1977 ANNUAL REPORT PHARMACEUTICAL MANUFACTURERS ASSOCIATION FOUNDATION, INC.



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INNOVATION AND FLEXIBILITY

O ACHIEVE MAXIMUM USEFULNESS, PRIVATE sources of funds for support of research and education must be guided by innovation and flexibility. Most private sources are unable to provide millions of dollars for a particular program, or to award multi-year million dollar grants to a single institution, or hundreds of thousands of dollars to one individual. Thus, non-public sources of funds should be willing to assume more "risk taking" in their programs than public sources may be able to accept.

Innovation and flexibility were the touchstones of the PMA Foundation's efforts this past year. Experience with the Foundation's clinical pharmacology programs had shown a growing need to assist developing clinical pharmacology units. As a consequence, a developmental grant program for such units was offered for 1978. The program is designed to provide research operating support to more readily enable a new unit to compete for larger support from other sources.

The year witnessed still another Foundation innovation. With new federal policies limiting the length of fellowship support, students in disciplines vital to the pharmaceutical industry were finding themselves without support in their final year or two of predoctoral study during which time their thesis research is undertaken. In this situation, the PMA Foundation's advisory committees identified a role for the Foundation. A program of advanced predoctoral support for students in the fields of pharmacology and toxicology was developed and offered.

To maintain current programs, the PMA Foundation has always aimed at flexibility particularly in modifications as needed. Changes were introduced during the year in the level of support in the medical student program, the research starter grant program, the faculty program in basic pharmacology and the fellowship program in clinical pharmacology. These changes have further enhanced the Foundation's overall value to the scientific community.

The ability to be alert to the need for new programs and to change existing ones result from the excellent guidance provided by the Foundation's advisory committees, and from the financial capability to be able to act positively on the advice of the committees. All this has been made possible by the increasing support of the Foundation's contributors.

This winning combination of expert advice and increasing financial resources has enabled the Foundation to develop innovative ways to use the funds entrusted to it. But, as important as new programs are in an ever changing scientific field, the Foundation has also valued the flexibility to hone its existing programs to serve better the disciplines vital to the body of biomedical knowledge on which depends the advancement of the public health.

INTERACTION











he eighth in a series of yearly meetings with recipients of awards under various postdoctoral educational programs and members of the Foundation's advisory committees was held December 4-5, 1977.

Daniel C. Searle, Chairman of the PMA Foundation Board of Directors, opened the meeting with a review of the continuing growth of the Foundation, in both programs and financial support. The keynote speaker for the general session was Edgar Haber, M.D., Professor of Medicine, Harvard Medical School and Chief of Cardiology, Massachusetts General Hospital, who covered the topic "Antibodies as Specific In Vivo Diagnostic and Therapeutic Agents". In separate sessions, the clinical pharmacologists, the fellows in pharmacology-morphology and the faculty awardees in basic pharmacology developed their own programs. The clinical pharmacology session was moderated by Leon I. Goldberg, M.D., Ph.D., Chairman of the Clinical Pharmacology Advisory Committee and Chairman, Committee on Clinical Pharmacology, University of Chicago. In this session, a panel of committee members led a discussion of "Clinical Pharmacology-Past, Present and Future: An Examination of Issues Shaping the Discipline". The panelists were: Dr. William B. Abrams, Deputy Executive Director, Merck Sharp & Dohme Research Laboratories; Dr. Edward A. Carr, Jr., Professor and Chairman, Department of Pharmacology and Therapeutics, State University of New York and Dr. Leon I. Goldberg.

The pharmacology-morphology fellows split their time between discussions of the research efforts of some current fellows and the presentation by Dr. Don W. Fawcett, Hersey Professor of Anatomy, Harvard Medical School, who talked about "Pharmacological-Morphological Approaches to the Control of Fertility in the Male".

The faculty awardees in basic pharmacology delved into the author-editor relationship. Dr. Eva Killam, Editor, *Journal of Pharmacology and Experimental Therapeutics*, and Professor-in-Residence, Department of Pharmacology, University of California, Davis, led the discussion.

These yearly meetings continue to provide opportunities to assess how well each program is progressing.

A similar, shorter meeting is held each year with the research starter grantees during the fall meeting of the American Society for Pharmacology and Experimental Therapeutics. The speaker this year was Richard Simon, Project Manager, Laboratory Animal Data Bank, Battelle-Columbus Laboratories, covering the topic "The Laboratory Animal Data Bank: A Status Report".

