

HIGHLIGHTS IN THE
HISTORY AND ORGANIZATION
OF THE
NATIONAL INSTITUTES OF HEALTH
1945-1975

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service National Institutes of Health

INTRODUCTORY NOTE

This chronology lists some milestones in the history of the National Institutes of Health from 1945 to 1975.

The material presented is of three types:

First, a chronology of principal legislative and organizational actions affecting NIH.

Second, a summary of ways in which the National Institutes of Health has broadened the national base of biomedical research, education, and communication.

Finally, there is a list of scientific advances resulting from research conducted or supported by the National Institutes of Health.

This inventory is neither all-inclusive nor selective. Prepared with the assistance of the scientific staff of each of the Institutes, it is intended primarily to serve as a resource document in responding to requests for examples of tangible results of NIH research programs.

Office of Communications
National Institutes of Health

Chronology of Legislative
and Organizational Actions

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Chronology of Legislative and Organizational Actions

PRIOR TO 1945 - The National Institutes of Health had its origins in 1887 when a research laboratory was founded at the Marine Hospital, Staten Island, N.Y., to meet new responsibilities of the Marine Hospital Service. In 1891 this was renamed the Hygienic Laboratory and moved to Washington, D.C. In 1902, an Advisory Board was established for the Laboratory; this was later to become the National Advisory Health Council. In the same year, Congress gave the Service responsibility for control of biologics. In 1912 the name of the Public Health and Marine Hospital Service was changed to Public Health Service. In 1930, the Hygienic Laboratory was renamed the National Institute of Health. In 1937 Congress authorized the National Cancer Institute and the first research grants were made. In 1938 the National Institute of Health moved to Bethesda, Md. In this same year the National Cancer Institute awarded the first research fellowships. In 1944, the Public Health Service Act consolidated and revised existing public health legislation, and gave NIH general legislative authority to conduct research.

- 1946 - A Research Grants Office was created at the National Institute of Health to administer the Office of Scientific Research and Development projects transferred to the Public Health Service at the end of World War II, and to operate a program of research grants and fellowship awards.
- 1947 - The Division of Research Grants was established to process NIH grants and fellowships to non-Federal institutions and scientists. The first training grants were awarded.
- 1948 - The National Heart Act authorized the National Heart Institute and changed the name of the National Institute of Health to National Institutes of Health. The National Heart Institute was established.
- The National Dental Research Act authorized the National Institute of Dental Research.
 - The National Microbiological Institute and the Experimental Biology and Medicine Institute were established.
- The Rocky Mountain Laboratory and Biologics Control Laboratory became two of the four components of the National Microbiological Institute.
- 1949 - The National Institute of Mental Health was established.

- 1950 - The Omnibus Medical Research Act authorized the National Institute of Neurological Diseases and Blindness and the National Institute of Arthritis and Metabolic Diseases, the latter absorbing the Experimental Biology and Medicine Institute. The Act also gave the Surgeon General authority to establish new institutes. The National Institute of Neurological Diseases and Blindness and the National Institute of Arthritis and Metabolic Diseases were established.
- 1953 - The Clinical Center opened, thus extending the clinical dimension of NIH research. The Clinical Center, providing twice as much laboratory space as patient-care space, and laboratories in corridors adjacent to hospital rooms, became the prototype for many other research hospitals.
- The Public Health Service became a part of the new Department of Health, Education, and Welfare.
- 1955 - The biologics control function was placed in the newly formed Division of Biologics Standards.
- The National Microbiological Institute became the National Institute of Allergy and Infectious Diseases.
- 1956 - The Health Research Facilities Act, establishing a program of matching grants for research construction in non-Federal institutions, was enacted.

1958 - The Division of General Medical Sciences was established, extending medical research into diseases not being investigated by other NIH components.

1960 - The Public Health Service Act was amended to provide for general support of research and research training programs in nonprofit institutions. The International Health Research Act was adopted; NIH extended its international programs.

1962 - The National Institute of Child Health and Human Development was authorized and the Division of General Medical Sciences was redesignated the National Institute of General Medical Sciences.

- The Division of Research Facilities and Resources was created. The National Library of Medicine, a part of the Public Health Service since 1956, moved to the NIH reservation.

1964 - The Division of Computer Research and Technology was established.

1965 - The Heart Disease, Cancer and Stroke Amendments of 1965 authorized regional medical programs to combat three "killer" diseases. The Division of Regional Medical Programs was established the following year to administer grants under these amendments.

1966 - The Division of Environmental Health Sciences was established.

1967 - The National Institute of Mental Health was separated from NIH and became a bureau of the Public Health Service. NIMH's Intramural Research Program, comprising activities conducted in the NIH Clinical Center and other NIH facilities, continued at NIH.

1968 - Under a reorganization of health activities, NIH became an operating agency within HEW; the Bureau of Health Manpower, later renamed the Bureau of Health Professions Education and Manpower Training, and the National Library of Medicine became components of NIH.

- The Division of Regional Medical Programs was transferred to the Health Services and Mental Health Administration.
- The John E. Fogarty International Center for Advanced Study in the Health Sciences was established.
- The National Eye Institute was created to build an enlarged program based on blindness research formerly conducted by the National Institute of Neurological Diseases and Blindness. The National Institute of Neurological Diseases and Blindness became the National Institute of Neurological Diseases and Stroke.
- The Lister Hill National Center for Biomedical Communications was established at the National Library of Medicine.
- The National Center for Population Research was established in the National Institute of Child Health and Human Development.

- 1969 - The Division of Environmental Health Sciences became the National Institute of Environmental Health Sciences.
- The Secretary of HEW redesignated the National Heart Institute as the National Heart and Lung Institute, reflecting expansion of its functions.
- 1970 - Amendments of the PHS Act authorized mission-related clinical training by the National Institute of General Medical Sciences.
- The Health Training Improvement Act of 1970 extended and amended allied health professions training and established eligibility of new Health Professions Educational Assistance Schools for "start-up" grants.
- 1971 - The National Cancer Act of 1971 authorized a National Cancer Program, enlarged the authority of the National Cancer Institute, and established a National Cancer Advisory Board.
- 1972 - The Division of Biologics Standards was transferred from NIH to the Food and Drug Administration where it became the Bureau of Biologics.
- A National Sickle Cell Anemia Control Act established a national program for the diagnosis and treatment of, and counseling and research in, sickle cell disease.

- The National Institute of Arthritis and Metabolic Diseases was renamed the National Institute of Arthritis, Metabolism, and Digestive Diseases as part of a new emphasis on support of research and training in digestive diseases.
 - The National Heart, Blood Vessel, Lung and Blood Act expanded the authorities of the National Heart and Lung Institute to intensify the national effort against heart, lung and blood diseases.
 - The National Cooley's Anemia Control Act authorized additional funds for research on Cooley's anemia.
 - The National Commission on Multiple Sclerosis Act established a Commission charged with determining the most productive avenue of researching causes and cures of this disease.
- 1973 - The Bureau of Health Manpower Education was transferred from NIH to the new Health Resources Administration. The Bureau was renamed the Bureau of Health Resources Development.
- 1974 - The National Cancer Act Amendments of 1974 permitted NCI to designate additional Comprehensive Cancer Centers; required peer review of grant applications and contract projects; and called for a more effective worldwide dissemination of cancer knowledge. The 1974 Amendments also established the President's Biomedical Research Panel to review research programs conducted by NIH and

by the Alcohol, Drug Abuse and Mental Health Administration (ADAMHA) and to recommend policy regarding their operation.

- The National Research Act of 1974 established a National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. It also consolidated all research training authorities of NIH and ADAMHA into a unified National Research Service Awards Authority
 - The Research on Aging Act authorized establishment of an eleventh Institute at NIH, the National Institute on Aging.
 - The National Diabetes Mellitus Research and Education Act established a National Commission on Diabetes to formulate a long-range plan for diabetes research; directed the establishment and expansion of diabetes research and training centers; and directed establishment of a committee to coordinate research activities of the NIH, as well as activities of other Federal agencies relating to diabetes.
 - The Sudden Infant Death Syndrome Act authorized the National Institute of Child Health and Human Development to carry out sudden infant death syndrome research, required Congressional reporting by the Institute, and provided for an information and counseling program.
- 1975 - The National Arthritis Act of 1974 established a National Commission on Arthritis and Related Musculoskeletal diseases to formulate a long-range plan to combat arthritis through research, training, services and data systems. It

also established an Associate Director for Arthritis in the NIAMDD and a HEW Intradepartmental Arthritis Coordinating Committee and an Arthritis Screening and Detection Data Bank. It provided three-year authorizations for arthritis screening, detection, prevention and referral projects and for arthritis research and demonstration centers.

- The National Institute of Neurological Diseases and Stroke was renamed the National Institute of Neurological and Communicative Disorders and Stroke.

Contributions
to a
Broadened National Scientific Effort

Over the years, the single most important contribution of the National Institutes of Health may have been its comprehensive broadening of the national biomedical research base. While individual events are not easily identified in this context, some summarization is possible to provide a measure of the NIH investment in American science.

These specific gains can be cited:

175,000 non-Federal biomedical scientists have been supported by 253,000 research grants. Among these were 58 recipients of the Nobel Prize in Physiology or Medicine; three of these were NIH scientists and another one is a former NIH intramural scientist recognized for work begun at NIH and subsequently supported by the NIH at a non-Federal institution.

More than 55,000 individual scientists have been supported in their professional development in basic science or clinical specialties by funds distributed to academic and research institutions for advanced training.

More than 10,000 different institutions have received support for research and training programs.

18 million square feet of space have been added to the nation's biomedical research plant.

Principal medical institutions in all parts of the nation established, with NIH support, 84 General Clinical Research Centers with 827 beds in which research knowledge is extended and applied expeditiously to care of patients.

Under the Medical Library Assistance Act of 1965, health science libraries expanded their services and established 11 regional medical libraries.

The computer-based MEDLARS (Medical Literature Analysis and Retrieval System) was pioneered and developed in the early 1960's, giving health professionals everywhere quick access to the world's biomedical literature.

Accomplishments of Research
Conducted or Supported
by the
National Institutes of Health
1945-75

NATIONAL CANCER INSTITUTE

Cause and Prevention

Demonstrated that animal tumors can be produced by the nucleic acid core of a tumor-causing virus, and that viral genetic material is incorporated into the cellular genetic material of animals with virus-induced cancer. (1968-1972)

Further elucidated the association of type-C RNA viruses with human acute leukemias, lymphomas and cancer of the connective tissue (sarcomas). (1972)

Shown that there is variation among individuals in the metabolism of hydrocarbon carcinogens, and that this variation is a genetically inherited trait. Individuals with one form of this trait are more susceptible to lung cancer, induced by smoking or other environmental factors. Since such unusually susceptible individuals should refrain from smoking, mass screening of the population for this trait may be a future medical development. (1972-1973)

Identified many of the more than 100 viruses known to cause cancer in experimental animals. (1960-1975)

Investigated the association of herpes-type DNA viruses with Burkitt's lymphoma, cancer of the postnasal space and cancer of the uterine cervix. (1970-1975)

Mapping of U.S. cancer mortality by county has uncovered geographic patterns and clusters that should help to identify previously unrecognized causes of cancer. The maps were published in 1975.

Identified approximately 50 environmental agents associated with increased cancer in persons exposed, including certain metals, ores, air pollutants, and oils. This resulted in reduction of levels of exposure to many of these agents.

Described and characterized the role of endogenous (genetically transmitted) and exogenous (horizontally transmitted) RNA viruses as causative factors in neoplasia in certain animal models.

Determined that the use of high porosity paper, smoke dilution devices and certain reconstituted tobacco sheets help decrease the risk of disease, and lung cancer in particular, in the cigarette smoker.

Confirmed that the reduction of tar and nicotine emission of commercial cigarettes have resulted in a reduction of lung cancer mortality, therefore suggesting that further reductions could be achieved by cigarettes with progressively lower yields of tar and nicotine.

Established rigorous methods and extensive resources for long-term animal bioassays of environmental chemicals suspected of causing cancer; determined the evidence for carcinogenic activity of several hundred environmental chemicals. This already results in protective measures implemented in several countries to eliminate or reduce exposure of the population to many cancer-causing agents.

Developed and defined methods to induce neoplastic transformation of mammalian cells in culture with chemicals. These represent a breakthrough in carcinogenesis studies and testing, because of their short-term duration and because the effects of environmental chemicals can be studied directly on the target cells.

Developed animal models to study the induction and causative factors of major types of cancer as seen in humans (e.g., carcinoma of bronchus, larynx, large bowel, pancreas, breast, skin, etc.) and elucidated specific susceptibility factors.

Developed methods for the study of the effect of cancer-causing chemicals directly on human tissues and cells isolated in culture.

Demonstrated synergistic interaction between different chemicals and between chemicals and radiation in the induction of several cancers.

Developed very sensitive analytical methods for the identification of several carcinogens and their metabolites in tissues and from environmental sources (e.g., polycyclic hydrocarbons, nitrosamines).

Demonstrated that transplacental effects of carcinogens on the fetus can induce a large number of cancers at young adult age and developed methods for study of transplacental carcinogenesis.

Demonstrated the formation of carcinogenic N-nitrosamines in the body by interaction of nitrites and secondary or tertiary amines, and conditions controlling this reaction.

Detection and Diagnosis

Demonstrated that mammographic screening for breast cancer is an efficient technique for detecting early cancers in asymptomatic women and on the average diagnosed the disease a year earlier than would have been accomplished with existing techniques. Nearly doubles the proportion of cases found to be localized, and should thus increase the fraction of cases cured by one-third. Work done around 1970.

