PROBING THE UNKNOWN

1969 ANNUAL REPORT

PHARMACEUTICAL MANUFACTURERS ASSOCIATION FOUNDATION, INC.

CONTENTS

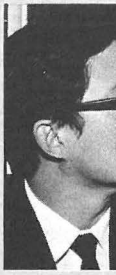
PROBING THE UNKNOWN

The 1960's have ended. For half of this decade, the PMA Foundation has played its unique role in expanding man's scientific knowledge.

These years have seen two manned lunar landings, achievements so monumental as to overshadow in the public eye virtually all other attempts by this generation of Americans to push back other frontiers—the earthly probes into the space of the unknown in medical research which have continued, daily and methodically, so that progress essential to improving the quality of life may go on. Support of this kind of space exploration by the PMA Foundation continued during 1969 in a growing number of diverse, yet related, research efforts and education programs.

The 1970's now begin. The PMA Foundation looks forward with confidence in its prospects for continued growth. It is the record of the activities reflected in this report on which this confidence is based. However, to continue to write a record of this kind, the Foundation's support system depends on three groups—the same contributors which have given substance to the aims and purposes of the Foundation during the latter part of the 1960's. It is to the Foundation's advisory committees, its many financial supporters, and to the individuals who submit the many well-conceived applications for consideration, that the Board of Directors must continually look. For their past efforts, a sincere expression of thanks is extended.

EXPANDED COMMUNICATIONS



Andrew K. S. Ho, Ph.D.

Lester F. Soyka, M.D.

Arthur H. Hayes, M.D.

Timothy H. Mathew, M.B., B.S.

John O. Lindower, M.D., Ph.D.

Communications between the PMA Foundation and its many contributors have been achieved primarily by the written word, such as periodic and annual reports, or through presentations by the chairman of the Foundation's Board of Directors at the PMA Mid-Year and Annual Meetings or at meetings of the PMA Board of Directors. A special session was held this year with the main objective of meeting those individuals who have received support from the Foundation. The conference was held in Chicago on December 7, 1969, to which representatives of all PMA Member Firms, other contributors, those receiving grant support and professional associations were invited. This one half day meeting entitled "The PMA Foundation, Past, Present, and Future" and chaired by Dr. E. Gifford Upjohn, was attended by about 100 persons.

The keynote speaker was William S. Middleton, M.D., Former Chairman, Drug Research Board, National Academy of Sciences, National Research Council. He recounted some of the circumstances surrounding the origins of the Foundation and parallel activities of the Drug Research Board during the first years of both of these groups, which had common origins in the Commission on Drug Safety, a group of experts brought together by the PMA in 1962 to study the entire issue of drug safety.

With Dr. Middleton's presentation as background, each chairman of the three advisory committees to the Foundation's Board of Directors spoke on his committee's current and anticipated activities. The chairmen are Irwin C. Winter, M.D., Ph.D., Vice President, Medical Affairs, G. D. Searle & Co., and Chairman of the Scientific

William S. Middleton, M.D.

Stanley C. Ushinski, M.D.

John S. Holcenberg, M.D. *(left)* and John L. McNay, Jr., M.D.

Pate D. Thomson, M.D.

Donald S. Robinson, M.D.

William J. Scott, Jr., D.V.M., Ph.D.

Walter F. Riker, Jr., M.D.

Advisory Committee; Thomas C. Chalmers, M.D., Director, Clinical Center and Associate Director, National Institutes of Health, and Chairman of the Faculty Development Awards in Clinical Pharmacology Advisory Committee; and Walter F. Riker, Jr., M.D., Chairman, Department of Pharmacology, Cornell University College of Medicine, and Chairman of the Fellowship Awards in Pharmacology-Morphology Advisory Committee.

The program then shifted to presentations by those persons who had successfully competed for awards under the two postdoctoral Foundation-sponsored educational programs. Eight of the ten awardees under the Faculty Development Awards program composed a panel, moderated by Dr. Glenn W. Irwin, Jr., Dean, School of Medicine, Indiana University, and a member of this advisory committee. Each panel member had an opportunity to express opinions on a number of questions in the field of clinical pharmacology posed by Dr. Irwin.

The second panel was composed of four of the five individuals who had received fellowships in pharmacology-morphology. Following the same format as the previous panel, Dr. Walter Riker, Jr., as moderator, posed questions in this inter-disciplinary field, with each panel member having an opportunity to express opinions.

E. Gifford Upjohn, M.D. *(left)* and C. Joseph Stetler

The meeting accomplished its purpose of opening up new avenues of communications among those who give substance to the Foundation—those supported through Foundation funds, those contributing these funds, and those charged with the responsibility of administering the funds.

The meeting also provided the setting for an event, filled with regret—the stepping-down from active involvement in the programs of the Foundation of E. Gifford Upjohn, M.D., who had served as Chairman of the Foundation's Board of Directors since its inception. He actively championed the formation of the Foundation as a member of the PMA Board of Directors. At the December 7, 1969, meeting of the Foundation's Board of Directors, Dr. Upjohn resigned as a member of the Board, following his retirement as Chairman of the Board of Directors of The Upjohn Company. The esteem with which the Board of Directors regards Dr. Upjohn is best expressed in the words of the citation presented to him by C. Joseph Stetler, President, PMA Foundation, on behalf of the Board of Directors:

> "With deep appreciation, the PMA Foundation expresses its sincere gratitude to E. Gifford Upjohn, M.D., upon his retirement as Chairman of the Board of Directors. He served as Chairman with distinction from the Foundation's inception in 1965 to December, 1969.
>
> Under Doctor Upjohn's outstanding leadership, the PMA Foundation has emerged as an important component of the scientific community through its commitment to education and research. As a result of Doctor Upjohn's dedicated efforts and unusual insight the Foundation has experienced steady growth. The Foundation expresses its esteem and affection and wishes him happiness and best of health in the future."

ACTIVITIES

Since its formation, over $2.2 million have been authorized by the PMA Foundation for a variety of workshops, conferences, research projects and educational programs. The Foundation truly represents the national concern of its supporters in promoting the science of therapeutics. This section describes highlights of the various activities the Foundation has supported during the year.

Workshops and Conferences

Workshops and conferences are important educational devices. One of the initial grants from the Foundation was for support of a workshop in drug metabolism in 1966. Conferences and other pertinent meetings continued to receive support.