Such meetings contribute much to the vitality of the PMA Foundation. The opportunities to evaluate each program and to innovate are greatly enhanced through the interaction between advisory committee members and awardees.



















ACTIVITIES

INCE ITS FORMATION IN 1965, ABOUT \$8 million has been authorized by the PMA Foundation for a variety of workshops, conferences, research projects and educational programs. Of this amount approximately \$2.4 million has been used to support research and about \$5.2 million has gone into educational awards. The remaining \$438,000 has provided financial assistance for scientific meetings, along with a small portion for publications.

As in recent years, virtually all of the 1977 grants and awards were made within programs sponsored by the Foundation. These include two faculty level programs of salary and fringe benefit support, four fellowship programs—two postdoctoral, one at the advanced predoctoral level and one at the medical student level—plus a program of research starter grants for beginning investigators wishing to move into areas of independent research.

Through these programs the Foundation in 1977 assisted 56 individuals, all of whom were helped at a crucial time in their career development. The Foundation has, in its twelve years of existence, helped about 470 individuals through its research and educational support programs.

EDUCATION AND TRAINING PROGRAMS

To further its objectives in the field of education, the PMA Foundation sponsors three programs in clinical pharmacology, one in the combined field of pharmacology-morphology, one in pharmacology or toxicology and one in basic pharmacology. Each program is intended to achieve a specific goal, either for a particular rung on an individual's career ladder or in a particular discipline.

Also, a new program was offered in 1977, with the first awards in July, 1978. This is a program of support for new clinical pharmacology units or for units with a change of directorship.

CLINICAL PHARMACOLOGY

The three clinical pharmacology programs provide educational opportunities at the student, fellow and faculty levels. Through the Faculty Development Awards in Clinical Pharmacology program, the Foundation makes two-year awards to medical schools for salary and fringe benefits support of full-time junior faculty members. The level of support varies, in keeping with the salary structure of the applicant university. The Foundation has set a ceiling of \$30,000 on the amount of its participation in the total yearly salary and fringe benefit for any candidate.

With the new awards scheduled to begin July 1, 1978, a total of 44 individuals have been supported under this program since 1967. They apply for a two-year period, with a third year option.

Recipients of the four awards to begin July 1, 1978 are:



Robert M. Graham, M.B., B.S.



Fred E. Karch, M.D.



Juan J. L. Lertora, M.D., Ph.D.

• ROBERT M. GRAHAM, M.B., B.S., Instructor, Departments of Pharmacology and Internal Medicine, University of Texas, Southwestern Medical School. Dr. Graham is developing model systems *in vitro* in man and in animals for characterizing alpha-adrenergic regulatory receptors. Particular emphasis will be on the presynaptic a₂ receptor which down regulates norepinephrine release from sympathetic neuron terminals. Initially, he will attempt to demonstrate why the reflex tachycardia, renin release and sexual failure common to alpha-blocking agents is absent with prazosin. Subsequent studies including biochemical characterization of plasma membrane alpha receptors will be done to study their heterogeneity and possibly abnormalities thereof in disease states.

Dr. Graham also will have teaching responsibilities for up to four lectures in basic and clinical pharmacology. He will be responsible for the Hypertension-Clinical Pharmacology consulting service for two months each year.

• FRED E. KARCH, M.D., Assistant Professor, Department of Pharmacology and Toxicology, University of Rochester, School of Medicine and Dentistry. Dr. Karch is studying the problem of drug reactions occurring during the routine use of drugs in medical practice. Initially, the research will determine the frequency of serious drug reactions, the drugs responsible for these reactions, and the circumstances in which patients are at greatest risk for a drug reaction. Using this information Dr. Karch plans to design specific programs in a general medical practice. This work is aimed at improving the understanding of drug reactions and suggesting ways to improve both physician prescribing and patient use of medications.

• JUAN J.L. LERTORA, M.D., Ph.D., Assistant Professor, Departments of Medicine and Pharmacology, Northwestern University, Medical School. Dr. Lertora's research interests are in the field of cardiovascular clinical pharmacology. He has studied the actions of practolol, a beta-receptor blocking agent, on cardiac and peripheral vascular beta receptors in man, showing that the "cardioselectivity" of this agent was a dose-related phenomenon. He is participating in the studies on the actions of NAPA, an active metabolite of procainamide, in patients with ventricular arrhythmias. He will pursue the investigation of the hemodynamic actions of NAPA in animals and man. Further work in relation to the hemodynamic and peripheral vascular actions of beta-adrenergic blockings agents, antiarrhythmic and anti-hypertensive drugs may also be undertaken.