Development and demonstration of the usefulness of exfoliative cytology (Pap Test) as an important detection tool in the mass screening for cervical cancer. (1945-1975)

Clinical evaluation of the use of computerized axial tomography (CAT) in the diagnosis of cancer, especially cancer of the central nervous system and the kidney, is presently being conducted. This new technique is being called a "major break-through" by radiologists primarily because of its superior ability to detect abnormalities as compared with conventional radiological techniques and because of the relatively noninvasive character of the procedure. (1974-1975)

Treatment

Developed an effective, frequently curative, chemotherapeutic regimen for choriocarcinoma, a rare but once fatal tumor which arises from the placenta. (1956)

Identified the excess risk of cardiovascular death associated with estrogen treatment for patients with prostatic cancer. This work has led to the widespread adoption of a lower dose which is adequate to control the cancer but does not carry the excess risk. This work was done around 1967.

Research, development, and demonstration related the the usefulness of high-LET radiation therapy as a modality for cancer treatment has been supported by NCI since 1938. The importance of dose localization within the tumor volume with minimum dose to healthy surrounding tissue has been an inherent limitation in the use of x-rays, and led to the use of higher energy radiation for more effective treatment of deep-seated tumors. (1938-1975)

Established the effectiveness of the majority of the 42 most frequently used cancer drugs, primarily through studies done by the national clinical cooperative groups program. Results of this program have also shown that combined treatment modalities are often more effective than drugs alone. For this reason, the clinical cooperative groups are increasing their emphasis on combination treatment research, using surgery, radiation, chemotherapy, and immunotherapy. In 1975, the 23 groups in the program involved 21,000 patients, and influenced the treatment of at least 210,000 additional patients. (1955 - present)

Demonstrated the effectiveness of chemotherapy in the early stages of breast cancer in preventing recurrences in high risk patients. Work done in 1975.

Developed or participated in the development of more than 40 drugs useful in the treatment of advanced cancer.

Discovered that under certain laboratory conditions a group of new drugs related to vitamin A (retinoids) can revert squamous metaplasia in animals, at very low concentrations, and can prevent the induction of certain types of cancer (anticarcinogenesis) in animal models.

Developed experimental models for BCG immunotherapy.

Extended life for children with acute leukemia to almost 3 years after diagnosis, contrasted with the 2- to 3-month survival common in 1945, thanks to new forms of combination therapy and supportive care.

Developed the technique of platelet transfusions to prevent fatal hemorrhage in patients with acute leukemia receiving cytotoxic therapy.

Developed supportive techniques, including relatively "germfree" environments and transfusions of white blood cells, to prevent fatal infections among patients with acute leukemia undergoing myelosuppressive therapy.

Achieved a cure of 90 percent of patients with early-stage Hodgkin's disease through high-dose, intensive radiotherapy to affected lymph nodes and adjacent lymph node regions.

Achieved freedom from all evidence of advanced-stage Hodgkin's disease for 5 years for 75 percent of patients in a group treated with a combination of 4 anti-cancer drugs.

Basic Biology

Synthesis of biologically functional genes, including a small 77-unit gene that comes from a yeast cell and the more complicated 126-unit tyrosine transfer RNA (ribonucleic acid) gene. (1970)

The demonstration that the specific sites exposed on the membranes of virus-transformed cells can be masked, causing the cells to behave normally; and that these sites, which are exposed on malignant cells throughout the cell cycle, are exposed on the surface of normal cells only during cell division. (1972)

The radiosensitivity of cells varies significantly at different stages of the cell cycle suggesting that inducing partial tumor cell synchrony either by chemical inhibition, or by using the mitotic delay produced by radiation response is a real possibility. Cell population kinetics data and the development of techniques for sensing parasynchronous variations in the cell cycle in vivo are being explored. (1972)

Conducted basic research leading to the prediction of the existence of an RNA-dependent DNA polymerase, or reverse transcriptase, associated with RNA tumor viruses. Subsequently demonstrated such an enzyme in more than 30 viruses known to cause cancer in animals, in human leukemia cells,

and in some human milk specimens from women with family histories of cancer. The evidence suggests that the enzyme may be a key element in the change of normal cells to cancer cells. (1964-1975)

Developed a specialized cancer data base. Cancerline, as the system is called, contemplates the addition of 10,000 cancer chemotherapy abstracts annually, and will also include about 10,000 descriptions of current cancer research, including protocol summaries.

Identified the metabolic enzyme pathways which control the activation or detoxification of several carcinogens in tissues, and developed techniques to measure such enzyme activity in human cells or as a means to identify highly susceptible individuals.

Identified the chemistry and mode of action of complement components.

NATIONAL HEART AND LUNG INSTITUTE

Cause and Prevention

Discovered (1945-1946) a then common but unrecognized pernicious anemia-like affliction of young infants and prematures called megaloblastic anemia of infancy and showed the cause to be lack of an essential vitamin, folic acid. Showed that the deficiency of the substance was potentiated by poor vitamin C intake. These studies lead to modification of infant diets that has virtually eliminated megaloblastic anemia.

Demonstrated (1949) the nature of Sickle Cell Anemia as a genetic disorder involving a double dose of the sickling gene and (the same year) as a biochemical defect resulting in the complete replacement of normal adult hemoglobin by the abnormally viscous sickling hemoglobin. By contrast the relatively harmless sickling trait was shown to be the carrier state where a single abnormal gene is paired with a normal gene and the hemoglobin produced by these two genes is a mixture of normal and abnormal hemoglobin. These discoveries opened up the whole field of human biochemical genetics.

The recognition of folic acid as a vital substance in the metabolism of precursor blood cells in the bone marrow paved the way for the concept of "anti-metabolites" as a means of controlling the growth of malignant (leukemic) cells. This (1949) became the point of departure for the modern treatment of leukemia which in children today yields 5. year cures in 50% of the cases.

Established the importance of three risk factors in the development of arteriosclerotic heart disease in men. Use of three factors in combination—blood pressure, relative weight and serum cholesterol permitted the separation of men into groups with highly divergent risks of arteriosclerotic heart disease. (1950-1957)

Established the association of cigarette smoking to incidence of fatal and non-fatal coronary heart disease. (1957-1965)

Developed new statistical methodology making possible the establishment of multiple risk functions applicable to the measurement of risk of cardiovascular disease. (1967)

Disclosed, in 1969, that persons with heterozygous as well as homozygous antitrypsin deficiency are subject to chronic obstructive lung disease at a relatively early age.

Using powerful statistical techniques, a seven variable predictor of coronary heart disease based on the Framingham Study experience was made available for general use. These seven risk factors are age, sex, cigarette smoking, blood pressure, serum cholesterol, glucose tolerance and electrocardiographic findings. (1971)

Established the importance of precursor risk factors for atherosclerotic brain infarction and for intermittent claudication. The relationship of these risk factors was as strong for women as for men and included the same factors as found important determinants of coronary heart disease. (1972)

Established that certain American populations (Japanese-American and Puerto Rican men) have less than one-half the incidence of coronary heart disease than found in Framingham men thereby suggesting that natural factors resulting in low coronary disease rates should become identifiable. (1972-1974)

Provided evidence that certain inherited forms of atherosclerosis are the result of a genetic defect in cellular membranes. Membrane receptors which "sense" serum cholesterol levels and are a link in the control of cholesterol biosynthesis by cells were shown to be defective. (1973)

Established that men who discontinued cigarette smoking have a reduced incidence of coronary heart disease compared with men who continued their smoking habit. (1974)

A highly useful "coronary profile" by which physicians can identify highly susceptible individuals long before the disease produces clinical signs has received widespread acceptance and provides a basis for preventive measures. (1971-1974)

Major clinical trials to determine the extent to which morbidity and mortality from hypertension and coronary heart disease can be reduced have been initiated in populations at high risk of cardiovascular disease. These major tests of the potentials for prevention are now in progress. (1973-1975)

Failed to find evidence of reduction of mortality among men who used cholesterol lowering drugs following recovery from a myocardial infarction. Factors reflecting the state of the myocardium were more important determinants of survival following a heart attack than was the level of blood lipids. Thus the factors of importance following a heart attack appear to be different from those factors that lead to a heart attack. (1975)

Traced the enzymatic reactions involved in the metabolism of red corpuscles and discovered a number of genetically determined enzyme defects associated on the one hand with certain congenital anemias, on the other with the occurrence of acute (hemolytic) anemia upon exposure to common drugs and household poisons, such as anti-malarials or naphthalene, as in so-called G-6PD deficiency. At the same time "sex-linked" genetic transmission of this anomaly was shown and screening tests were developed, permitting rapid diagnosis and proper treatment as well as prevention (by avoidance of exposure to potentially harmful drugs) for the large population at risk (almost 10% of U.S. black males).

Developed a method of prophylaxis against RH hemolytic disease which, by giving RH negative mothers anti-RH serum immediately after delivery, has virtually eliminated RH hemolytic disease as a cause of infant mortality and morbidity.

Discovered the condition known as DIC (disseminated intravascular clotting), now known to be a common hazard for patients in shock, after certain generalized infections and in various other conditions. The recognition of this syndrome made possible rational and effective treatment with the anti-clotting substance heparin.

Discovered vitamin B-12 as the substance whose inadequate absorption is responsible for pernicious anemia, leading to the development of a simple, effective, permanent replacement therapy with a pure substance.

Detection and Diagnosis

Developed in the late 1940's, shortly after the discovery of RH factor and its role in the causation of stillbirth and hemolytic disease of the newborn, methods for prenatal diagnosis using the pregnant mother's serum, and for treatment (exchange transfusion with RH negative blood) of the disease in the newborn.

Introduced a simple urinary test for malignant carcinoid (1955). This tumor, often involving intestinal tissues, was virtually unknown before 1954, but as a result of the diagnostic test, was subsequently found to occur rather frequently.

Developed, in 1958-59, the transeptal method of inserting catheters into the left heart chambers.

Improved diagnostic accuracy for the detection of deep vein thrombosis has been achieved through the development of radioisotope techniques. (1964)

Reported, in 1967, that electrophoretic analysis of blood lipoprotein patterns provides a simple, low-cost method of detecting and classifying blood lipid disorders. The report emphasized the importance of differentiating cholesterol and triglycerides disorders on the basis of the lipid transport vehicles that carried them. This has led to the present concepts and approaches to blood fat disorders as different types of hyperlipoproteinemia.

Successfully delineated the antigenic and coagulation properties of Antihemophilic Factor, thus leading to the development of a potentially accurate method for the detection of hemophilia carrier states. (1971)

In 1974, developed a new instrument for visualizing heart defects without the sometimes risky insertion of catheters and dyes into the bloodstream. The new 2-dimensional technique, called "echocardiography," is particularly valuable in diagnosing heart defects in the small hearts of infants and young children.

In 1975, reported a simple non-invasive technique for tagging and photographically visualizing myocardial infarcts as "hot spots" through intravenous injections of a bone-scanning agent, ^{99m}Tc stannous pyrophosphate. The technique is valuable not only for establishing the presence or absence of an acute myocardial infarct but also for estimating its size.

A novel diagnostic technique for detecting hyaline membrane disease in the fetus involves sampling amniotic fluid (amniocentesis). This rapid and easy test for surfactant provides the ability to predict hyaline membrane disease and permits the earliest possible medical care.

Applied the methods of molecular genetics to Cooley's anemia, a genetic defect affecting large numbers of persons of Mediterranean and Asian ancestry, showing that the defect in this condition involves a genetic disturbance in the quantitative regulation of hemoglobin production and to making possible the development of a screening test for carriers of the "Cooley's trait" with application to genetic counseling.

Genetic basis for emphysema. A screening test for alpha-1-antitrypsin deficiency has been developed. This phenotype has been shown to be associated with the development of a severe form of familial emphysema which affects young adults.

A new and sensitive method as been developed for the early detection of changes in lung function which appear to be the first sign of chronic obstructive pulmonary disease. The measurement of "closing volume" may be useful as a mass screening test for COPD.

A sensitive test to detect asthmatics has been developed. Asthmatic patients even in an asymptomatic stage can be identified when exposed to methacholine.

Treatment

Successfully applied, in 1952, repetitive electrical stimuli to sustain effective human heartbeat in the first of a family of heart pacemaker devices whose development has progressed through portable battery-powered pacemakers, including completely implantable versions, to nuclear-powered pacers currently in clinical use.

Reported, in 1952, the first successful use of an artificial valve in the human circulatory system. By demonstrating the feasibility of such a prosthesis Dr. Charles Hufnagel paved the way for subsequent development of the wide variety of artificial valves in use today.

Developed the first successful heart-lung machine, used in 1953, to maintain heart and pulmonary function during open-heart surgery; the success of this and other pioneering advances stimulated development of many highly efficient machines employing a variety of new pumping and oxygenating principles.

Discovered the anti-hypertensive effectiveness of chlorothiazide (1957). Chlorothiazide was found to be selective for hypertension, effective orally, and free of severe side effects. It was also found that chlorothiazide not only lowers blood pressure directly when used alone, but also greatly enhances the effectiveness of other anti-hypertensive agents when used in combination with them.

Conducted pioneering research on enzyme inhibition as an approach to hypertension, in the process demonstrating (1959) the clinical effectiveness of alpha-methyl DOPA, now a standard for the treatment of high blood pressure.

Developed, in 1960, the first practical technique of transplanting the heart—the one in widest use today. This technique leaves in place a portion of the recipient's right and left atria, simplifying and shortening the operation.

Since 1963, evolved a highly promising artificial lung (spiral coil membrane blood oxygenator) which is undergoing nationwide clinical trials of its ability to provide total respiratory support for periods of days or weeks to patients with acute, potentially reversible respiratory failure.

In 1965, introduced an entirely new approach to the production of concentrated anti-hemophilic globulin (AHG) used for treating hemophilia patients. It was shown that, using a standard double plastic bag set, any hospital or blood bank can easily make concentrates of AHG averaging 30 times the potency of frozen plasma, in such a way that the whole blood from which the concentrate was made can be "reconstituted" and banked for other uses.

Produced knowledge leading to the elucidation of the complex functions of blood platelets and established the effect of aspirin and other drugs on these functions, forming the basis for clinical use of anti-platelet agents in the treatment of certain hypercoagulable states. (1965-1975)

In 1971, developed an electro-optical device, called the "Optisat," that provides continuous measurements of blood-oxygen levels during the use of heart-lung machines or respiratory assist devices.