Clinical Pharmacology. *A workshop on the* Principles of Drug Evaluation in Man *was held June 9-13, 1969, at the National Bureau of Standards in Gaithersburg, Maryland.* This workshop was sponsored by the Drug Research Board, National Academy of Sciences–National Research Council, the American Society for Pharmacology and Experimental Therapeutics, The National Bureau of Standards, the Johns Hopkins University and the Pharmaceutical Manufacturers Association Foundation. The enabling grant of $16,000 for the workshop was provided by the Foundation. The workshop director was Louis Lasagna, M.D., Associate Professor of Medicine and Pharmacology, Johns Hopkins University. The program was developed to emphasize the design and methodology in clinical drug evaluation. The meeting, limited to 40 participants and a small number of observers, had over 200 applicants.

The participants were drawn from the academic community, the pharmaceutical industry and government. The faculty came from an equally broad base.

The obvious interest and the number of excellent applicants who could not be accommodated at the first workshop led to a Second Workshop on the Principles of Drug Evaluation in Man. This is scheduled for June 15-19, 1970, at the University of Kansas Medical Center in Kansas City, Kansas. The workshop director is Daniel L. Azarnoff, M.D., Professor of Medicine and Pharmacology, University of Kansas. Sponsors are the American Society of Pharmacology and Experimental Therapeutics, the Drug Research Board–National Academy of Sciences–National Research Council, the PMA Foundation, the National Institute of General Medical Sciences, NIH and the University of Kansas Medical Center. An enabling grant of $21,200 was made by the PMA Foundation.

The program will be aimed at the same kinds of individuals who attended the first workshop, individuals whose professional activities are related to pharmacologic investigations in man. Particular preference will be given to those whose training is directed toward a career in clinical pharmacology, whether academic, industry or government oriented.

Attendees at the first supplemental training program for graduate students in pharmacology, hosted by the University of Minnesota, Department of Pharmacology, directed by Gilbert J. Mannering, Ph.D. (front row, left of center)

An award of $176,880 was made in 1967 to support a four-year effort by the American Society of Pharmacology and Experimental Therapeutics directed at advanced pharmacology students. The funds will support four to six week courses in advanced pharmacology for Ph.D. candidates and will be offered at various universities selected for their specialization in the selected fields. Up to 50 doctoral candidates can be accommodated at each yearly session. The American Foundation for Pharmaceutical Education is also providing financial support for this activity.

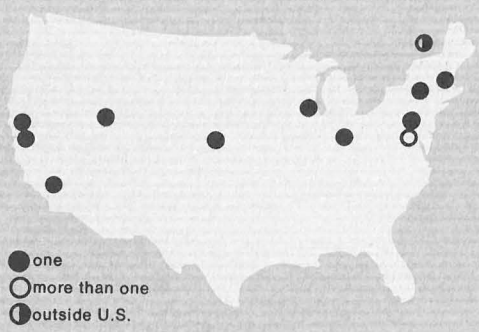
The purpose of these summer sessions is to overcome a basic problem in pharmacology education. Pharmacology departments are just not large enough to provide experience in all major research areas and teaching interests. Graduate students may not, therefore, be fully aware of some of the major problems or opportunities in pharmacology as they prepare for their postdoctoral careers.

The University of Minnesota, Department of Pharmacology, was the host for the 1969 summer session, the first offered under the award. This session ran for four weeks and dealt with drug metabolism and biochemical pharmacology. The director of the session was Gilbert J. Mannering, Ph.D., Professor of Pharmacology.

The second session is scheduled for the College of Physicians and Surgeons, Columbia University, New York City. The director is Brian F. Hoffman, M.D., Chairman, Department of Pharmacology. The area of instruction will be cardiovascular pharmacology. This session will also be for four weeks, beginning July 6, 1970.

For the last two sessions currently funded, the universities which will serve as hosts are:

- The University of California, San Francisco, Department of Pharmacology, host for 1971. The course will deal with neuropharmacology and mechanisms of drug actions;
- Vanderbilt University, Department of Pharmacology, host for 1972. The course will deal with psychopharmacology.



Geographical distribution of Foundation research grants, 1966-1969.

Research Grants

One of the most important Foundation activities is support of fundamental research in drug toxicology. Since 1966, a total of 15 research grants have been made for this purpose. Support has terminated on three grants. The remaining twelve grants will continue through varying periods of time through 1971.

In 1969, new grants were made to three institutions. They are: The University of Colorado Medical Center, Division of Dermatology, Denver, Colorado; Rutgers University, College of Pharmacy, Newark, New Jersey; and Georgetown University School of Medicine–School of Dentistry, Department of Pharmacology, Washington, D.C. Nine grants current in 1968 continued into 1969 are: Georgetown University, Renal and Electrolyte Division, Washington, D.C.; Albany Medical College of Union University, Institute of Experimental Pathology and Toxicology, Albany, New York; University of Utah, Department of Pediatrics, Salt Lake City, Utah; Children's Hospital Research Foundation, Institute for Developmental Research, Cincinnati, Ohio; University of Southern California, Department of Medicine, Los Angeles, California; University of Montreal, Department of Pharmacology, Montreal, Quebec, Canada; University of Chicago, Department of Obstetrics and Gynecology, Chicago, Illinois; Johns Hopkins University, Department of Pediatrics, Baltimore, Maryland; and Universities Associated for Research and Education in Pathology, Washington, D.C.

Continuing Education: *Support for the first time was authorized during 1969 for a specific program in continuing education in drug therapy topics for practicing physicians.* A grant for this purpose of $2,000 was made to Seymour M. Farber, M.D., Dean of Education Services and Director of Continuing Education, Health Services, University of California, San Francisco Medical Center. This fund will be used to bring speakers from out of the area to the university's annual drug therapy conference, thereby increasing the interest in and the number of participants and hopefully, that the expanded program will become self-sustaining.

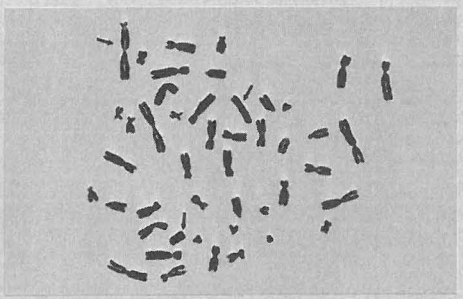
Another activity in continuing education was a grant of $5,000 for one year to the American Therapeutic Society and the American Society of Clinical Pharmacology and Chemotherapy. These funds will assist the societies to activate an Adjunct Speakers Program which will seek qualified speakers in areas of concern in drug therapy and make them available to interested hospitals and medical societies.

