five-day illness.

Mr. Cunningham was a cost accountant in the Financial Management Branch, Office of the Director, OAM.

He is survived by his wife, Mrs. Gertrude Cunningham who works for DRG and lives in Burtonsville, Md.; and two daughters, Mrs. Anne Lee and Miss Jean Cunningham.

Mr. and Mrs. Cunningham both transferred to NIH in April 1956. Mr. Cunningham had previously served with the Department of the Navy, Headquarters, United States Marine Corps.

Dr. Kimler Named Head Of Media Section, LAB

Dr. Alexander Kimler has been appointed Chief of the newly combined Media and Glassware Section, Laboratory Aids Branch, ODS.

He formerly directed the laboratory at the Jackson Memorial Hospital in Miami, and also taught in the Department of Bacteriology at the University of Miami in Florida.

Dr. Kimler received his Ph.D. in Bacteriology from Vanderbilt University in 1948. He reported for duty here on October 28. This is his first assignment in PHS.

The Scene Changes as Buildings Rise Around the Reservation



Construction ranges from a hole-in-the-ground to near-completion. Clockwise, from left: 1. The circular CC surgical wing takes on substance as forms are prepared and concrete poured for the first floor slab. 2. The National Library of Medicine rises to the basement level. 3. The reinforced concrete frame of the Dental Building is filled by exterior masonry as far as the first floor. 4. Excavation for the new office building is completed and the southwest wall form is under construction. 5. The DBS building's interior finishing is almost complete, and the electrical wiring and air conditioning installations are progressing.



NEWS BRIEFS

Dr. Roger L. Black has been appointed Assistant Chief of the Arthritis and Rheumatism Branch, Clinical Investigations, NIAMD.

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Dr. Frederic C. Bartter, Chief, Section on Clinical Endocrinology, General Medicine and Experimental Therapeutics Branch, NHI, recently spent two weeks in Mexico City as visiting professor in the School of Nutrition, University of Mexico. He also addressed the Mexican Society of Biochemistry and the National Academy of Medicine there. The trip was sponsored by the International Educational Exchange Service, U.S. Department of State.

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Dr. Fay M. Hemphill has been appointed chief of the newly established Statistical Design and Analysis Section of DRG's Statistics and Analysis Branch. The new Section will design guidelines for developing the Branch's statistical projects.

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Dr. Winfred G. Helmes has been appointed assistant to Bertha S. Adkins, Under-Secretary of DHEW. Dr. Helmes will work primarily in the area of public affairs, particularly in connection with the Under-Secretary's official relations

with educational institutions, national organizations, and other groups.

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Dr. G. Halsey Hunt, Chief, DGMS, has been appointed a member of the American Hospital Association's Committee on the care of the Chronically Ill and of the Aged.

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At the request of the World Health Organization, Dr. Justin M. Andrews, NIAID Director, met in Geneva during the week of November 23 with the WHO Scientific Group on Malaria. The group reviewed current research and considered ways and means of accelerating the WHO malaria research program.

Following this, Dr. Andrews went to Rio de Janeiro to attend a meeting on malaria eradication sponsored by the Pan American Health Organization.

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Dr. Ernest M. Allen and Frank Schmehl, DRG, and Dr. L. Edgar Lee, DGMS, participated in a meeting of the Veterinary Division of the American Association of Land Grant Colleges and State Universities in St. Louis on November 11.

Dr. Huebner Honored By St. Louis Alumni

Dr. Robert J. Huebner, Chief of the Laboratory of Infectious Diseases, NIAID, was given the Alumni Merit Award of St. Louis University during the celebration of Founders Day in St. Louis on November 23.

The award gives recognition before the community and the Nation to distinguished graduates who are exemplifying to an eminent degree the credo of St. Louis University.

Dr. Huebner and his associates have made important contributions to the knowledge about viruses and their relationship to diseases such as upper respiratory infections and cancer. Among their contributions was the development of one of the first vaccines effective against a new virus group, the adenoviruses, unknown until 1953.

Dr. Huebner is the fifth and youngest medical alumnus of St. Louis to be honored with the Alumni Merit Award.

DRS Establishes Instrument Shop At St. Elizabeths

A small instrument shop is to be established soon by Laboratory Aids Branch, DRS, at the Clinical Neuropharmacology Research Center of NIMH at Saint Elizabeths Hospital.

The Instrument Section, LAB, will provide service under arrangements similar to those provided by the DRS satellite instrument shops to the Clinical Center and NCI. The three shops, operating under the administration and guidance of Dr. Fred Alt, Chief of the Instrument Section, enable DRS engineers to work closely with scientists in developing needed instrumentation.

Paul P. Dirlik, instrument maker in the Instrument Section here, will be assigned to the new shop. Additional personnel will be supplied by DRS when the need arises.

Foreign Grants Increase

NIH research grants were made to 874 institutions in the U. S. and foreign countries this year.

Of the 426 institutions receiving NIH research grants this year, nearly half received but one NIH grant.