Increased understanding of histocompatibility antigens, leading to HLA typing of platelets for transfusion. This is a critical development in the treatment of patients with acute leukemia receiving cytotoxic therapy. (1972)

Established that a significant reduction in mortality and morbidity from severe and moderately severe hypertension could be achieved by sustained anti-hypertensive drug therapy by a clinical trial conducted by the Veterans Administration. (1973)

The demonstration in 1973-74 that the size of the myocardial infarct, or portion of heart muscle which is killed by the occlusion of the coronary arterial branch supplying it, can be reduced--and vitally needed heart muscle saved--by the administration of nitroglycerin and methoxamine during the acute phase of the heart attack.

Developed a synthetic analog of lidocaine which is effective orally for the treatment of certain arrhythmias. (1973-75)

Devised a new system that eliminates the contamination of blood during processing. This sterile connecting technique will substantially increase the storage time of blood and its components for future transfusion to patients in need. (1975)

Unravelled the complex system of blood clotting factors, identifying among others the factors whose lack is responsible for two different kinds of hemophilia ("A" and "B"), thus permitting the use of specific plasma fractions for the treatment of hemophilia, factors VIII and IX.

Developed an effective procedure, well within the capability of the ordinary blood bank, for obtaining factor VIII, needed by the majority of hemophiliacs, by precipitating fresh plasma in the cold and resuspending the "cryoprecipitate" in a small volume of saline. This has revolutionized the treatment of hemophilia by making available a potent preparation which can be administered at home by the patients themselves or his families.

A further consequence of this development was fractionation of factor VIII from cryoprecipitates to relatively pure concentrates of known potency. Standardization of factor VIII content has made possible home care as well as treatment of bleeding complications for hemophiliacs including, even brain and open-heart surgery when indicated.

Basic Biology

Developed the spectrophotofluorometer (1954-55), an extremely sensitive instrument for identifying and quantifying biological substances.

Showed that microsomes located within cells of the liver are a principal means by which the body inactivates drugs (1955). The microsomes contain enzyme systems that can change foreign compounds into forms which the kidney can excrete.

Established during the 1950's that a number of drugs which act on the central nervous system and affect blood pressure also produce changes in the concentrations of amines such as norepinephrine and serotonin in nerve tissue. This prompted a wave of highly fruitful investigation into the functions of amines as nerve impulse transmitters and as possible mediators of both psychologic and blood pressure changes.

Challenged classic concepts of heart action in health and disease, and provided a valuable index of heart performance. In 1957, it was found that the tension developed by the fibers of the heart muscle at each beat--not the amount of blood it pumps or the length of the muscle fibers--governs its demands on the coronary blood supply for oxygen.

Produced knowledge of the chemical structure, physiologic role and clinical potential of the calcium-regulating thyroid hormone, thyrocalcitonin, in 1968. NIH studies defined the structural interrelationships of the 32 amino acids in the thyrocalcitonin molecule, and developed a sensitive method for assay of the hormone in the blood. They also provided the earliest demonstration of the therapeutic potential of this hormone in patients with hypercalcemic bone demineralization disorders.

Developed a red blood cell-freezing process in 1969 which will preserve blood safely for several years.

In 1971, elucidated the complete amino acid sequence of the first of six known protein components of lipoproteins, the transport molecules for most of the fatty substances (lipids) in human blood.

The adaptation in 1974-75 of cell fusion methods (e.g. hybrids of human x rodent blood cells) to exploration of genetic hemoglobin abnormalities such as Cooley's anemia.

Identified the globin (protein) portion of the adult hemoglobin molecule as consisting of two pairs of amino acid chains (called alpha and beta) produced by two corresponding pairs of genes, and showed the sickling abnormality to be a point-mutation involving the substitution of a single amino acid in the beta chain. This was the beginning of molecular biology in human genetics, leading to the discovery of many of the abnormal hemoglobins (to date over 100 have been identified) and to mass screening and accurate diagnostic procedures for sickling and to a rational approach to sickle cell disease.

The complete amino acid sequence of four of approximately ten protein components of lipoproteins, the transport molecules of blood fats, has been elucidated.

An enzymatic procedure for dispersing lung tissue into separate viable cells has been developed. Since the lung is a complex structure of over 40 different cell types, this opens the possibility of isolating and culturing the types of cells associated with various lung disease states.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Cause and Prevention

Found the organism causing a new disease called rickettsialpox, showed where the organism was harbored, and how it was spread. (1946)

Discovered that cases of Q fever in southern California were related to contact with dairy cattle or raw milk. (1947)

Isolated Histoplasma capsulatum (the fungus causing the disease histoplasmosis) from natural reservoirs such as soil, and bird and bat roosts. Evidence accumulated over subsequent years identified pigeon droppings as a similar important reservoir for the fungus Cryptococcus neoformans causing the sometimes fatal disease, cryptococcosis. (1948)

Isolated the adenoviruses leading to the development, from 1955 on, of effective live vaccines particularly useful in preventing epidemics of severe acute respiratory disease in some civilian populations and in military training camps. (1953)

Established Colorado tick fever as a disease entity of viral origin and not a mild form of Rocky Mountain spotted fever. Discovered that the virus persists for months in red blood cells, making victims of Colorado tick fever hazardous blood donors. (1950-1973)

Made the first isolation of Toxoplasma gondii from a human eye and demonstrated that some forms of eye disease can be caused by this parasite. The domestic cat was identified as a natural host in the parasite life cycle, suggesting a possible relationship between cats and toxoplasmosis in humans. (1954-1964)

Defined specific autoantibodies responsible for autoimmune connective tissue diseases. (1960)

Discovered and isolated the virus that causes Bolivian hemorrhagic fever, showed how the disease was spread, and brought a major epidemic under control. (1960's)

Discovered the causative parasite of eosinophilic meningo-encephalitis in the spinal fluid of victims. Further study showed that the land crab is the source of many infections. (1960's)

Described the basic chemistry and function of components of the complement system leading to recognition and description of complement deficiency diseases. (1960)

Determined that the causative agent of primary atypical pneumonia is not a virus but Mycoplasma pneumoniae. Also established the benefit of tetracycline treatment of this common respiratory infection. (1962)

Isolated members of other virus families--the parainfluenza and respiratory syncytial viruses--and, in work continuing to the present, showed them to be leading causes of serious respiratory illnesses in infants and young children. (1958-1963)

Identified IgE as the humoral antibody factor responsible for immediate hypersensitivity and manifestations of allergic disease in man. (1967)

Discovered that cholera enterotoxin directly stimulated adenyl cyclase activity in gut mucosal cells, but in a different way than naturally occurring hormones. These results have opened a whole new area of biological research involving the cAMP system as well as identifying a mechanism involved in cholera diarrhea. (1968)

Developed attenuated strains of the important respiratory tract viral and mycoplasmal pathogens by production of conditional lethal, temperature-sensitive (ts) mutants. (1970)

Developed a rapid procedure, called the hemolymph test, to detect rickettsial infection in ticks. (1970)

Developed a highly sensitive test for antibody to hepatitis B virus; participated in the establishment of the chimpanzee as a useful animal model for hepatitis B; and, produced a prototype hepatitis B vaccine now being tested in animals. (1971-1975)

Found the sexual forms of reproduction of Histoplasma capsulatum; discovered similar forms of cryptococcus. Such forms were previously believed non-existent. Now, observations of mating between strains are giving researchers the opportunity for genetic studies which will explain more about disease-causing capabilities and geographic distribution of these medically important fungi. (1971-1975)

Cultivated a papova-like virus from the brain of a patient with progressive multifocal leucoencephalopathy (PML) complicating Hodgkin's disease. This newly isolated virus (called JC virus) apparently commonly infects persons in Wisconsin as revealed by serologic surveys for antibodies--60 percent of the adults had antibodies against the virus. (1972)

Developed the first hybrid, or recombinant, virus used for immunization of man against any disease. This technique was used to produce a recombinant influenza virus vaccine. (1972)

Developed a sensitive new test for detection of antibody to Mycoplasma pneumoniae, an organism that causes outbreaks of acute respiratory infections seasonally. The test, a modification of a radioimmunoprecipitation procedure, should enable scientists to learn more about the disease pattern of this organism in man. (1972)

Identified a specific enzyme called DNA polymerase, in the Dane particle cores associated with hepatitis B, and provided further evidence that the Dane particle is actually the virus of hepatitis B. (1973-1974)

Demonstration that herpes simplex virus established persistent infection in the trigeminal gangli of rabbits with recurrent eye infection. This supports the theory that in man these viruses are maintained in some quiescent state from which they may be reactivated to produce overt disease. (1973)

Photographed and identified the virus that causes hepatitis A. Developed a practical laboratory technique for detecting this virus and antibody to it. (1973-1975)

Studies of a dengue epidemic revealed that primary infection with dengue virus can cause severe hemorrhagic disease. It had been previously believed that the primary infection was mild and only a secondary infection produced severe disease. (1974)

Reinforced the concept that a woman with acute viral hepatitis B late in pregnancy or soon after delivery is much more likely to transfer the infection to her infant than the woman infected early in pregnancy or the woman who is an asymptomatic carrier. The infected mother-infant pairs add to the pool of hepatitis B virus within the community. (1974)

Identified, for the first time in the United States, a reovirus-like agent causing severe infant diarrhea, and developed a complement fixation test for the agent, using a closely related calf diarrhea virus as an antigen. (1974-1975)

Developed or played important roles in field testing vaccines against rubella, meningococcal meningitis, mycoplasma pneumonia, and pneumococcal pneumonia. (1960's)

Related the presence of a specific minor blood group substance (Duffy) on red cells to attachment and penetration of some malarial parasites, and the absence of this substance, to resistance to malarial infection. The widespread occurrence in West Africa of Duffy-negative persons may account for the absence, there, of one form of malaria. (1975)

Confirmed and extended studies showing that brain tissue and sera from multiple sclerosis (MS) patients contain what appears to be a small virus called the multiple sclerosis associated agent (MSAA). (1975)

Showed that glomerular blood vessels in the human kidney contain specific receptors that can bind immune complexes--aggregates of antigen, antibody and complement molecules--and cause serious kidney disease. (1976)

Evaluations were made of the efficacy of an antirabies vaccine produced in a human diploid cell culture (HDCS) when the vaccine is given after exposure to rabies virus. It was demonstrated that a single dose of

antirabies vaccine prepared by virus propagated in HDCS culture can completely protect monkeys from a virulent challenge with street rabies virus administered several hours prior to vaccination.

Demonstrated that the insect-borne LaCrosse (LAC) encephalitis virus is passed from one generation of mosquitoes to the next in the female's eggs. This mechanism--never before demonstrated in a mosquito-borne virus--probably explains the virus' ability to survive freezing winters. LAC virus, a member of the so-called California Encephalitis Group, has plagued parts of rural Wisconsin for about 20 years. The virus attacks young children primarily, causing severe illness with high temperature, headache, nausea, vomiting and convulsions. New knowledge of LAC virus gained in these studies may help efforts to control the agent.

Showed that in syphilis infections there is a generalized suppression of the host cellular immune response, particularly of the lymphocyte system.

Successfully used human fetal liver cells to reconstitute immunologic function in infants with severe combined immunodeficiency. (1975)

Detection and Diagnosis

Developed fluorescent antibody tests utilized in procedures for diagnosis and research in infectious and immunological diseases. (1956)

Description of antibody binding test and development of radioimmune assay procedures with feasible clinical application for the identification of serum constituents, e.g., hormones. (1961)

Development of penicillin derivative agents suitable for use in the diagnosis of penicillin allergy. (1962)

Developed the histamine release test from leucocytes of sensitive individuals to provide a sophisticated methodology for diagnosis and research in allergic diseases. (1967)

Supported the development of a tissue-matching test, employing mixed leukocyte cultures that led directly to the first successful bone marrow transplant between persons other than identical twins. Later supported refinement of the technique so donors and recipients can be more rapidly typed for specific lymphocyte-defined (LD) antigens, thus facilitating better matched transplants. (1967-1975)

Development of XC plaque test used to detect in cells one type of leukemia virus. (1970)

Developed a radioactive antigen binding assay for anti-pili antibody showing great promise as a specific test for gonococcal infection, especially in the asymptomatic person. The inability to detect the

asymptomatic carrier is one of the major problems in the current gonorrhoea epidemic. (1973)

Supported the development of highly sensitive techniques to measure the immunologic compatibility of cells from organ transplant donors and recipients.

Treatment

Refinement of the oral fluid replacement treatment for cholera. In use since 1966, oral fluid replacement has saved thousands of lives in situations where intravenous fluid replacement was not possible.

Use of enhancing antibody-containing serum for successful bone marrow transplantation in the treatment of immune deficiency diseases (subsequently utilized in the treatment of aplastic anemia). (1971)

Development of a new approach for treating life-threatening bacteremias caused by Gram-negative bacteria by production of an effective antiserum made against the exposed core of the E. coli. (1975)

Zoster immune globulin is the first effective therapeutic agent for both prevention and attenuation of varicella (chickenpox) in exposed high-risk and moderate risk individuals who are immunologically normal.

Synthesized three broad spectrum antibiotics, oxytetracycline, chlortetracycline, and tetracycline. All three of these antibiotics are used to combat the organisms responsible for certain pneumonias and other respiratory disorders, yaws, syphilis, cholera, anthrax, meningitis, typhus, whooping cough, scarlet fever, skin and eye disorders, and food poisoning caused by salmonella germs.