The twelve current research grants fall into the following categories:

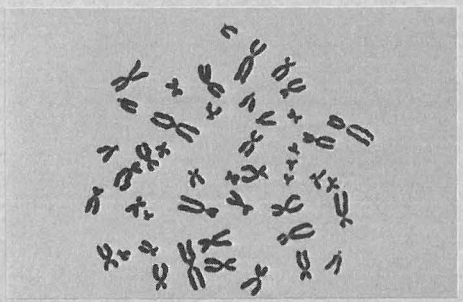
Animal-Human Predictability Studies. *The original grant of $68,549 for a two year period beginning January 20, 1969, made to the Department of Obstetrics and Gynecology, Chicago Lying-In Hospital, Pritzker School of Medicine, University of Chicago, was increased by $10,105 during 1969 to bring the total grant to $78,654.* The principal investigator is Anthony P. Amarose, Ph.D., Assistant Professor, Department of Obstetrics and Gynecology, and the co-investigator is Charles R. Schuster, Ph.D., Associate Professor of Psychiatry. This work is intended to determine whether a relationship exists between chromosome damage and drug intake. Chromosomes, the threadlike structures in the nucleus of a cell, carry the hereditary elements that enable human beings to reproduce. The study measures the response in the chromosomes of lymphocytes (a form of the white blood cell) and bone marrow cells to drug stimuli.

Many drugs administered during *in vitro* studies demonstrate chromosome damage. The basic question, however, is whether these drugs will produce *in vivo* the same damage after therapeutic dosages. The *in vivo* studies with animals consist of as close an *in vivo* comparison of drug effects to both validate the animal system and evaluate results reported to be noted in the chromosome studies of man.

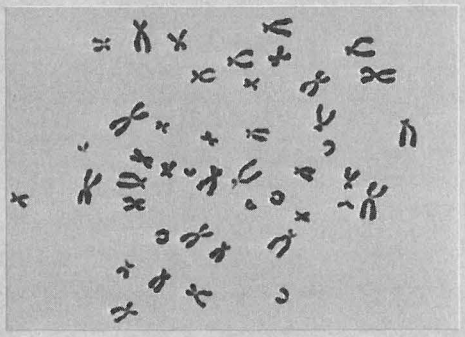
Human volunteers in the study are former drug addicts who have been using opiates, pschodelics, amphetamines, or barbiturates. The research team is studying various parameters, the most important of which is the chromosomology of the volunteers' bone marrow and peripheral blood. The ultimate target would focus on human germ cells, but because of the present impossibility of studying such cells at will, a related cell replenishment system, namely the hematopoietic system is being utilized.



A metaphase cell from the peripheral blood of a former drug addict. Arrows indicate residual chromosome damage months after total withdrawal of all drugs. 1600 X.



A bone marrow cell (direct preparation) from same subject showing normal number of 46 chromosomes with no visible damage. 1600 X.

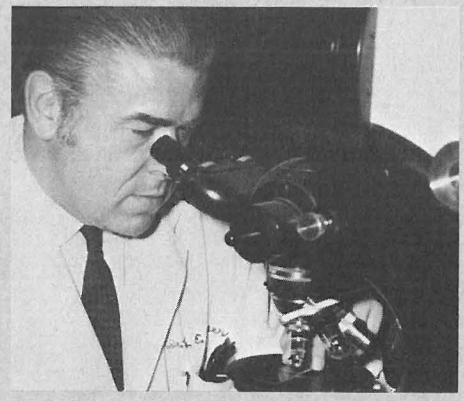


A normal metaphase cell with 44 chromosomes from a rabbit lymphocyte after *in vitro* culture. 1600 X.

A grant of $26,000 for a two year period beginning September 1, 1968, was made to Gabriel L. Plaa, Ph.D., Professor and Chairman, Department of Pharmacology, School of Medicine, University of Montreal. This remains the only grant made by the Foundation to an institution outside the United States. The grant supports a number of studies dealing with the production of intrahepatic cholestasis, a reaction

characterized by the development of jaundice and changes in the liver function which can occur in susceptible individuals following treatment with certain drugs.

The overall goal is to develop an experimental animal system which can be employed to detect intrahepatic cholestasis in the investigational stage of drug development. Changes in liver function are correlated with changes in the liver structure in three species of experimental animals—the rat, mouse and golden hamster. The parameters used to assess the hepatic dysfunction in the preliminary experiments have included: elevation of serum, bilirubin, serum glutamic-pyruvic transaminase (SGPT) or serum alkaline phosphatase (SAP) and changes in bile flow.



Dr. George E. Schreiner viewing the biopsy slide of a patient with toxic nephropathy.

Clinical Pharmacology. A grant of $20,000 for one year beginning July 1, 1970, was made to William T. Beaver, M.D., Associate Professor of Anesthesiology, Department of Pharmacology, Georgetown University Schools of Medicine and Dentistry for the establishment of a facility for studying the comparative effects of drugs on subjective responses. The primary concern will be the evaluation in patients of drugs whose major theraputic effects are in the control of pain, anxiety and nausea. Efforts during the initial year will be directed toward the evaluation of potent analgesics, both oral and parenteral, in general postoperative pain, pain associated with trauma and orthopedic surgery and pain associated with oral surgery in patients. In addition, techniques will be developed for the evaluation of mild oral analgesics, like the aspirin and dextro-propoxyphene class in outpatients who have had extractions and other painful dental procedures.

Dialyzable Drugs. A grant of $20,000 a year, for up to five years, for a total of $100,000, beginning January 1, 1967, to the Renal and Electrolyte Division, Georgtown University Hospital completed its third year during 1969. George E. Schreiner, M.D., Professor of Medicine and Director, Renal and Electrolyte Division, is the principal investigator. The funds have been used to support research related to the hemodialysis of drugs and poisons and to produce an annual registry of dialyzable drugs in cooperation with the American Society of Artificial Internal Organs. Hemodialysis is the removal of certain elements (in this case, drugs) from the blood by the diffusion through a semi-permeable membrane. The artificial kidney uses this procedure.

In 1969 the research group prepared and published, as it had in the previous two years, a review of dialyzable drugs and poisons. This article appeared in the Transactions of the American Society of Artificial Internal Organs, Volume XV.

Drug-Related Structural Studies. A grant of $25,000 a year for a four-year period totaling $100,000, beginning August 1, 1967, to the Institute of Experimental Pathology and Toxicology of the Albany Medical College of Union University, Albany New York, entered its third year in 1969. The principal investigator is Frederick Coulston, Ph.D., Director of the Institute. Funds during the first two and a half years have accelerated the Institute's studies of the relation of structural changes in the subcellular organelles of important tissues to the actions of chemicals and drugs. This program has as its purpose the establishment of selected critical areas of experimentation in animals with the anticipation that a valid prediction of safety can be made in man with limited but precise investigation.

An area of growing concern by this research group is the possible effect of chemical agents on reproductive physiology. Initial studies will aim at gaining a basic understanding of the reproductive process in primates. In these studies, the rhesus monkey is being used.

Drug Surveillance. *A grant of $48,000 made for a two-year period beginning January 1, 1968, to the University of Southern California for partial support of a continuing study of adverse reactions to drugs at the Los Angeles County General Hospital concluded at the end of 1969.* The program, under the direction of Robert F. Maronde, M.D., Associate Professor of Pharmacology and Medicine, is part of a larger project composed of two parts: an adverse drug reaction study of hospitalized patients; and an inquiry into drug ordering and dispensing for outpatients.

Involved in the adverse drug reaction reporting phase of the study are approximately 20,000 patients admitted yearly to the medical ward in the Los Angeles County General Hospital. During the two years of support, primary efforts have been devoted to the development of computer programs. A physician's surveillance team gathers the necessary information. These physicians note the significant patient events and other circumstances outside the specific areas of recognizable side effects. A nurse monitoring team has also been involved to record similar information. The use of the two different surveillance techniques will provide an opportunity to evaluate the relative merits of the approaches within the one study.

A grant of $20,543 was made to the Universities Associated for Research and Education in Pathology for continuing support during 1969-1970 of the Registry of Tissue Reactions to Drugs, Armed Forces Institute of Pathology. The registry is co-sponsored and equally supported by the American Medical Association, the Food and Drug Administration, the National Institutes of Health and the Foundation, Nelson S. Irey, M.D., is the Registrar.

The Registry obtains biopsy and autopsy tissue specimens on a voluntary reporting basis from participating pathologists. The Registry subjects the specimens to microscopic examination and reports its findings to the referring pathologist. As of the end of 1969, the Registry had accessioned 1,396 cases in its active files. Over 9,000 cases continued to be available to the Registry in its reserve file.

A set of educational publications which have been produced by the Registry entitled "Diagnostic Problems and Methods in Drug-Induced Diseases", are available to medical schools along with a set of lantern slides.

Fetal-Neonatal Pharmacology. *An award of $18,000 for an additional year on a two year grant which expired during 1968 was activated in 1969.* The grant, totalling $54,000, to the Department of Pediatrics, University of Utah and Alan K. Done, M.D., Professor of Pediatrics is for a study of the drug potentiation of kernicterus, a condition of hyperbilirubinemia associated with jaundice which may produce brain damage in the newborn.

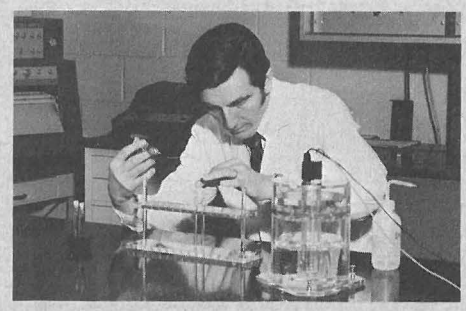
During the two years of the grant, the research team found that many of

the *in vitro* procedures which have been used to measure the ability of drugs to compete with bilirubin for protein-binding were unreliable and were not consistent with the findings in the Gunn rat, which has an inherited inability to conjugate bilirubin. Further data were needed concerning the identity of sites for drugs and bilirubin binding, and to show that competition does in fact occur. The third year's funds will enable the research team to collect this data.

The results of the first two year's study have pointed the direction for the third year. The research team has found that the procedures of bilirubin ultrafiltration, measurements of dye-binding capacity and kinetic measurements of binding offer the greatest promise among the *in vitro* techniques for determining drug inhibition of bilirubin-albumin binding. These techniques are being emphasized during the third year. Most needed studies are additional parallel comparisons of the results obtained with these three methods and their correlation with the *in vivo* studies in the Gunn Rat.

A grant of $50,000 a year for five years for a total of $250,000 was made in 1967 to Josef Warkany, M.D., Professor of Research Pediatrics, on behalf of the Children's Hospital Research Foundation for partial support of the activities of the Division of Fetal Pharmacology of the Institute of Development. The Institute, which opened in June 1968 has used Foundation support primarily in the Division of Fetal Pharmacology to support staff and purchase the equipment needed for the basic research within this unit. Ernest F. Zimmerman, Ph.D., is the Director of the Division.

Dr. Zimmerman has become interested in the molecular mechanisms by which glucocorticoids induce cleft palate in mice. One recurring finding in teratology is that the most sensitive period of administration of a teratogen is several days before the morphologic appearance of the organ which is ultimately transformed. It has been shown that there is a sequential



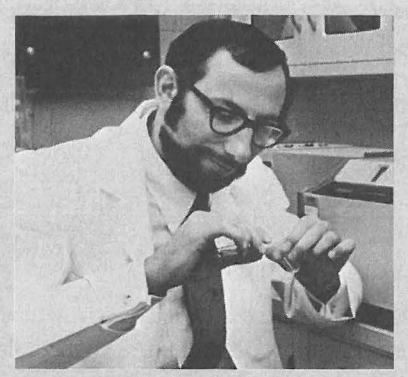
Dr. Ernest F. Zimmerman is studying the mechanism by which glucocorticoids induce cleft palate in mice. He is determining whether palate proteins, separated by acrylamide gel electrophoresis, are delayed in their appearance after triamcinolone administration.

synthesis of different messenger RNA (m RNA) molecules during development. This results in translation of proteins at later times. A tentative posulate put forth by Dr. Zimmerman is that such an inhibition of m RNA synthesis early in development by the glucocorticoid triamcinolone leads to a later inhibition of protein synthesis and thus congential malformation.

Dr. Roger Ganschow, Associate to Dr. Zimmerman, has been studying mechanisms of genetic control of enzymes in higher organisms using inbred mouse strains with altered enzyme characteristics. Activities of James G. Wilson, Ph.D., Director of the Division of Pathologic Embryology, have received some support from the Foundation's funds. He is primarily interested in the descriptive aspects of experimental teratology. In a paper before the Teratology Society in July, 1969, Dr. Wilson reported that in general, rats are more susceptible to the teratogenic actions of a variety of drugs than are rhesus monkeys.