Basic Biology

Supported immunology research which led to the first case in which the life of a human was saved by transplanting a kidney from another human. (1955)

Intensive studies of the nutritional requirements of cells led to development of an artificial medium (Eagle medium) now widely used in tissue culture, a technique that revolutionized the study of viruses and cell biology and has made possible the study of many viruses that may be implicated in cancer. (1955)

Described and demonstrated transfer factor, a material obtained from leucocytes of individuals with specific delayed hypersensitivity. Showed potential application in transfer of cell mediated immunity to patients manifesting a lack of protection in some infectious and immunological diseases. (1958)

Characterization of protein and genetic structures of human viruses--parvo, adeno, papova, and pox viruses. (1960's)

Found that different animal tumors induced by the same virus (polyoma) contained a new common antigen distinct from the viral antigens. Experimental animal tumors induced by viruses were shown to contain antigens of the virus long after recoverable virus had disappeared from the tumor tissue. (1961-1963)

Development of models to explain the immunologic aspects of the etiology and pathogenesis of kidney disease, i.e., glomerulonephritis. (1961)

Described and developed methods for the study of products released from mast cells responsible for immediate hypersensitivity mechanisms and manifestations of allergic diseases. (1961)

Discovered the drug resistance transfer factors in gram-negative bacilli which play an extremely important role in the evolution of bacterial drug resistance. (1963)

Developed basic animal models for the study of genetics and genetic control of immune responses suggesting potentially important applications for the development of tolerance in allergic and immunologic diseases. (1963)

Defined IgA and secretory antibody function in surface immunity. (1965)

Discovery that cells malignantly transformed by adenovirus continue to carry at least part of the viral genome. The transformed cells do not produce infectious viruses, but they continually produce some viral proteins, or T antigens. (1960's)

Demonstration that genes controlling immune response determine the ability of lymphocytes to recognize antigens specifically. Genetic factors on the same chromosomal regions also determine the presence of certain cell surface components called transplantation antigens. (1965)

Developed in vitro methods for the study of cell mediated immunity and especially lymphokines, soluble products of lymphocytes responsible for immune functions in infectious and immunological diseases. (1966)

Achieved the first test tube synthesis of fully infectious virus deoxyribonucleic acid (DNA), an important preliminary to understanding virus duplication in cells. (1967)

Discovery that a diabetes-like syndrome can be produced in mice infected with encephalomyocarditis (EMC) virus. Effects of this virus were studied in mice of varying genetic constitutions to try to determine the role of heredity in development of human diabetes. (1968)

Described the molecular structure of immunoglobulin leading to an increased understanding of the chemistry of antibodies and their function in immunological disease. (1968)

Discovery that interaction of T and B lymphocyte cell types is necessary for development of an adequate immune response. (1969)

Discovered a viral enzyme, reverse transcriptase, which enables the ribonucleic acid (RNA) in certain animal viruses to produce deoxyribonucleic acid (DNA). This finding may have important implications for cancer research. (1970)

Showed that treatment of mouse cell cultures with either of two specific chemicals (IUDR and BU DR) rapidly activates mouse leukemia virus from DNA of seemingly normal cells. Demonstrated definitely that in animals some oncogenic viruses can be inherited as part of an animal's normal chromosomal material. (1971-1975)

Developed a gene transplantation technique by combining DNA from different bacterial sources into biologically functional plasmids and reported the first successful propagation of animal cell genes in bacteria. (1973)

Extended the work on genetics of the immune response to define the role of immune response genes and their relevance in heredity of allergic disease. (1974)

Cause and Prevention

Found that the lungs of infants who died from the respiratory distress syndrome attributed to hyaline membrane disease are deficient in surfactant. (1959)

Surfactant, normally produced by the alveolar cells of the lungs, lubricates the surface of the lungs' air sacs and prevents their collapse. (1955)

Ample evidence now links a specific lung cell, the type II cell, with surfactant production. Surfactant and its alteration seems to play a functional role in a number of pathological conditions including neonatal and adult respiratory distress syndrome, oxygen toxicity and pulmonary edema. (1970)

Demonstrated in fetal sheep that when a fetus has insufficient oxygen the first pathological change occurs in the brain's electrical activity and is accompanied by a changed heart rate. Extensions of this study may lead to new ways of preventing brain damage and mental retardation. (1966)

Developed various life-saving devices, such as a "fetal intensive care unit" that allows sensitive monitoring of the fetus during labor and delivery. This unit, when used in combination with observations of the mother, permits researchers to identify subtle alterations in the physiological state of the fetus before gross changes become clinically evident. (1970)

Anorexia nervosa has been studied in young women, and the data conclusively indicates that a large component of the disease is related to disordered hypothalamic function. Cyproheptadine, has been shown to be effective in treating a number of these women. (1975)

A new inborn error of metabolism has been identified as being due to gamma-glutamyl transpeptidase deficiency. Another inborn error of metabolism associated with oxyprolinuria has been shown to be associated with marked reduction of glutathione synthase. (1974)

Low sodium diets in sheep were shown to be associated with a significant increase in fetal mortality. (1975)

Provided evidence that victims of sudden infant death syndrome (SIDS) although appearing normal, have detectable irregularities in respiration, and experience apnea during sleep. Increased frequency and duration of apneic episodes appear to characterize those infants found by other criteria to be at high risk for SIDS--low birth weight, shortened gestation, and mild upper respiratory infection. (1973-1974)

Demonstrated that food supplementation for poor, pregnant women markedly decreased the number of low birth weight babies. In addition, children receiving protein-calorie supplements performed significantly better on tests measuring motor, manipulative, and cognitive skills. (1966-ongoing)

Developed evidence that readers, both children and adult, convert visually presented letters and words of short-term memory storage into phonetic form. This finding is important for training normal and dyslexic children to read since it suggests that early emphasis on translating script into sounds could result in significant improvement in reading skills. (1976)

Two case-control studies of breast cancer and oral contraceptive use have found no difference in the overall risk of breast cancer among women on the pill as compared to controls. However, one of the studies has shown an increased relative risk of breast cancer among certain subgroups of women. (1975)

Several studies are concerned with determining the effect of contraceptive agents which are used immediately before or around the time of conception, and the occurrence of birth defects. In one of these it has been found that among the offspring of 100 women with known first trimester exposure to estrogen and/or progestogen, nine offspring were observed with major and minor birth abnormalities. These included four major and four minor cardiovascular defects. (1976)

Women in the U.S. 18-39 years old, in 1975 as in 1974, overwhelmingly prefer having two children. Three-fourths of women 18-24, compared to less than half in 1967, expected to have no more than two children. Moreover, the proportion of women having a child in the first two years of marriage is lower than the period 1955-1965. There is also evidence of increasing birth intervals between first and second and subsequent births, although the incidence of childbirth before and just after the first marriage is on the rise. (1972-1975)

There are some new preliminary findings concerning the social and psychological factors influencing illegitimacy. They indicated that rates of premarital intercourse among adolescents are rising, with a greater increase for women than men. Similarly, a study of college freshmen has found that attitudes favoring sexual permissiveness has risen between 1967 and 1975, especially for females. It also has been found that the legalization of abortion in California correlated with a dramatic drop in the illegitimacy rate there. (1975)

Research findings dealing with the effects of family size on child development and achievement report an inverse correlation between intelligence of offspring and family size, even when socio-economic status and intelligence of parents are taken into account. A related study shows that educational achievement is lower, the larger the family size, even when income is held constant. (1975)

Studies have been conducted on the effect of family size and the spacing of children on health. Preliminary findings indicate that pregnancies conceived in less than twelve months from the last pregnancy have a higher risk of early fetal death, especially if the last pregnancy resulted in a live birth. In addition, pregnancy intervals of less than twelve months result in conceptions that have a higher post-neonatal mortality rate for live births, and significantly reduce second and third year survivorship of children born immediately preceding the pregnancy. (1976)

Decisions regarding family size have been found to be largely influenced by the potential income of the household, the cost of rearing children related to the cost of other goods, and the subjective preferences for children maintained by the household. Because of the finding that education and labor force status interact to explain much of the variation in completed fertility, it has been postulated that these factors considered along with age and marital status, form a solid basis for the prediction of fertility behavior by couples. (1976)

Research on the changing dynamics of migration in the U.S. in the 1970's has revealed that populations in urban areas outside of the "sunbelt" states are declining; center cities in major metropolitan areas are likely to suffer adverse effects from outmigration reminiscent of the problems encountered by declining rural areas in the 60's; and the return of retired persons to their place of origin is a growing component of migration. (1975)

Detection and Diagnosis

Developed a quick and easy inhibition assay test with a few drops of blood for detection of PKU (Phenylketonuria), a genetic biochemical defect which results in mental retardation unless controlled by a dietary regimen. (1963)

Shown that amniocentesis, performed for antenatal diagnosis, is safe for mothers and fetus. (1975)

Demonstrated the value of amniocentesis in diagnosing numerous fetal conditions: chromosomal abnormalities, enzyme defects, hemoglobinopathies. The enzyme defect has been demonstrated in over 100 inborn errors in infants and children. (1965-ongoing)

Developed a fiberoptic fetoscope capable of identifying gross anatomic abnormalities of the fetus. (1974)

Means have been devised for the accurate pre-surgical diagnosis of medullary carcinoma of the thyroid. (1972)

Developed in utero screening tests for detection of specific enzyme defects causing Gaucher's, Niemann-Pick, and Tay-Sachs diseases, which result in mental retardation or physical disability. Screening

tests have also been developed for detection of Wilson's disease, meta-chromatic leukodystrophy and abnormalities of amino acid metabolism. (1968)

A technique based on operant conditioning has been used successfully to detect hearing problems in babies permitting early recognition of a handicap and early therapy. (1973)

Treatment

Revealed that newborns exposed to long periods of artificial light do not develop hyperbilirubinemia, which causes jaundice that can lead to brain damage and retardation. The light treatment is particularly effective for premature babies. (1969)

A therapeutic advance in the treatment of hyaline membrane disease--continuous positive airway pressure--used in conjunction with artificial ventilation keeps the infant lung expanded and oxygen exchange functioning. (1972)

Electrical surface mapping of the heart has permitted precise surgical interruption of the tracts from aberrant nodal foci in Wolf-Parkinson-White syndrome. (1972)

Significant advances have been made in the metabolic control of carbohydrate metabolism in relation to hypoglycemia in infants and children. (1973)

Retarded children have been taught to communicate without speech using a simplified symbolic language. (1975)

Clinical studies on the safety and efficacy of ethynyl estradiol and conjugated natural estrogens as postcoital contraceptive agents have been completed in about 650 women. The efficacy of these drugs was found to be excellent, as expected, and no major side effects have been encountered.

Basic Biology

The elucidation of the metabolism of vitamin D in humans has been accomplished in the last 5 years. (1970)

Significant advances have been made in the understanding of the physiological interrelationship of mother and fetus. (1976)

An animal model has been developed for the study of diabetes in pregnancy and the effects on the infant and fetus. (1971)

Significant insights have been accumulated regarding infant-maternal interaction, ability of the infant to be trained to perform conditioned responses, and the value to stimulation in early infancy in enhancing later performance. (1969)

There has been a rapid evolution of information about the immune mechanism which has been applied to the diagnosis, study, and treatment of infants and children with heritable and acquired disorders of their immune system. (1968)

Partial digestion of human growth hormone has been shown to increase the plasma half life of the modified hormone in human subjects and shown to be a consequence of prolonged half life in the subjects. (1975)

Polysaccharides from *E. coli* were shown to contain hybrids having an alpha 2,8 and alpha 2,9-linked heteropolymers of sialic acid, whereas meningococcus group C polysaccharide consisted of pure alpha 2,9-linked polymers of sialic acid. These identifications were carried out with nuclear magnetic resonance techniques which provided a new mode to solve problems which were virtually insoluble by previous techniques. (1975)

It was found that the terminal trypsin-digested fragment of hCG contained 123 carboxy terminal amino acid residue groups of the hormone subunit. It was found that this sequence was not duplicated in any other glycoprotein hormone. It was also shown that the immunological properties of the hormone are resided in the last 18 amino acid residues of the peptides studied. (1975)

The protein with properties of the receptor for testosterone has been demonstrated in cell sap from glomerulosa cells derived from preantral follicles of estrogen-primed hypophysectomized immature female rats. It was also shown that testosterone is translocated to the nucleus of these cells where the steroid is bound to a macromolecule. (1975)

Using radioligand-receptor assays and radioimmunoassay simultaneously, it has been possible to calculate with greater accuracy the affinities and the number of receptor sites in gonadal tissue in relation to growth and development. (1973)

Studies of the pregnant animals have shown that the placenta secretes an adrenocorticotrophic substance which maintains adrenal weight and prevents the decline of cortisol levels in maternal serum following hypophysectomy. (1974)

Reagents have been developed for detecting and measuring chorionic gonadotropin in rhesus monkey serum, and this technique has been used in the detection of early pregnancy in baboons, marmosets, and chimpanzees. This has been of great value to research workers using these animals in reproductive research. (1974)

Cortisol and thyroxin have been shown to have a profound effect on regulatory mechanisms involved in the maturation of the developing lung and the constituent surfactant. (1973)

Studies have shown that a monthly gonadotropin pattern exists prior to menarche in young women and at least in some girls prior to any signs of puberty. (1974)

An animal model for the study of intrauterine growth retardation has been developed, and studies are underway to determine the differences with the normal fetus. (1964)

Studies with pregnant sheep with methods capable of determining umbilical and uterine blood flow as well as catheterized samples from mother and fetus have been used to test the effect of a number of drugs that are used during delivery in relation to pregnancy. Some of these drugs have given quite unexpected effects on these parameters. (1975)

A bacteriophage lambda has been modified for use as a safer vector for the formation of recombinant DNA molecules. This phage should be of enormous value to a host of scientists whose research will now turn to the formation of recombinant DNA molecules utilizing DNA from prokaryotic organisms in culmination with that of higher organisms. (1975)

A new phosphonucleotide, guanosine tetraphosphate, has been found to have broad control effects on protein synthesis. (1973)

With a new technique, it has been shown that nuclei of infected cells contain the large RNA that comprises the entire viral DNA. (1973)

Studies of lens mRNA have shown that the delta-crystallin of chick lens genes are not amplified during differentiation and the study has provided evidence that transcriptional activity is responsible for the expression of the genes.