A grant of $50,000 over a two year period beginning January 1, 1969, was made to Robert E. Cooke, M.D., Given Foundation Professor of Pediatrics, Johns Hopkins University School of Medicine for basic and clinical research on the effects of drugs given to the developing organism. The work is being done in a new unit devoted to developmental pharmacology within the Department of Pediatrics under

Dr. Paul S. Lietman, with the technical assistance of Mrs. Elizabeth Moen, has investigated some effects of antibiotics on mammalian cells, especially with respect to mitochondrial protein synthesis.



Dr. Guinter Kahn determining the absorption of hemoglobin from photohematized material.

the direction of Paul S. Leitman, M.D. Emphasis in the laboratory is being placed on the pharmacologic agents affecting protein synthesis and its regulation.

Nutritional Deficiencies—Drug Action. A grant of $29,459 over a two year period was made to Christina VanderWende, Ph.D., Associate Professor of Pharmacology, Rutgers University. The funds will provide support for studies of the interaction of vitamin deficiencies and drug action. The extension of these studies would eventually include studies of protein deficiencies and a generalized malnutrition state on drug action and drug toxicity. Preliminary studies have shown that in mice fed a thiamine deficient diet for one week, the sleeping time after phenobarbitol is increased three to fourfold. If the deficiency is allowed to continue for three weeks, a dose which proved to be safe for control animals, killed all of the deficient animals. These studies, in a preliminary fashion, make it apparent that both the pharmacologic activity and the toxicity of drugs can be markedly influenced in deficiency states. The ultimate objective of the project, therefore, is to systematically determine what kind of deficiencies can alter drug actions and which classes of drugs are most likely to be altered.

The investigators will use widely prescribed drugs such as barbiturates and tranquilizers and over-the-counter items, such as aspirin. The study will also include amphetamines and narcotics (morphine) because of their wide-involvement in drug abuse. The deficiency states to be studies in rats will be those involving the B vitamins, and vitamins A, E, K and C.

Photoactive Compounds. A grant of $14,500 for one year, beginning July 1, 1969, was made to the University of Colorado Medical Center for support of a study of the possible beneficial effects of light on drugs. The research is under the direction of Guinter Kahn, M.D., Assistant Professor of Dermatology and will involve study of the changes which occur when drugs are exposed to various wave lengths of radiation. The research team will evaluate the effect on cell growth of the new compounds which are affected by light and will determine if drugs with new uses are brought about by changes in radiation of well-known photoactive drugs. The effects of such drugs will be examined in cultured human cells and bacteria.

While the study will focus on drugs which can harness the energy of long-wave ultraviolet light to cause useful anti-cellular effects, the research also will attempt to determine if these photosensitizing drugs can enhance the effect of X-ray radiation on any part of the cell. A byproduct of this activity could be a means to increase the effects in certain forms of radiation therapy.

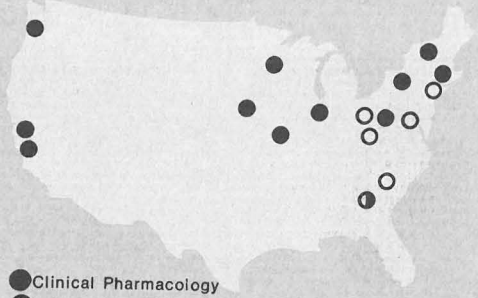
Publications

A grant of up to $18,500 has been authorized for the preparation of the book entitled "The Fundamentals of Drug Metabolism and Disposition." The contents of this book are being drawn from the presentations at three workshops on drug metabolism supported by the PMA Foundation in 1966, 1967 and 1968. Wider availability of the information presented at these workshops was considered highly desirable, since the meetings were limited to 40 participants each. The editors of the book are the directors of the workshops, Doctors Bert N. La Du, New York University; H. George Mandel, George Washington University; and E. Leong Way, University of California, San Francisco. The contributing authors in most instances are the members of the faculties at the three workshops. The Foundation is cooperating with the Drug Research Board, National Academy of Sciences–National Research Council in the effort. The estimated publication date is January 1971.

A grant of up to $22,000 was made to the American Society for Pharmacology and Experimental Therapeutics for support of the preparation and publication of a recruitment brochure for the field of pharmacology. Over the past several years, the American Society of Pharmacology and Experimental Therapeutics has distributed nearly 450,000 copies of a brochure entitled "A Career in Pharmacology." written for the high school and beginning college student. The new brochure, prepared to reflect the changes occurring in the sciences over the past ten years, will be aimed at a somewhat more advanced student. About 200,000 copies are expected to be published.

Education and Training Programs

To further its objectives in the field of education, the Foundation sponsors two programs in clinical pharmacology and one in the combined fields of pharmacology and morphology. The two clinical pharmacology programs have provided educational opportunities for a number of individuals at both the student and the faculty level.



Geographical distribution of Foundation awards under its "Faculty Development Awards in Clinical Pharmacology" program, 1966-1969; and Fellowship Awards in Pharmacology-Morphology, 1968-1969.

Clinical Pharmacology. Through the "Faculty Development Awards in Clinical Pharmacology" program, the Foundation makes two-year awards to medical schools for salary support of full-time junior faculty members. The level of support is variable but in keeping within the existing salary structure of the applicant university. The Board of Directors has established a yearly fund of $100,000 for this program.

With the awards made in 1969 and scheduled to begin July 1, 1970, thirteen individuals have now been supported under this program since its inception in 1967. While the award is for a basic two-year period, a third year of support is available to those awardees who, at the end of their first year, show sufficient need for the third year. An additional fund of $50,000 has been authorized to provide for the contingency of requests for a third year of support.

Recipients of new faculty awards beginning July 1, 1970, are:

- Arthur J. Atkinson, M.D., Assistant Professor of Medicine, Department of Medicine, Northwestern University Medical School. Dr. Atkinson will be training under a program developed by the Department of Pharmacology and the Department of Medicine. His

Arthur J. Atkinson, Jr., M.D.

Samuel A. Cucinell, M.D.

Aryeh Hurwitz, M.D.

major responsibility will be the development of an active program of education in clinical pharmacology and his research will involve studies of cardiac drugs in relation to their effectiveness. He will participate in the teaching of the pharmacology courses for second-year medical students.

• Samuel A. Cucinell, M.D., Assistant Professor of Medicine, Emory University School of Medicine. The award will enable Dr. Cucinell to continue his research efforts on drug metabolism in man. These activities will include investigations of both new and established drugs. Dr. Cucinell is currently collaborating on a project to define possible interactions with those drugs which are used in epileptic patients. He will also be involved in all phases of evaluation of new drugs in man and will have teaching assignments in the Division of Clinical Pharmacolgoy.

• Aryeh Hurwitz, M.D., Assistant Professor of Medicine and Pharmacology, Clinical Pharmacology-Toxicology Center, University of Kansas Medical Center. Dr. Hurwitz will divide his time between research, teaching and service. His major research interest is the mechanism of action of compounds which are poisonous to liver cells and treatment of the resulting damage. Studies will be carried out in experimental animals as well as humans. Teaching duties will involve ward rounds in the general medical and surgical services and supervision of medical students in the outpatient clinic. Dr. Hurwitz will participate in the medical and graduate-student teaching programs in basic pharmacology. He will have direct supervision of fellows in clinical pharmacology and will participate in the consultation services, seminars and conferences of the clinical pharmacology section.

Recipients of the awards which began July 1, 1967, are:

• Faruk S. Abuzzahab, Sr., M.D., Ph.D., Assistant Professor, Department of Psychiatry and Pharmacology, University of Minnesota, is conducting research in both basic and clinical pharmacology.

• John S. Holcenberg, M.D., Assistant Professor, Division of Clinical Pharmacology, Department of Medicine, University of Washington, Seattle, is extending his training in biochemical approaches to clinical pharmacology.

• John L. McNay, M.D., Associate Professor of Medicine and Assistant Professor of Pharmacology, Emory University, is conducting research in renal physiology and pharmacology.

Recipients of awards which began July 1, 1968, and which were extended until June 30, 1971 are:

• William Y. W. Au, M.D., Assistant Professor of Pharmacology and Medicine, University of Rochester, is engaged in research on the effects of hormones and other agents affecting bone metabolism.

• Arthur H. Hayes, M.D., Assistant Professor, Pharmacology and Medicine, Cornell University, is furthering his training in the cardiovascular field.

• Donald S. Robinson, M.D., Assistant Professor of Medicine and Pharmacology, University of Vermont, is involved in studies in biochemical pharmacology.

Recipients of awards which began July 1, 1969, are:

• Vincent S. Aoki, M.D., Assistant Professor, Department of Internal Medicine and Pharmacology,

University of Iowa, is involved in studies of the effects of drugs on the pulmonary vascular bed.

- Lester F. Soyka, M.D., Assistant Professor of Pediatrics, Department of Pediatrics, Stanford University, is involved in research dealing with immaturity at the biochemical level and other developmental studies.
- Pate D. Thomson, M.D., Instructor, Department of Medicine, University of California, San Francisco Medical Center is involved in research to determine the effects of diseases on the pharmacokinetics of drugs used in their treatment.
- Stanley C. Ushinski, M.D., Assistant Professor of Pediatrics and Pharmacology, University of Pittsburgh, is engaged in research in experimental-analytic laboratory techniques, with emphasis on the study of bronchial smooth muscle in "normal" and "allergenic" individuals.

The "Medical Student Traineeships in Clinical Pharmacology" offered for the first time in 1966, provide opportunities to medical students to become aware of the basic techniques used in the field of clinical pharmacology. Hopefully, these students will sustain their interests in clinical pharmacology and chose this field as a career. The program provides a stipend of $1,000 to each student for a three-month period. A yearly fund of $20,000 has been authorized for this program. Since 1967, when the first awards were made, 60 awards have been made to medical schools across the United States.

The universities and students receiving awards in 1969 are:

University of Arkansas
Donald C. Thompson

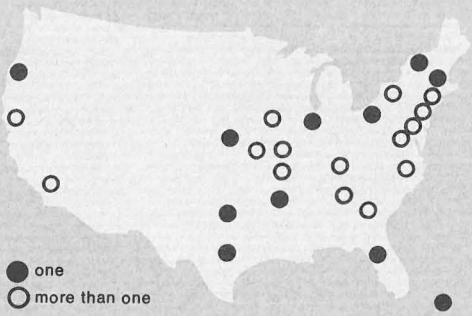
University of California
Ross R. Sedler

Case Western Reserve University
Gerald L. Moriarty

University of Chicago
Perry V. Halushka, Ph.D.

Cornell University
Richard A. Katz

Duke University
Arnold S. Grandis



Geographical distribution of Foundation awards under the "Medical Student Traineeships in Clinical Pharmacology" program, 1967-1969.

Emory University
Anthony S. Jennings

Emory University
C. Kenneth McAllister

Hahnemann Medical College
Mark Berger

University of Iowa
Steven P. Combs

University of Kansas
Larry L. Abrams

University of Kentucky
Carter B. Carr
William G. Uhron

University of Maryland
Warren P. Magid

New York University
Tsun-nin Lee

University of North Carolina
Larry L. Adams

University of Puerto Rico
Carlos R. Roman

University of Rochester
Paul R. Goodyer
Alan L. Cowles

University of Vermont
Norbert J. Gilmore

Pharmacology-Morphology. A postdoctoral program offered by the Foundation is the "PMA Foundation Fellowship Awards in Pharmacology-Morphology". Recent developments indicate the need for studies of drug-evoked changes in structure and their functional significance. When the program was initially offered in 1967, it was referred to as pharmacologic-pathology. The name was later changed to pharmacology-morphology to more clearly reflect the intent of

Andrew K. S. Ho, Ph.D.

William J. Scott, Jr., D.V.M., Ph.D.

the program. The aim of the program has not changed. It seeks to advance understanding of drug action through discovery of specifically related cellular and tissue changes; and, concurrently, to uncover associations between normal and abnormal function in particular tissues and cellular structure.

The awards are for two years each and, in exceptional circumstances, may be extended for an additional year. The level of support is variable and is aimed at keeping within the existing stipend levels for similarily trained individuals within the applicant university.

The fellowship program is designed to support individuals trained to study the actions of drugs in relation to morphologic approaches (cytology, histology, ultrastructure, pathology). This pursuit applies an interdisciplinary training. Although the program requires that a candidate be qualified primarily either in a morphologic specialty or in pharmacology, training in the complementary discipline need not be formal. The aim is to have the candidate gain familiarity with a new disciplinary approach by using his primary discipline as a medium for acquiring the second. A yearly fund of $70,000 has been set aside for this program.

Recipients of the awards which began July 1, 1969, are:

- Andrew K. S. Ho, Ph.D., Research Scientist, New York University Medical Center, New York, New York. Dr. Ho will extend his training through studies of the effect of cell structure and tissue function of the various psychopharmacologic drugs by a combination of techniques of electron microscopy, histochemistry and biochemical pharmacology. The findings are correlated to the theraputic use of these drugs and their effect on behavior.
- William J. Scott, Jr., D.V.M., Ph.D., Postdoctoral Fellow, Children's Hospital Research Foundation, Cincinnati, Ohio. The award will enable Dr. Scott to advance his training through a series of studies in rats and primates of the teratogenicity of a group of carbonic anhydrase inhibitors. He will attempt to determine the mechanism of teratogenetic action.