Studies of the immunological gene in the mouse have indicated support of the notion that the immunoglobulin diversity arises through a process of somatic mutation in which specific regions of the immunoglobulin genome undergo highly specific genetic alterations. (1975)

A model system was developed in the study of the basis of synapse formation when it was demonstrated neurons from continuous cell lines are capable of forming synapses with skeletal muscle. The synapses are cholinergic and have many of the characteristics of immature synapses. (1975)

Phenobarital was shown to have selective effects on neuronal responses excited by glutamate or inhibited by gamma-amino butyric acid. (1975)

Rats raised in enriched environments exhibited 20-30% greater brain RNA diversity than rats raised in an impoverished environment. No change was found in the liver RNA. (1975)

A study of hormones produced in nerve cells has provided the information that peptide hormones are first synthesized as protein precursors which then undergo post-translational cleavage; this processing of the precursor appears to occur in the Golgi as well as in the neurosecretory granules. Processing can occur intragranularly during axonal transport, the rate of appearance of newly synthesized peptides is directly correlated with

spike frequency, synaptic (dopamine) or behavioral input to the neuron can regulate synthesis and transport of the peptide. (1975)

A unique regulatory mechanism for the active form of glycogen synthetase has been demonstrated. This enzyme is manganese dependent. (1974)

Two enzymes have been discovered which mediate the first step in the alternate route of the metabolism of the intermediates of lysine during degradation. (1975)

Studies have revealed that the pineal gland is markedly temperature influenced in the synthesis of melatonin. (1974)

A method for culturing pineal glands has been developed and with it the adrenergic-cyclic AMP regulation of pineal in acetyl transferase activity has been studied. (1974)

It has been shown that cyclic AMP and nerve growth factor increase tyrosine hydroxylase levels in nerves. (1975)

Behavioral studies have shifted attention in the families with small or newly-born infants while the mother-infant interaction to incorporating the role of the father on both interactions. No one has previously looked at this area. (1975)

The discovery of a substance produced in the testes is of potentially great significance both in the advancement of knowledge of how male reproductive processes are controlled and in the development of a male contraceptive. The investigators have demonstrated that Sertoli cells produce a substance (Sertoli Cell Factor) which directly inhibits the secretion of follicle stimulating hormones (FSH), whose primary function in the male is the production of sperm. It appears that the Sertoli Cell Factor is the long sought after "inhibin" of the testes. Inhibin has been thought to function in male reproduction as an inhibitor of FSH secretion by the pituitary gland, and thus may serve as a basis for the development of a male contraceptive. (1976)

Preliminary experiments in monkeys show agreement between ovum detection and blood serum levels of luteinizing hormone and estradiol. This preparation could provide an excellent means of checking indirect, non-invasive approaches to ovulation detection. (1975)

The study of the role of oviduct in gamete transport has been considerably advanced through the development of sensitive microminiature force and optical transducers. Special coating techniques have been adopted for insulation of transducers from body fluids which should result in needed improved lifetime of these instruments. (1975)

Progesterone produced by the corpus luteum and the placenta plays a crucial role in reproductive processes. The quest for an antiprogestational agent involving synthetic steroid research has resulted in some novel steroids (androstenediol derivatives) which have shown interesting antifertility properties in hamsters, rats, and baboons. (1974)

Cause and Prevention

Produced proof that subacute sclerosing panencephalitis (SSPE), a fatal brain disease of children, is caused by a measles virus which may reside in the body for many years after the acute infection. (1970)

Discovered that certain degenerative neurological disorders of man such as Kuru and Creutzfeldt-Jakob dementia are caused by viruses of the slow and latent type. (1965-1975)

Detection and Diagnosis

Identified usefulness and limitations of elevated IgM levels in cord serum as indicator of perinatal infections. (1965)

Identified three new forms of muscular dystrophy, and screening tests can now detect 65 percent of the carriers of progressive muscular dystrophy, the most common form. (1965-1968)

Developed the first simple and rapid test for detection of German measles (rubella). The complement-fixation blood test, which provides identification of antibodies to rubella infection within 24 hours, laid the ground work for the subsequent development of the Hemagglutination-Inhibition test currently being used. (1967)

Developed a new tool, evoked response audiometry, for detecting hearing loss in babies and brain-damaged children, providing an early indication of the brain's response to sound. (Late 1960's)

Developed serologic diagnostic test for CMV and Herpes I and II infections using the indirect Hemagglutination method. (1968-1969)

Developed a brain scanner for detection of radioisotopes that is now widely used to diagnose and locate brain tumors. By following the flow of cerebrospinal fluid into which radio-iodinated human serum albumin has been injected, scientists can detect tumors, brain cysts, and derangements caused by injury, through modification in the brain scanning technique.

Developed lactate infusion method for diagnosis of myasthenia gravis which is safer than the generally used curare test for evoking myasthenic weakness. (1973-1975)

Extended diagnostic use of the muscle biopsy by devising histochemical criteria for identifying various myopathies and neuropathies. (1973-1975)

Contributed information leading to development of computerized axial tomography. (1973-1975)

Established that high spinal fluid measles antibody titers are diagnostic for SSPE thus replacing brain biopsy as a diagnostic method. (1973-1975)

Developed test suitable for the prenatal detection of individuals who will later develop one of the various sphingolipidoses. (1973-1975)

Treatment

Aided in development of surgical treatment (stapedectomy) for restoring hearing to more than 90 percent of patients with middle ear deafness (otosclerosis). (Late 1950's)

Cooperated with a pharmaceutical company in evaluating a new anti-convulsant drug (Tegretol), prior to its approval for prescription use by FDA. Tegretol is the first new anticonvulsant drug to be made available since 1960, and the first major advance in 20 years in the long-term treatment of grand mal and psychomotor epilepsy.

Developed and established alternate day steroid therapy for myasthenia gravis. (1973-1975)

Introduced acetazolamide treatment for hypokalemic periodic paralysis. (1973-1975)

Developed methods for activating paralyzed muscles in patients with quadraplegia; supported development of bladder evacuation prosthetic device for use by spinal cord injury patients. (1973-1975)

Introduced peripheral decarboxylase inhibitors (carbidopa) as a potentiator of the therapeutic effects of L-Dopa in Parkinson patients. (1973-1975)

NATIONAL EYE INSTITUTE

Cause and Prevention

Almost completely eliminated retrolental fibroplasia, once a common cause of blindness in premature babies, following clinical confirmation of the hypothesis that the disorder resulted from exposure to high levels of oxygen in incubators. (1950's)

Provided the first detailed clinical description of the pathology and natural history of diabetic retinopathy, the most common eye complication of diabetes and a leading cause of blindness in the United States. (1960's)

Provided evidence that retinitis pigmentosa, a usually hereditary disorder which causes its first degenerative changes in childhood or adolescence, may result from a defect in the pigment epithelium, a single-cell layer adjacent to the retina. Work is continuing to elucidate further the role of the pigment epithelium in retinitis pigmentosa as well as other hereditary retinal degenerations. (1970's)

Demonstrated that the abnormal activation of an enzyme, aldose reductase, triggers the formation of sugar cataract. Subsequently, a series of chemical inhibitors of that enzyme have been developed. It is now possible to retard sugar cataract formation in laboratory animals and to reverse the cataractous process in the test tube. Work is now underway to develop more potent inhibitors of aldose reductase and thereby establish a means of medically treating this type of lens opacity which occurs in people with diabetes. (1970's)

Demonstrated that aggregation of protein in the lens may be responsible for formation of senile cataract, the most common form of this disease and a leading cause of blindness in the United States. Research has identified calcium as a probable cause of the protein clumping, and further work is being pursued to elucidate the role of calcium in cataract formation. (1970's)

Established more clearly the role of heredity in primary open-angle glaucoma, the most common form of this potentially-blinding disease. (1950-1970)

Developed a rhesus monkey model of glaucoma which closely simulates the human chronic disease. Simulated glaucoma is induced by applying laser burns to the area of the eye through which aqueous fluid normally drains, thus causing blockage of fluid outflow, a rise in intraocular pressure, and subsequent optic nerve damage. The animal model is already proving useful in research efforts to understand better the basic processes underlying glaucoma and to facilitate investigations aimed at finding means of curing or preventing the disease. (1970's)

Provided cumulative evidence that environmental experience early in life is important for the full maturation of the visual nervous system. This work has added considerably to understanding the normal visual process and how childhood disorders such as amblyopia and strabismus can cause lifelong visual impairment. (1945-1975)

Detection and Diagnosis

Refined techniques for more accurately diagnosing retinoblastoma, a tumor in the eye of children. Radiologic study, histologic examination, ultrasonography, and other tests are now being used to detect retinoblastoma and to differentiate between those ocular tumors which are melanomatous and those which are not. Through prompt diagnosis followed by adequate treatment (usually enucleation of the eye), in most cases retinoblastoma need not endanger life. (1950-1975)

Developed ultrasonic techniques which have proved useful for evaluating the health of the retina when it cannot be examined directly because of opaque areas in the eye. Such tests are particularly valuable prior to cataract, corneal, and vitreous surgery, thus making it possible to predict with greater accuracy beforehand whether that patient will be able to see following the operation. (1965-1975)

Developed a means for dual visualization of the related but separate retinal and choroidal circulatory systems, providing an important new research tool for observing blood circulation in these two tissues. The technique may also prove helpful to clinicians by facilitating the differential diagnosis of retinal and/or choroidal disorders which often appear similar but require different forms of management. (1970's)

Perfected a technique, called gonioscopy, for accurate and rapid differentiation between open- and closed-angle glaucoma, resulting in improved management of these two distinct forms of the disease through prompt and appropriate treatment. A leading cause of blindness in the United States, glaucoma need not cause severe visual loss if it is diagnosed promptly and adequate treatment is begun immediately. (1965-1975)

Treatment

Introduced new techniques for surgical removal of the cloudy vitreous humor from the center of the eye, through development of new microsurgical instruments which combine cutting, suction, and replacement of the fluid with saline. Vitrectomy can restore some degree of vision to certain people blind from hemorrhage within the eye due to diabetic retinopathy and other disorders which affect the clarity of the vitreous. This procedure is being evaluated in a nationwide clinical trial in order to determine when in the course of diabetic retinopathy it may be most effectively applied. (1970's)

Demonstrated conclusively through a cooperative clinical trial that photocoagulation, the therapeutic use of intense focused light, is dramatically effective in reducing the risk of blindness for patients with moderate to severe proliferative diabetic retinopathy. The study, the largest multi-center clinical trial in the history of eye research, is continuing in order to allow long-term evaluation of photocoagulation treatment for this major cause of blindness. (1970's)

Developed techniques for more successful reattachment of retinal separations, such as cryosurgery, laser photocoagulation, and diathermy, as well as refinements in scleral and encircling buckling procedures. These advances have led to improved restoration of vision in cases of retinal detachment. (1955-1965)

Developed means for making cataract surgery safer, easier, and more successful through advancements in suture techniques, improved microscopic instrumentation, and other technological improvements. (1945-1975)

Demonstrated that useful vision can be restored in children with congenital cataract by removing with suction the soft, immature lens through a small incision (aspiration). Visual acuity may then be corrected by the fitting of a corneal contact lens. (1965-1975)

Discovered an effective drug treatment for herpes simplex keratitis, a common viral infection of the cornea. The drug, idoxuridine (IDU), was the first generally effective antiviral chemotherapeutic agent to be introduced into medicine. Another drug, vidarabine, tested and approved for ocular use in the 1970's, appears to be even more effective than IDU against herpes simplex keratitis, especially in treating recurrent disease; development of even more effective drugs is now underway. (1963)

Demonstrated that the soft hydrophilic contact lens--originally developed as an alternative to the conventional hard lens in correcting refractive errors--can be successfully used in treating bullous keratopathy, a blistering condition of the cornea, and as a protective bandage for treating other painful corneal diseases. (1968-1973)

Advanced the surgical technique of corneal transplantation enabling sight to be restored in a greater number of cases and also improved tests for assessing the vitality of donor material. Freezing techniques were devised for long-term preservation of donor corneas, and a corneal tissue culture solution was developed which has both extended the period of safe storage for fresh donor corneas and increased the availability of superior tissue for transplantation. (1950-1970's)

Demonstrated that acetazolamide (Diamox), an effective inhibitor of aqueous humor production, is a valuable adjunct in the treatment of chronic open-angle glaucoma. This and other advances in effective drug treatment for glaucoma coupled with new means of early identification of the disease have led to improved control of this major cause of blindness. (1950's)

Helped demonstrate that the Ocusert, a thin plastic wafer which is placed in the eye under the lower lid, can be used for the continuous release of medication in the treatment of chronic open-angle glaucoma. The system has proved effective in controlling intraocular pressure more comfortably and conveniently for some patients than eye drops. (1970's)

Introduced new surgical methods for treating those cases of glaucoma which do not respond well to drug treatment. Further work is continuing in the development of a type of "chemical surgery" to affect certain nerve pathways to the eye, thus enhancing the effect of medications in lowering intraocular pressure. Also underway are investigations of the effect of enzymes on aqueous outflow resistance and the use of the laser to change outflow pathways in closed-angle glaucoma. (1960-1970)

Development of sensory devices which electronically translate visual images into patterns of mechanical stimulation of the skin. These devices are providing a new dimension of aid in reading and mobility to blind people. (1960-1970)

NATIONAL INSTITUTE OF DENTAL RESEARCH

Cause and Prevention

Established a scientific base for water fluoridation as an effective caries-preventive procedure by demonstrating conclusively that the daily human intake of one part per million of fluoride ion in communal water reduces the incidence of dental caries (tooth decay) up to 60 percent. (1945-1960)

Contributed to an understanding of the mechanism by which the fluoride ion is incorporated in the developing tooth structure and acts to enhance its resistance to caries by changing the molecular structure and properties of the mineral components of tooth enamel. (1948-1965)

Provided more specific evidence that caries results from the interaction of three factors: a susceptible tooth, specific microorganisms, and a diet rich in fermentable carbohydrates. (1954-)