Recipients of awards which began July 1, 1968, are:

- David W. Hiott, Ph.D., Department of Pharmacology, Medical College of South Carolina. He is gaining additional experience with the procedures of audio-radiography and in certain techniques and interpretations of histochemistry, particularly at the electron microscopic level. His research efforts are directed toward the investigation of ultrastructural changes in the canine and hamster cardiac muscles by quinidine and daunomycin.
- John O. Lindower, M.D., Ph.D. Department of Pharmacology, The Ohio State University. Dr. Lindower is engaged in studies of the effect of digitalis by correlating the changes the compound produces in heart cells. Isolated small animal hearts are perfused with the digitalis medium while a recording device measures the more forceful contraction that the drug produces in the heart. After the drug effect has been demonstrated, small samples of the heart muscle are examined by the electron microscope to detect any changes that have been produced by the drug.
- Timothy J. Mathew, M.B., B.S., Renal and Electrolyte Division, Georgetown University Hospital. He is engaged in studies directed to examination of platlets in the pathogenesis of transplant rejections. An attempt is being made to alter histologic pattern rejection by using drugs directed at changing the platlet function.

FOUNDATION FINANCES

Contributions are accepted from corporate and individual sources. The Foundation does not accept contributions which are so restricted as to place their use outside the policies of the Foundation. Contributions to the Foundation are deductible for Federal income tax purposes.

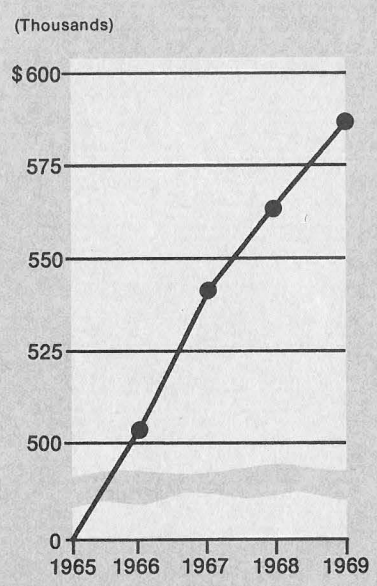
The Board of Directors of the Foundation decided at the offset that, as a minimum, annual contributions of $500,000 would be sought for each of the first three years of the Foundation's activities, extending through 1968, with larger amounts anticipated thereafter. In requests for voluntary support to PMA Member Firms, a guideline is suggested. Each firm is asked to consider a contribution equal to .015% of its domestic and international pharmaceutical sales.

Income. The total income in 1969 was $652,861. Of this amount $587,220 came from contributions. The balance of $65,641 came from investments and a refund on an unexpended balance on a grant. The 1969 contributions represent an increase of approximately 4% over the $567,951 received in 1968, an 8% increase over the $543,392 received in 1967 and approximately a 16% increase over the $503,297 received during the Foundation's first contribution period covering 1965-66.

Contributions were received from approximately three of every four PMA Member Firms. About one half of the PMA Associates also join in supporting the Foundation. Contributions were also received during 1969 from several individuals and groups in the health field.

Expenditures. Grants, foundation-sponsored programs, and administrative expenses for 1969 amounted to $620,527. Of this amount $549,030 represented expenditures for grants and Foundation-sponsored programs. There was a fund balance of $757,905 as of December 31, 1969. This figure, however, does not reflect the

PMA Foundation
Contribution Income
1965-1969



tentatively authorized, undisbursed amounts for some of the grants and programs described earlier. The Foundation reports these amounts as expenditures when the funds are distributed. As of December 31, 1969, this contingency liability totaled $891,995. Some of these grants represent amounts to be paid over the next two years. Part of this liability will be met from anticipated income in 1970 and succeeding years. During 1970 the estimated amount to be paid on this tentative commitment is $573,601.

Financial Reports. The Foundation's financial position as of December 31, 1969, has been audited by the accounting firm of Ernst and Ernst. Copies of this statement will be supplied upon request.

Financial statements have been issued to contributors quarterly during 1969. These reports are prepared by the Washington, D.C. accounting firm of Buchanan and Company. Quarterly reports will continue to be distributed to the Foundation's contributors during 1970.

STATEMENT OF INCOME AND EXPENDITURES

For the year ended December 31, 1969

Income

Contributions—Note a	$587,220
Income from Investments	58,892
Refund of unexpended balance of prior year's grant	6,749
TOTAL INCOME	$652,861

Expenditures

Grants—Note b	
Student Traineeship in Clinical Pharmacology	$20,000
Georgetown—Kidney Fund	20,000
Children's Hospital Research Foundation	50,000
University of Southern California School of Medicine	24,000
University of Chicago	56,915
American Society of Clinical Pharmacology and Chemotherapy	5,000
Johns Hopkins University	25,000
Institute of Experimental Pathology and Toxicology	25,000
Drug Metabolism Book	1,847
Faculty Development Awards in Clinical Pharmacology	152,341
Pharmacology and Pathology Fellowship Awards	61,500
University of Colorado Medical Center	14,500
ASPET: Brochure	5,000
Workshop	15,964
Supplemental Training	20,420
University of Utah	18,000
University of Montreal	13,000
University Association for Research and Education in Pathology	20,543
	$549,030
Administrative expenses	71,497
Total expenditures	$620,527
Excess of income over expenditures	32,334
Fund balance at January 1, 1969	725,571
Fund balance at December 31, 1969	$757,905

Note a—The Foundation received contributions of $95,650 prior to December 31, 1969, which the Foundation considered applicable to 1970 and, therefore, are not recorded as income in 1969.

Note b—The Foundation has committed itself, subject to review, to make certain research grants. At December 31, 1969, the amounts still to be disbursed with respect to these grants aggregated $891,995, of which approximately $573,601 is expected to be disbursed during the year 1970. No liability has been reflected for these amounts at December 31, 1969.