Contributed--through collaborative studies with Interdepartmental Committee on Nutrition for National Defense--to establishing correlation between poor oral hygiene and periodontal disease. (1958-1964)

Developed important basic knowledge on the composition and structure of certain components of periodontal and other connective tissues, including (a) discovery of a previously unrecognized tissue fiber (oxytalan fiber) (1958), and (b) the finding that defects in the intramolecular crosslinking patterns in collagen may strongly influence the tissue breakdown which occurs in periodontal disease. (1960's)

Discovered that a specific bacterium, Bacteroides melaninogenicum, found in periodontal disease can make a collagen-destroying enzyme. (1960)

Demonstrated that the frequency of eating, as well as the constituents of the diet, have a marked effect on the incidence and severity of caries in experimental animals. (1962)

Established experimentally that cleft palate is uniformly produced in the offspring when pregnant animals are exposed to certain stress situations or to certain drugs during critical stages of gestation. (1962-1975)

Provided laboratory evidence that genetic susceptibility to dental caries is related at least in part to the animal's tendency to support bacteria in sufficient numbers to allow destruction of the tooth, rather than the ability of the tooth itself to resist attack. (1965)

Increased understanding of the mechanism by which bacterial plaque deposits operate in the causation of tooth decay, suggesting possibility of control through enzymatic, antibiotic, and antibacterial approaches. (1965-1969)

Developed a substantial body of laboratory data demonstrating that dental caries is an infectious, transmissible disease caused by specific microorganisms. (1965-1969)

Developed evidence that inflammation which leads to tissue damage in periodontal disease may be a cellular hypersensitivity reaction to bacterial products. (1966)

Demonstrated in man that herpes simplex virus is shed from oral ulcers in high titers. Established that a small percentage of these virus-antibody complexes remain infective and may cause recurrent infections even though, normally, serum antibodies combine with and inactivate most viral particles. (1966)

Demonstrated that a virus may stimulate formation of antibodies against non-viral proteins which ordinarily are completely tolerated. This suggests that even mild viral infections could trigger autoimmune response, making an individual allergic to his own proteins. (1968-1972)

Accumulated evidence that cleft lip, with or without cleft palate, is a different disorder than cleft palate alone. (1968-1973)

Developed improved agents and techniques for topical fluoride applications to increase the resistance of teeth to decay-producing acids. (1968-ongoing)

Discovered that polymorphonuclear leukocytes, another white cell, can make a collagen-destroying enzyme. (1969)

Discovered the existence of a connective tissue-disrupting enzyme, collagenase, in gingival tissue under normal conditions, and markedly increased amounts of this enzyme in patients with periodontal disease. (1970)

Reported that school children in rural areas where natural fluoride in water is deficient can be given considerable protection against tooth decay by increasing the fluoride in the water system of schools. (1972)

Discovered products from human lymphocytes which could be responsible for collagen and bone destruction in chronic inflammatory diseases. (1972)

Demonstrated through extensive field trials that adhesive pit-and-fissure sealants for preventing caries in the chewing surfaces of the teeth, which are particularly prone to decay, are effective and safe. (1972-1976)

Established that caries can be prevented in animals (primates and rodents) by immunization (1972-ongoing); that protection can be passively transferred in experimental animals. (1975)

Found that levels of prostaglandin, which is capable of causing bone resorption, were elevated in diseased human gingiva. (1973)

Demonstrated that direct cell-cell transfer of herpes virus may protect virus from immunological neutralization, important factor to consider in protective vaccination. (1973)

Identified what appear to be the probable microbial agents in the genesis of periodontitis. (1973-1975)

Demonstrated bone resorption by a new pathway involving complement activation and prostaglandins. (1974)

Demonstrated that the immune response to herpes simplex virus is divided into two phases: a specific antigen recognition phase and a non-specific effector phase which in part operates through immunologically induced interferon. (1974)

Demonstrated that frequent exposure to low levels of fluoride in drinking water given rats greater protection against tooth decay than the incorporation of large amounts of fluoride into enamel, suggesting that benefits from fluoride also derive in a major degree from local effects in the mouth. (1974)

Demonstrated that rats subjected to protein deficiency during periods of gestation and nursing and subsequently replenished still suffered from growth stunting and increases in tooth decay later in life. (1974)

Reported that an osteoclast-activating factor is secreted by lymphocytes and could initiate bone loss near areas of chronic inflammation. (1974)

Demonstrated that herpes simplex virus can be isolated from the sensory ganglia of the nervous system of mice weeks after infection of the cornea, skin, lips, or vagina, and that injury to the nerve can reactivate the virus. These experiments provide a model for studying the different kinds of herpetic infections in humans, such as fever blisters (Type I HSV) and genital lesions (Type 2 HSV). (1974)

Obtained evidence indicating that several clinically distinct forms of periodontal disease are caused by different microorganisms. (1974)

Showed that corn and nut extracts can induce immunological reactions on the part of human white blood cells, adding substance to a long-held idea that foods, when impacted between the gum and the tooth, probably contribute to periodontal problems. (1975)

Found that specific groups of anaerobic, Gram-negative bacteria isolated from patients with periodontitis cause severe loss of periodontal bone in gnotobiotic animals. (1975)

Found that a relationship exists between activation of complement in serum and prostaglandin synthesis in gingival and synovial tissues which could help explain pathologic breakdown of bone in periodontal diseases and rheumatoid arthritis. (1975)

Launched 3-year cost-benefit demonstration programs involving weekly fluoride mouth-rinsing to prevent caries in schools in seventeen communities with an estimated 75,000 children participating. (1975)

Reported that bacterial endotoxins can stimulate both T and B lymphocytes to divide and release active substances that attract wandering cells (macrophages) and induce them to release an enzyme which destroys tissues that support teeth. (1975)

Showed significant correlation between Sjogren's syndrome and the presence of specific histocompatibility type, suggesting probable genetic factors in the development of this disease. (1975)

Demonstrated that in certain strains of mice encephalomyocarditis virus can attack the beta cells of the pancreas and produce a diabetes-like syndrome characterized by hyperglycemia, glycosuria, polydipsia, polyphagia, and hypoinsulinemia. (1975)

Demonstrated that herpes simplex virus is latent in autonomic ganglia. Since autonomic ganglia control all involuntary functions, this finding may have implications not only for oral disease but also other diseases including the gastrointestinal tract (e.g., peptic ulcers). (1975)

Demonstrated that herpes simplex virus can produce a latent infection of the vaginouterine tissue of mice. (1975)

Demonstrated that immunization of mice can prevent the development of a latent infection of sensory and autonomic ganglia with herpes simplex virus type 1. (1975)

Reported that topical fluoride treatment effectively prevents the rampant caries and eating problems that result from head and neck irradiation of cancer patients. (1975)

Detection and Diagnosis

Devised a periodontal index with which comparable records could be made by different investigators of the conditions of gums and teeth in populations all over the world. (1953)

Established growth rate changes in facial bones between ages 3 and 20 years; these data have assisted in determining the proper timing of orthodontic treatments. (1962-1973)

Developed methods for examination of the mouth and pharynx of infants and adults by which evidence of neurological impairment can be revealed. (1967-1972)

Described and classified patterns of disabilities in swallowing, including those with acute respiratory obstruction. (1968)

Developed new instrument which directly measures motion of the soft palate. (1969)

Reported that knowledge of the rate of salivary flow and the ratio of sodium to potassium in saliva can be used both to diagnose the presence of adrenal gland tumors causing aldosteronism, and for early evaluation of the success of therapy. (1969)

Reported a new cluster of congenital face, skull, and other deficiencies. Retarded body growth and sexual development; hidden palatal clefts with accompanying speech defects; unusually shaped skulls and faces; and deficiencies in ability to feel, taste, and smell are the principal abnormalities. (1970)

Demonstrated that an intraoral source of x-radiation can improve radiographic signal to noise power ratio per unit of absorbed radiation dose relative to conventional techniques. (1972)

Developed a method for studying the immune response of certain white blood cells to viral infections. The test is specific in that it not only differentiates between viruses, but even between two closely related strains. The technique should be helpful in diagnosis of certain viral infections. It can also indicate within a few days of exposure to a virus whether or not sensitization has taken place, and whether the immune reaction is strong or weak. (1972)

Treatment

Contributed significantly to improvement and refinement of methods of general anesthesia for ambulatory dental patients by identifying, for the first time, the full range of physiological responses to a variety of general anesthetic agents. (1956)

Developed new and improved diagnostic, surgical, and speech therapy techniques to enable cleft lip/palate victims to achieve near-normal appearance and function. (1956-1975)

Demonstrated effectiveness of team treatment and habilitation of cleft lip/palate patients, coordinating help from such diverse disciplines as plastic surgery, orthodontics, speech therapy, and psychology. (1956-1975)

Increased effectiveness and safety of high-speed drill by providing information and guidelines on optimal cutting speeds and proper use of coolants. (1957)

Detailed functional and anatomical studies of the developing child have given clues to the predictability of success of speech training exercises. (1964-1970)

Demonstrated that a new silane adhesive be used to attach porcelain teeth to a plastic denture base without pins, resulting in improved methods of denture construction and repair. (1967)

Developed new alloys having greater strength, lighter weight, and less corrosiveness than commonly used compounds for dental appliances. One improvement increases ductility by adding tantalum instead of precipitating carbides in the cobalt-chromium-nickel mix. (1967-1974)

Reported that, in general anesthesia, thiopental causes a postoperative cardiovascular and respiratory depression that delays the resumption of normal activity. (1969)

Developed formulation on which are based several composite restorative materials now universally used for filling decayed front teeth. (1970)

Reported that a considerable proportion of heart irregularities associated inhalation anesthesia can be prevented by selective and cautious use of propranolol hydrochloride. (1970)

Documented long-term changes in adjacent bone and in central portion of upper jaw which indicate that extraction should be avoided in treating youthful periodontosis. (1970)

Reported that double-blind study of meprobamate compared with a placebo shows the drug helps relieve painful symptoms of temporomandibular joint dysfunction. (1971)

Reported that diazepam (Valium^R) given intravenously with lidocaine (Xylocaine^R) is useful as an adjunct to local anesthesia because it not only relaxes anxious patients but also safely removes most memories of the operation. (1972)

Reported that the distance between canine teeth in the lower jaw is a better frame of reference for planning orthodontic treatment than the time-worn Pont's Index, which keys the ideally shaped dentition to the width of the four upper front teeth. (1972)

Reported that, in terms of psychological consequences for patients undergoing oral surgery, sitting upright is least desirable and semi-reclining at a 45-degree angle is best for the usual office operations. (1972)

Tested tetracyclines as possible adjunct in treatment of chronic periodontitis. (1974)

Determined that the lymphoproliferative response of a periodontally diseased patient to pooled plaque antigens can exist for many years, even after all teeth have been extracted. (1974-1975)

Established that combined programs of pit-and-fissure adhesive sealant and fluoride treatment, though expensive, will largely prevent caries in children. (1975)

Pre-surgical topical application of chloramine-T significantly reduces the frequency of bacteremia occurring after oral surgical procedures. (1975-ongoing)

Observed that transient bacteremia after oral surgical procedures is a common event and that the majority of bacteria isolated were demonstrated to be strict anaerobes. (1975-ongoing)

Demonstrated that moderate volumes (175 ml) of sterile normal saline lavage following extraction of mandibular 3rd molars reduced the incidence of localized osteitis (dry sockets) approximately 50% compared with that observed when only a low volume (25 ml) was utilized. (1975-ongoing)

Basic Biology

The Syrian hamster was introduced as a new experimental animal to study caries. It is particularly suitable for dental research because the molars can be seen in the living animal. They get both caries and periodontal disease if kept on suitable diets and otherwise treated, although neither disease occurs in the wild animals. (1941)

Provided evidence for the presence of an organic matrix in mature dental enamel and demonstrated the relationship between this matrix and the mineral phase. (1952-1962)

Reported the amino acid composition of enamel and dentin and devised techniques for studying these substances under the electron microscope. (1953)

Developed new basic knowledge on the development and structure of dental hard tissues including ultrastructural definition of the processes of matrix formation and of mineralization. Specifically demonstrated that mineralization of dental enamel involves two steps, and initial rapid nucleation of crystals accounting for 30% of the mineral followed by a much slower process of crystal growth during which the remaining 70% are acquired. (1955-1964)

Perfecting a modified microtome capable of producing high-quality, ultra-thin sections for electron microscopy study, permitting the observation of the structures of cells which form enamel and dentin, as well as the tissues themselves. (1956)

Demonstrated that lack of lysine in the diet prevents bone from retaining calcium and makes it grow poorly; also that lysine is a necessary precursor for collagen formation. (1958)

Found that more strontium collects in young teeth than elsewhere--one way to study fall-out. (1959)

Developed improved methods for studying mineralized tissues by a combination of microradiography, x-ray diffraction and electron microscopy and used

this combined approach to develop important basic knowledge on the prism structure and mineral distribution in both normal and abnormal enamel. (1960-1972)

Demonstrated conjugation bridges between bacteria, a mechanism for handing genetic material from one type of bacterium to another, which explains many puzzling developments in various diseases, in which some forms suddenly become either benign or malignant. (1962)

Measured for the first time the specific area of the mineral-matrix interface in hard tissue. Also demonstrated that fluoride reduces the area of this interface by increasing the size of the mineral particles. This effect may partially account for the increased resistance of F-containing enamel apatite to the destructive influences of carious acids. (1962-1965)

Demonstrated that, when used during pregnancy or infancy, tetracycline sometimes causes enamel hypoplasia, a defect which makes the enamel much thinner and more crumbly, and often leaves it permanently stained. (1963)

Showed that tetracycline can cause hypoplastic lesions in dental enamel and defined host conditions, systemic as well as local, which influence this effect of the drug. (1965-1975)

Accumulated definitive spectroscopic data on the important chemical bonds in the apatite structure. Knowledge of such atomic-scale details provides a more rational basis for chemically altering hard tissue mineral to therapeutic advantage. (1967-ongoing)