PURPOSE

The PMA Foundation was established to promote the betterment of public health through scientific and medical research, with particular reference to the study and development of the science of therapeutics. In achieving this goal, the Foundation plans and initiates scientific and medical research activities, collects and disseminates the results of these activities, and provides financial support and aid to individuals or institutions whose purposes are scientific, educational or charitable. Certain guidelines have been developed to promote the wise and proper use of the limited resources available. The areas of interest agreed to initially, and which still govern the distribution of funds, are *support of fundamental research in drug toxicology,* and *support of programs of research and training for personnel in clinical pharmacology and drug evaluation.*

Throughout the year, programs have been supported and developed which provide the means of achieving the goals of the Foundation. Many worthwhile proposals have been submitted. It has been necessary to limit support to those which hold the highest promise of advancing the purposes of the Foundation.

Those areas *not* supported within the existing guidelines are:

(1) Research on specific drugs. This exclusion is not meant to preclude support of projects which, of necessity, use a number of drugs or a class of drugs to establish a methodology or screening program of potential general applicability. It does exclude those efforts primarily aimed at learning more about specific drugs or classes of drugs.

(2) Funds for construction. The Foundation is not unmindful of the needs and the tremendous pressures for private funds for construction projects. However, it is believed that the scientific community can better be served by channeling the Foundation's available resources into other areas.

(3) Funds for travel.

(4) Funds to cover entertainment costs.

In 1968, a policy was instituted which limits research support to no more than a two-year commitment, but allows the grantee to request an extension for a third year at the end of the first year's activity, with a report of the first year's activity.

BEGINNINGS

For those of you who, through this Annual Report, learn of the Pharmaceutical Manufacturers Association Foundation for the first time, a brief resumé of the history which led to its formation is in order.

One event most influential in promoting the establishment of the PMA Foundation was the work and the Final Report of the Commission on Drug Safety, a study group formed by the Pharmaceutical Manufacturers Association in the Fall of 1962. The Commission was charged to make a study of the entire problem of drug safety and to come forth with recommendations. It carried out its work during the time of the urgency of the thalidomide situation. Special attention was given by the Commission initially to drug-induced fetal malformations. It became evident, however, that the most profitable line of inquiry would be to attack the overall problem of drug safety.

This Commission of distinguished membership, experts from universities, industry and government, arrived at a series of recommendations.

A continuing theme expressed in a variety of ways by these authorities was that the pharmaceutical industry should show more interest in the conduct of basic studies in drug toxicology, with the suggestion that co-operative sponsorship of such fundamental projects would have the greatest potential for uncovering new information. To make such studies possible, the Commission suggested a number of alternative mechanisms.

One was to establish a foundation. This, as well as many of the Commission's other recommendations, was considered by the PMA Board of Directors for some months following publication of the Commission's report. On May 31, 1965, the PMA announced the establishment of the PMA Foundation. The initial operating funds were supplied by the PMA, and sustaining support for the Foundation has come from voluntary contributions of PMA Member Firms and Associates, industrial concerns, organizations and individuals with an interest in health care.

ORGANIZATION AND ADMINISTRATION

The PMA Foundation operates through a Board of Directors and three advisory committees. The Chairman of the Board is Henry W. Gadsden, C. Joseph Stetler is President, Raymond M. Rice, M.D., is Vice President, and Thomas E. Hanrahan is Executive Director. Mr. Gadsden was elected to the Chairmanship of the Board in December, 1969, following the retirement of Dr. E. Gifford Upjohn. H. W. Blades, President, Wyeth Laboratories, was elected Vice Chairman and Daniel C. Searle, President, G. D. Searle & Co., was elected Secretary-Treasurer.

At the PMA Annual Meeting in 1969, Fred A. Coe, Jr., President, Burroughs Wellcome & Co. (USA) Inc., was elected to the Board of Directors of the Foundation to fill the vacancy created by the resignation of John J. Powers, Jr., President, Chas. Pfizer & Co., Inc.

In continuing to seek the most worthwhile activities for support, the Board of Directors has had the advice of extremely knowledgeable individuals, serving on three advisory committees.

The Scientific Advisory Committee has the responsibility of making recommendations to the Board of Directors on all scientific grant requests and on self-initiated scientific undertakings. Irwin C. Winter, Ph.D., M.D., Vice President, Medical Affairs, G. D. Searle & Co., Chicago, Illinois, is Chairman of this committee. To increase its effectiveness, the Chairmen of the Medical and the Research and Development Sections of the PMA are invited to serve as *ex-officio* members of the Committee.

Henry W. Gadsden

C. Joseph Stetler

Raymond M. Rice, M.D.

Thomas E. Hanrahan

The Advisory Committee to the "Faculty Development Awards in Clinical Pharmacology" program is charged with making recommendations to the Board of Directors on all applications received for these awards, as well as those applications received under the "Medical Student Traineeships in Clinical Pharmacology" program. The Chairman of this committee is Thomas C. Chalmers, M.D., Director, Clinical Center and Associate Director, National Institutes of Health, Bethesda, Maryland.

The Advisory Committee to the "PMA Foundation Fellowship Awards in Pharmacology-Morphology" program has the responsibility for making recommendations to the Board of Directors on all applications under this program. The Chairman of this committee is Walter F. Riker, Jr., M.D., Chairman, Department of Pharmacology, Cornell University Medical College, New York, New York.

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** Resigned from the Board of Directors, December 7, 1969*

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Thomas C. Chalmers, M.D.

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National Institutes of Health
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* Irwin C. Winter, Ph.D., M.D.
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Chicago, Illinois

** ex officio—as Chairman of Scientific Advisory Committee*

PMA Foundation Fellowship Awards in Pharmacology-Morphology Advisory Committee

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Sinai Hospital of Baltimore, Inc. and
Professor of Surgery
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David A. Wood, M.D.
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San Francisco Medical Center
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Warren-Teed Pharmaceuticals, Inc.
Winthrop Laboratories
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Reader's Digest Foundation
Sheffield Tube

** Contribution made in the memory of Mrs. Robert K. Cutter*

APPLICATIONS

The Foundation welcomes requests for support and suggestions for projects from qualified institutions and individuals.

It is suggested that requests for assistance take the form of a letter, outlining the subject, purposes, scope, brief description of methods or procedures to be used, principal researchers, percentage of time to be devoted to project by each of the principals, curriculum vitae, bibliographies of the principal researchers, the budget, other sources of present or anticipated financing of this same undertaking, a listing by title of other research projects presently involved in by the principal researchers and the amount of time devoted to each, and the amount and source of funds of these activities. These letters should be addressed to:

C. Joseph Stetler, President
Pharmaceutical Manufacturers
Association Foundation, Inc.
1155 Fifteenth Street, N.W.
Washington, D. C. 20005

Pharmaceutical Manufacturers Association Foundation, Inc.
1155 Fifteenth Street, N.W., Washington, D.C. 20005