Demonstrated a piezoelectric effect, similar to that exerted by pressure on quartz crystals, as a property of collagen and keratin, may explain electro-mechanical and bone remodelling reactions of biological systems. (1967)

Found that the degenerative protein, amyloid, is a cross-beta fiber. This finding was critical in establishing the immunopathic origin of this principal tissue component of human amyloidosis. (1968-1974)

Disclosed, in experiments with cats, a region of the cerebral cortex which may play a role in visual attention and orientation; three distinct visually responsive cell groups are found in this area. (1969)

Reported that the microfibrils of elastic fibers are composed of at least one connective tissue protein which is neither elastin nor collagen. (1969)

Published new descriptions of the anatomy of the human infant head as revealed by dissection and radiographic methods. (1970)

Showed that some bacteria form plaque by synthesizing dextran, while other bacteria can stick directly to enamel, and still others are bound to the teeth by salivary polymers. (1970)

Defined and characterized chemotactic mediators from human blood responsible for the accumulation of leukocytes at sites of inflammation. (1970)

Elaborated the morphological and chemical changes that occur when mineral ions are transformed into calcium phosphate salts that act as analogues to skeletal mineral. (1970-1975)

Developed a model of how the enzyme transglutaminase functions in cross-linking fibrin in blood clotting. (1970-ongoing)

Obtained data which show that the extracellular water in calcified tissue (except enamel) is associated principally with the collagen component. (1970-ongoing)

Established that amorphous calcium phosphate is a unique chemical and structural entity and not a cryptocrystalline form of one of the well-known crystalline calcium phosphates. (1970-1973)

Demonstrated the close relationship of autonomic nerve endings to the secretory cells of the rat parotid gland, and provided ultrastructural cytochemical evidence that a single secretory cell may be innervated by both sympathetic and parasympathetic nerves. (1970-1972)

Studied the ultrastructure of the lingual serous (von Ebner's) glands of the rat, and correlated their morphological development in fetal and newborn animals with the accumulation of the secretory enzyme lingual lipase. (1970-1975)

Discovered some of the biochemical mechanisms that operate to regulate glycolysis in oral streptococci. (1971)

Developed methods to evaluate the toxicity of liquid, powdered, and solid biomaterials as well as gaseous products. (1971)

Demonstrated that collagen, the major structural protein of teeth, bones and soft tissues, occurs as tissue specific types under separate genetic control. (1971)

Characterized the morphological and cytochemical properties of the Golgi apparatus of the serous secretory cells of the rat parotid and lingual serous glands. (1971)

Found that collagen is made by cells in a precursor form which is enzymatically converted to its final form outside the cell. (1971)

Showed that darkness at any hour reduces the flow of saliva from the parotid gland by about 75 percent below its daylight rate. (1972)

Developed fluorescent antibody reagents to identify in plaque the microorganisms responsible for human caries. (1972)

Studies of endotoxin activation of complement led to the discovery of the alternative complement pathway and its role in human disease. (1972)

Discovered the molecular defect in two hereditary connective tissue diseases, e.g., Ehlers-Danlos syndrome. In one, conversion of procollagen to collagen is incomplete; in the other, the ratio of two types of collagen is incorrect. (1972-1974)

Developed the non-disruptive hydrazine procedure for isolating bone and tooth mineral free of surrounding organic matter. (1972-1973)

Developed improved techniques for identification and classification of bacteria associated with oral disease. (1973)

Established the complex pathways by which amorphous calcium phosphate, an important component of hard tissue mineral, is formed in vitro. Also clarified the mechanism by which this mineral precursor converts into crystalline apatite. (1973)

Devised transport medium to enable microorganisms in samples of dental plaque from various population groups studied to remain viable at room temperature for sufficient time to permit shipment to a central laboratory; this technique also permits a quantification of various bacteria. (1973)

Demonstrated that elastin, the elastic protein of aorta and other tissues, is composed of mobile polypeptide chains and derives its elasticity by the same mechanism as does rubber. (1973-1974)

Discovered importance of cross-links between proteins introduced by transglutaminases, in several tissues indicating the broad biological importance of these enzymes. (1973-ongoing)

The cell types and some of the neuronal circuitry in the trigeminal brain stem pain pathway have been described. This information helps explain unique functional aspects of acute and chronic pain. (1974)

Demonstrated that solutions with the electrolyte composition of interstitial fluids always have the potential to form hard tissue crystallites unless inhibited from doing so. (1974)

Developed electron spin resonance criteria for studying chemical bonds between apatite crystals and matrix macromolecules in test tube systems. (1974-ongoing)

Showed that a bone mineral maturational defect associated with progressive experimental chronic uremia can be reversed with vitamin D metabolite and diphosphonate therapy. (1974-ongoing)

Developed procedures for the use of the bifunctional imidoester, dimethyl-suberimidate, as a fixative for light and electron microscopy and cytochemistry. (1974-ongoing)

Demonstrated differences in the types of collagen present in the matrices of certain tumors. These types are also different from normal collagen, and the finding is useful in diagnosis of neoplasms. (1974-ongoing)

Developed cell-free system for collagen synthesis which enables study of the factors which regulate collagen formation. The technique is finding application in studies of the inflammatory process, a condition of marked connective tissue changes. (1974-ongoing)

The finding that low molecular weight formylmethionyl peptides, possibly related to bacterial factors, strongly attract phagocytes has made feasible the study of how these cells are involved in periodontal and other inflammatory lesions. (1974-ongoing)

Demonstrated that the collagen fibril is built from collagen molecules by a specific, spontaneous packing mechanism which produces a rope-like structure with several levels of coiling. (1975)

Experimental pain produced by heat stimuli exhibits summation and outlasts the period of stimulation, and thus has characteristics similar to some chronic pain conditions. It may serve as a useful model for studying chronic pain. (1975)

Found that strontium is elevated in tooth enamel from lifetime residents of many areas having unusually low levels of caries. (1975)

Showed that mediators made by leukocytes influence other cells in inflammation by affecting intracellular cyclic nucleotides. (1975)

Demonstrated that a vasoactive amine, serotonin, activates leukocytes to produce factors which augment the inflammatory reaction. (1975)

The peripheral nerve populations that are essential for detection of warm sensation in monkeys and humans have been identified. (1975)

Demonstrated with reflex responses of the tongue that newborns can tell the difference between flavored and unflavored water, thereby separating for the first time touch and taste components of sensitivity. (1975)

Derived a model for the structure of proteoglycans, the protein-carbohydrate complex found in cartilage and other connective tissues, which should lead to an understanding of its synthesis and function. (1975-ongoing)

Cause and Prevention

Provided the first descriptions for a number of genetic defects, clarifying the basic error of metabolism in these and other birth disorders, such as galactosemia (1957), Lesch-Nyhan Syndrome (1967), phenylketonuria (1956), cystathionuria (1964), Hurler's syndrome (1972), and I cell disease (1972). Initiated the technique of pre-birth, intrauterine diagnosis of certain of these disorders, and developed methods of control, which in some cases prevent severe mental retardation and death.

Elucidated the causative mechanisms of gout (1957) and aided in providing highly effective treatment methods (1960, 1964) that make this painful disorder one of the most controllable and manageable of the arthritic diseases.

Through identification of specific inherited antigens in blood platelets and their corresponding clinically-induced antibodies, demonstrated the immunologic basis of some life-threatening purpuras, the bleeding disorders that result from a deficiency in the number of blood platelets, and provided rationale for preventing antibody formation through platelet typing and matching prior to platelet transfusion and for treating patients with high titer antibody levels by exchange transfusion. (1962)

In addition to developing a specific diagnostic test for Wilson's disease, a rare but usually fatal metabolic disease caused by abnormal accumulation of copper in the body, Institute grantees devised ways to identify those who may be carriers and those in the early asymptomatic stages of the disease who may then be aided by reducing dietary copper intake. (1962) Normal copper balance was later attained in such patients with long-term therapy with D-penicillamine. (1971)

Discovered that the Pima Indians in Arizona have a rate of diabetes 15 times that of any population on record, as well as an extraordinarily high incidence of gallbladder disease. Such epidemiological findings provide working theories of the cause of disease. (1965)

The cause of milk intolerance in certain otherwise normal adults (predominately Blacks and Orientals) was traced to a deficiency in the intestinal enzyme lactase which converts lactose or "milk sugar" to its simple sugar components, thus providing a rational cause for many previously unexplained chronic gastrointestinal complaints in target populations which had ingested milk, obviating much exploratory surgery. (1966)

Discovered and elucidated the role of the hormone glucagon in diabetes. Findings of excessive glucagon secretion in diabetes and demonstration of its role in contributing to high blood sugar levels provided the basis of the first conceptual advances in the etiology of diabetes since the discovery of insulin fifty years ago. (1971)

Demonstrated that the protein deposits in amyloidosis, an often fatal disease associated with rheumatoid arthritis and other long-term chronic diseases, consist of fragments of antibody molecules, thus opening the way to further investigations on a molecular level on what may be the final common pathway to immunoglobulin breakdown in a variety of infectious or metabolic diseases. (1971)

Discovered that obese persons, who are generally more predisposed to gallstones than their non-obese counterparts, are even more susceptible during a period of active weight reduction and should, therefore, avoid the see-saw of alternately losing and regaining weight in order to reduce the likelihood of gallstone formation. (1974)

Significant inflight losses of calcium, nitrogen and phosphorus from bone and muscle of Skylab astronauts were demonstrated which suggests that counter-measures should be taken to protect the musculoskeletal systems of astronauts on prolonged space flights. (1974)

Found that interstitial nephritis comprises a significant proportion (33%) of newly diagnosed chronic renal disease and that long-term use of relatively large quantities of analgesics (such as acetophenetidin and aspirin) is a common cause of this disease. (1975)

Showed that some cases of severe insulin resistance are due to antibodies to cellular insulin receptors. (1976)

Detection and Diagnosis

In collaboration with scientists of the NIAID, perfected an accurate, rapid and simple diagnostic test for rheumatoid arthritis, called the Bentonite Flocculation test (BFT). (1958)

Developed sensitive and practical techniques for the quantitative determination of formiminoglutamic acid (FIGlu), an intermediate product of histidine metabolism that accumulates in persons with folic acid deficiency, that serves as an index of folic acid deficiency and also detects impending toxicity resulting from leukemia therapy with folic acid antagonists. (1958)

Developed improved diagnosis of cystic fibrosis particularly in carriers of the disease by using the "sweat test" (1962), and demonstrated decreased mucociliary transport in the lung which could be therapeutically stimulated by the use of a pharmacologic agent, terbutaline. (1974)

Together with scientists of the Division of Biologic Standards, following the earlier demonstration that Australia antigen in the blood in many patients with serum hepatitis was the hepatitis virus itself, developed sensitive immunologic tests which aid in diagnosis of the disease and in screening for hepatitis carriers. (1969)

Demonstrated that low levels of complement in synovial fluid is of value in the diagnosis and classification of rheumatoid arthritis particularly in the absence of rheumatoid factor in the blood. (1974)

Demonstrated the value of endoscopy in diagnosis of acute upper gastrointestinal bleeding. The flexible fiberoptic panendoscope provides a more detailed diagnostic picture than do radiographic studies for this purpose. (1975)

Treatment

Introduced the first effective synthetic corticosteroid drugs to clinical use for the treatment of rheumatoid arthritis. (1954)

Developed a pain-killing drug, phenazocin (1957), analogous to morphine which can be synthesized by chemical methods in the laboratory and thus makes us less dependent for morphine-like analgesics or importation of opium and its derivatives.

In the late 1950's and early 1960's, identified and isolated various hormones that control the body's most vital functions making possible diagnosis and treatment of such endocrine disorders as hypopituitary dwarfism, thyroid abnormalities, Addison's disease, and the severe symptoms of menopause.

Developed a simple effective remedy--a solution of table salt, baking soda and water, to be taken by mouth--for the emergency treatment of shock due to burns. (1961) This is an important large-scale disaster aid (including civil defense disasters) to substitute for the conventionally used plasma or blood transfusions which require trained personnel and special supplies.

Developed a method of long-term frozen storage of human sperm which makes possible effective artificial insemination from banked sperm. (1967)

Developed an effective treatment of hypopituitary dwarfism in children based on the injection of human growth hormone. (1960-1963)

Developed a new technique involving permanent surgical insertion of plastic tubes into blood vessels in the arms of candidates for artificial kidney treatment, thus permitting frequent and easy attachment of the artificial kidney to the patient for regularly repeated life-saving treatment. (1960) Development of this technique made possible the entire current life-saving artificial kidney effort.

Between 1967 and 1972 developed the hollow fiber artificial kidney and other novel dialyzers which provide clear advantages in shortening the time of an improving the quality of dialysis treatment, and made possible the introduction of relatively inexpensive home dialysis; developed specific sorbents for metabolic wastes which resulted in the development of a

Basic Biology

In 1954 defined the hexosemonophosphate shunt as an alternate pathway to the Embden-Myerhof-Parnas scheme of glycolysis followed by the Krebs citric acid cycle in the metabolism of sugars and starches thus providing the basis for better understanding of human bio-chemistry.

Discovered bacterial enzymes important in the biosynthesis and metabolism of the precursors for deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). This accomplishment formed the basis for elucidating nucleic acid biosynthesis, for which the Nobel Prize was awarded in 1959, and for characterizing many of the functions of the nucleic acids in determining hereditary transmission.

"Cracked" the genetic code, an accomplishment which was later recognized by the award of the Nobel Prize for Physiology and Medicine. (1961)
By a partial decoding of the genetic information stored in the chemical structure of nucleic acids and relating it to the production of specific cell proteins, showed how instructions to cell structures for producing new cell protein are locked into the RNA that is passed from one cell generation to the next.

Institute scientists provided clarification, for the first time, of a mechanism by which steroid hormones exert their regulating influence. Through studies showing that steroid hormones cause a reversible inactivation of glutamic dehydrogenase, a key enzyme in mammalian cell metabolism, the mechanism was defined by which biochemical cell reactions are directed toward either chemical degradation to yield energy or toward protein synthesis to build tissues. (1960)

Synthesized important hormones (or their biologically active portions) such as adreno-corticotropic hormone (ACTH) (1960), insulin (1965), thyrotropin-releasing hormone (TRH) (1970), and parathyroid hormone (PTH) (1972). Discovery and synthesis of an entire series of new, biologically active hypothalamic hormones (1969-1976), has opened the way to eventual regulation of basic body functions that are controlled by the pituitary gland.

From work on the synthesis, structure and properties of the enzyme ribonuclease, proposed the theory (since confirmed) that the primary amino acid sequence of a protein determines its three dimensional structure. This accomplishment, which is of special importance in better understanding of metabolic disorders resulting from abnormal proteins, was recognized by award of the Nobel Prize in Chemistry in 1972.

Using x-ray crystallographic techniques, defined the exact structure of an antibody including the precise nature of the antigen binding site. This contribution to an international effort to determine the three-dimensional structure and chemical make-up of antibodies, may eventually make possible the manufacture of artificial antibodies. (1975)

Developed ultrasonic techniques so that internal organs can be visualized, tissue changes studied, and diagnostic procedures improved. (1974)

Achieved--in collaboration with the AEC--a number of advances in analytic instrumentation, including the zonal ultracentrifuge for precise separation and collection of subcellular particles and viruses, and a centrifugal fast analyzer system which performs accurately and in a single operation measurements of clinically important constituents of blood and other body fluids for as many as 30 patients in as little as 30 seconds. (1973)

Treatment

Synthesis of quinine (1950's) and vitamin B₁₂. (1972)

Developed a new drug, azaribine, which has been demonstrated to be effective in treatment of severe, recalcitrant psoriasis and psoriatic arthritis. This new drug is being marketed by a major pharmaceutical firm. (1964-1975)

Combined use of barbiturates and hypothermia for lowering increased intracranial pressure. (1975)

Development of silver sulfadiazine for treatment of infected burn wounds. (1973)

Basic Biology

Worked out the complete three-dimensional structure of a major enzyme involved in oxidation-reduction, and identified common elements of folded structure in other enzymes having related functions. (1970)

Developed a more sensitive method for visualizing macromolecules in the ultracentrifuge, making it possible to determine sizes and shapes of proteins at very low concentrations. (1969)

Worked out the mechanism of action of the proteolytic enzyme chymotrypsin, and showed how the process operated to regulate certain digestive processes. (1967)

Determined the size and shape of rhodopsin, the major protein in the retina. (1972)

Determination of the detailed structure of the enzyme ribonuclease. (1965-1970)

Discovery of the role of cyclic AMP in hormone action. (1969)

Determined the basic steps in the enzymatic breakdown of sugar and the synthesis of glycogen. (1952-1970)

Cause and Prevention

Showed that lung function in chronic cigarette smokers is reduced to the levels seen in non-smokers who are 10 years older, but when a person stops smoking, function returns to nearly the non-smoker level within 1-2 years even in heavy smokers 60 years of age or older. This gives physicians a strong argument to convince older patients to quit smoking even when they feel they are too old to change their habits. (1966)

Focused attention on possible complications that may arise from the use of certain oral medications used to treat diabetes by finding evidence that chlorpropamide, one of the most commonly prescribed oral drugs for older diabetic patients, may contribute to chlorpropamide hyponatremia, a serious and life threatening condition involving the inability to excrete wastes from the body. (1971)

Detection and Diagnosis

Developed normal values, adjusted for age, to measure kidney function that should improve the clinical diagnosis and treatment of kidney ailments in older patients. (1974)

Identification of marker enzymes specific for male germ cells which detect abnormalities in spermatogenesis.

In rodents, old animals forget acquired avoidance tasks at a faster rate than young adult animals: two year old animals forget faster than one year olds, who forget faster than young adolescent animals. This provides an indication of the rate of memory loss with age in rodents. (grantee)

In tests designed to measure verbal and nonverbal thought processes, elderly individuals with high blood pressure were found to perform more poorly than healthy subjects of the same age. Those whose blood pressure had been previously controlled by medication showed even poorer performance or greater deficiency in ability.

It is possible through training to produce significant increments in the intellectual performance of the elderly. Strategy training (test-taking strategy and training to improve cognitive skills) improved the performance of elderly people on tests of intelligence and cognitive functioning. The improved performance also showed up in the ability to generalize across tasks. This finding argues against the notion that intellectual aging decrements are irreversible. (grantee)

Treatment

Developed a nomogram which permits physicians to relate responses on standard glucose tolerance tests to a subject's age and his percentile ranking among people of the same age, thus providing clinicians with a useful tool for making clinical judgments related to treating the older diabetic patient. (1967)

Devised methods to at least partially correct learning deficits in older people by having subjects read aloud while learning and permitting them to respond frequently during learning situations. (1968)

Collaborated in the development of a relatively simple operant conditioning technique to train patients with chronic fecal incontinence to control their incontinence, thus providing a way to treat a problem for which there is no consistent or effective alternate therapy. (1974)

A classical technique used to improve memory (mnemonics) can be taught to old people. Once learned, it can be used in a variety of ways to improve a person's recall. The technique proved to be easily learned by older subjects was quite effective in helping them store auditory recall information. (1975)

Basic Biology

Clearly demonstrated that aging affects different organ systems at quite different rates even within the same individual, and that many people show negligible declines in certain organ systems well into their seventies. (1962)

The WI-38 cell strain derived from human fetal lung has a limited lifespan in vitro and retains the chromosomal configurations of the original tissue. Collagen is produced by the WI-38 cultures throughout their life cycle, but twice as much collagen is synthesized by the young cultures indicating that functional vitality also decreases with cell age.

Found that with advancing age there are reduced amounts of certain essential B vitamins in the blood even in a group of highly successful, community-living people with access to adequate diets. However, these reductions were substantially less in those subjects who included vitamin supplements in their diets. (1972)

Neither the adrenal cortex nor the postmenopausal ovary is the source of discernable estrogen secretion in postmenopausal women. Estrogen production in postmenopausal women arises exclusively as a consequence of the conversion of plasma androstenedione (secreted by the adrenal cortex) to estrone. (grantee)

Cause and Prevention

Discovered teratogenic effects of 2,4,5-trichlorophenoxy acetic acid (2,4,5-T) in animals. (1971)

Discovered carcinogenic effects of bis(chloromethyl)ether and certain of its analogs and demonstrated an increase in lung cancer in exposed workers. (1972-1974)

Identified vinyl chloride as a cause of angiosarcoma and demonstrated an increase in this kind of cancer in polyvinyl chloride workers. (1973-1975)

Demonstrated that carbamoyl chlorides, used as intermediates in several chemical manufacturing processes, are carcinogenic in laboratory animals. (1976)

Established the toxicologic effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), the most toxic man-made chemical and a contaminant of some herbicides and fungicides, in experimental animals.

Proved the synergistic effects of noise in combination with ototoxic chemicals and drugs (1972), and established the hazards of nursery noise to hearing in newborn babies. (1973)

Demonstrated pulmonary damage in animals from inhaled underarm deodorants containing aluminum and confirmed suspicions of lung damage in man from such deodorants. (1973)

Established the mutagenicity and possible carcinogenicity of hycanthone derivatives widely used for treating schistosomiasis. (1973)

Through continuing epidemiological studies, provided quantitative confirmation that asbestos causes several kinds of cancer in workers exposed to asbestos-containing materials in the building trades, as well as in asbestos miners, and established that cigarette smoking greatly increases the incidence of cancer in such workers. (1968-1976)

Demonstrated the development of emphysema in animals exposed to NO and ozone at levels prevalent in smog and at peak traffic hours in large cities. (1972-1975)

Demonstrated the protective effects of certain antioxidants, such as vitamins A and E and glutathione, against lung damage by oxidant air pollutants in animals. (1973-1976)

Established that low levels of lead, mercury and manganese can cause behavioral aberrations and learning deficits in animals. (1973-1976)

Established that low levels of cadmium and its compounds can be teratogenic, act as immunosuppressants, induce hypertension and affect reproductive capacity in experimental animals. (1972-1976)

Confirmed the inflammatory properties of nickel compounds in the lungs of animals and established a correlation between the nickel content of coal and coal miners' pneumoconiosis. (1974-1976)

Established that nickel subsulfide is carcinogenic in experimental animals. (1975)

Demonstrated that lead synergizes the effects of certain organochlorine pesticides (lindane and chlordane) on the nervous systems in experimental animals. (1974)

Demonstrated that deficiencies in dietary calcium, iron and certain vitamins increases the toxicity of lead and cadmium several-fold. (1969-1972)

Demonstrated in experimental animals that glutathione deficiency enhances the hepatotoxicity and carcinogenicity of alkyl and aryl chlorides and that high levels of glutathione will afford some degree of protection against toxicity. (1973-1976)

Demonstrated in laboratory animals that deficiencies in dietary copper and/or zinc cause accumulation of lipids in the bloodstream, which may contribute to arteriosclerosis. (1973)

Demonstrated in animals that deficiencies in dietary copper and zinc can be induced by thalidomide, salicylates and other metal-binding agents and that such deficiencies can result in birth defects. (1968-1969)

Developed new chelating agents for treatment of plumbism and mercurialism. (1970-1976)

Established that organophosphate insecticides can interfere with fetal development and cause birth defects at moderately high levels in experimental animals. (1971-1973)

Demonstrated that several organochlorine pesticides (aldrin, dieldrin and lindane) can cause at least short-term behavioral effects and learning deficits in experimental animals. (1972-1975)

Demonstrated that fiberglass and polyurethane form dusts induce emphysema-like changes and cancer in lungs of experimental animals on long-term exposure. (1972-1974)

Demonstrated that hexachlorophene and related compounds are powerful hemolytic agents and can cause neurological damage in animals. (1974)

Established that phthalate esters, widely used as plasticizers, cause pulmonary inflammation and edema of the interalveolar septa at dosages that may be present in blood stored in plastic bags and used for blood transfusions. Demonstrated that pathology and lethality in experimental animals can be prevented by pretreatment with the anti-inflammatory steroid, methylprednisolone. (1975)

Established localization of polychlorinated biphenyls (PCBs) in skin, which may account for the cutaneous toxicity of the compounds in man. (1974)

Showed localization of PCBs in lobster hepatopancreas, which indicates that most lobster from PCB-polluted waters may be eaten if the hepatopancreas is discarded. (1974)

Demonstrated that PCBs can cause chromosome breakage and cancer in experimental animals. (1972-1973)

Established through epidemiological studies that retired leather tanners have a higher incidence of bladder cancer than normal. (1973)

Established through epidemiological studies that heavy coffee drinkers, especially women, have a higher than normal incidence of lower urinary tract cancer. (1972-1973)

Discovered, identified and elucidated the pathogenesis of several new mycotoxins and phytotoxins, which cause various syndromes, including cancer, hepatotoxicity, renal toxicity, lung edema, blindness, and neuropathy. (1966-1976)

Developed new spectrally narrow, highly active lamps which reduce the time required for phototherapy of hyperbilirubinemia in infants. Lamps also used in refining studies of photosensitization and photocarcinogenesis. (1966-1976)

Detection and Diagnosis

Established animal models for diethylstilbesterol (DES) effects on offspring (1973), predicted from the model the effects of DES on male animals and effects in humans, which were confirmed in 1975-1976.

Established pharmacokinetic models for PCBs in animals, allowing predictions of PCB duration in the body, given the dose and time since the last exposure. These models may be used to predict the half-life of PCBs in man and are being applied to similar chemicals such as kepone. (1976)

Refined old and developed new in vitro tests for mutagenicity which facilitate correlation between in vitro tests and in vivo tests for carcinogenicity, permitting pre-screening of large numbers of chemicals. (1974)

Developed methodology for analysis of dioxins and other chlorinated compounds in the ppb range in body tissues and environmental samples, facilitating studies on these extraordinarily toxic compounds at threshold toxic levels.

Developed instruments and methodology for detection and identification of asbestos and other types of particulates in food, water and body tissues, which permits establishment of badly needed dose-response relations for such particulates. (1974-1976)

Developed a new fluorescent method for detection and quantification of lead in old paint, facilitating implementation of measures to prevent ingestion of lead paint by children. (1970-1971)

Developed a method for determining blood lead levels in a drop of blood obtained by finger prick, facilitating the rapid screening and identification of children at risk of lead poisoning. (1974)

Basic Biology

Established accurate dosimetry for microwaves in biological samples. This allows distinguishing between heating and microwave effects, lack of which was a major defect in work by Russians, Poles, etc., who may thus have over-emphasized dangers from microwaves. (1971-1973)

Characterized the skin and pulmonary chemical-metabolizing systems and by purification and reconstitution, established how these differ from those of other organs. This became the basis for understanding specific damage to lung or skin by chemicals and lung- or skin-specific carcinogenesis. (1970-1974)

Demonstrated that ozone induces lung fibrogenesis in experimental animals. (1972-1975)

Established that lipid peroxidation of cellular and subcellular organelle membranes occurs through a free radical mechanism and is an important first step in cellular damage by oxidant air pollutants. (1972-1976)

Established the mechanism of thiolsulfonate formation in individuals exposed to SO_2 and elucidated the kinds of reactions of SO_2 and sulfites with nucleic acid components, e.g., deamination of cytosine, transamination of cytosine, and saturation of uracil (sulfone formation). These reactions appear to account for demonstrated effects of SO_2 and sulfites on protein synthesis, RNA, and DNA. (1971-1976)

Established that carbon monoxide contributes to lipid accumulations in the blood, arteries and heart muscle on long-term exposure, which may contribute to arteriosclerosis. (1973-1975)

Established that nitrites used as food preservatives will react with amines in the stomach of experimental animals to form carcinogenic nitrosamines. (1973)