Dr. Lertora will have responsibility for teaching to medical students, house-staff and postdoctoral fellows in clinical pharmacology. In addition, he participates in the Medical Pharmacology Course for second year medical students and in the Applied Clinical Pharmacology Course for senior medical and graduate students.



Aubrey R. Morrison, M.B., B.S.

• AUBREY R. MORRISON, M.B., B.S., Assistant Professor, Departments of Medicine and Pharmacology, Washington University, School of Medicine. Dr. Morrison will study the role of endogenous prostaglandin biosynthesis in renal excretory and hormone function. The effects of unilateral ureter obstruction on prostaglandin biosynthesis and its effects on renal resistance will be studied. Modulation of the various pathways of endoperoxide metabolism by pharmacologic intervention and the effects of selective inhibitors on resistance and flow will be observed. In addition, the role of endogenous prostaglandins on renin release and the possible implications for pharmacologic intervention of prostaglandin biosynthesis in renovascular disease will be evaluated.

Those individuals whose awards began in July, 1977 are:

• STEVEN D. REICH, M.D., Assistant Professor, Department of Pharmacology, Northwestern University, The Medical School, at the time of the award. He terminated his award on December 31, 1977 to join a pharmaceutical firm.

• REYNOLD SPECTOR, M.D., Assistant Professor, Department of Medicine, Harvard Medical School.

• RAYMOND L. WOOSLEY, JR., M.D., Ph.D., Assistant Professor, Departments of Medicine and Pharmacology, Vanderbilt University, School of Medicine.

Those individuals who entered the second year of their award in July, 1977 are:

• WERNER A. BLEYER, M.D., Assistant Professor, Departments of Pediatrics and Medicine, University of Washington, School of Medicine.

• ROBERT C. BOERTH, M.D., Ph.D., Assistant Professor, Departments of Pediatrics and Pharmacology, Vanderbilt University, School of Medicine.

• CURT F. FREED, M.D., Assistant Professor, Departments of Medicine and Pharmacology, University of Colorado Medical Center.

Those individuals whose awards ended in June, 1977 are:

• NORBERTO T. DE GUZMAN, M.D., Assistant Professor, Department of Pharmacology, University of Miami, School of Medicine.

• PERRY V. HALUSHKA, M.D., Ph.D., Associate Professor, Department of Pharmacology, Medical University of South Carolina.



Fellowships for Careers in Clinical Pharmacology

The second program provides Fellowships for Careers in Clinical Pharmacology. This award offers clinicians an opportunity for intensive study in any of the basic sciences that fall within the general field of pharmacology. The program is open to physicians, dentists and veterinarians who are well into their clinical training and wish to pursue careers in clinical pharmacology. With the year or two of support offered by this fellowship program, depending on the particulars of the undertaking, the individual can pursue full time the basic pharmacologic sciences needed to complement his clinical skills.

The first awards under this program were made in 1973. Since that time, fourteen fellowships have been awarded.

Recipients of the four fellowships beginning July 1, 1978 are:



Robert L. Blum, M.D.

• ROBERT L. BLUM, M.D., Postdoctoral Fellow, Division of Clinical Pharmacology and the Department of Computer Science, Stanford University, School of Medicine. Dr. Blum's research efforts will be directed toward extending the capabilities and scope of the MYCIN Project, a computer-based system for providing therapeutic recommendations on the management of infectious diseases. The intended research will involve the development of fundamentally new capabilities for such expert consultation systems including the ability to calculate probabilities or response to therapy and adverse reactions, where possible, directly from a clinical data-bank. These probabilities will then be incorporated into equations used in decision theory to permit the system to calculate the comparative utilities of the various therapeutic options at any given stage of the case.



Brian R. Jones, M.B., B.S.



James R. Matson, M.D.



Douglas K. Reilly, M.D.

• BRIAN R. JONES, M.B., B.S., Post Doctoral Fellow in Departments of Medicine and Pharmacology, Cornell University Medical College. Dr. Jones' research efforts will be directed toward examining if individual differences in intracellular drug metabolism cause some of the individual variation in response seen in patients on immunosuppressive drugs. In this research, he will examine if variation in the intracellular enxyme activity levels for the activation or deactivation of purine analogs account for some of the variation in effects seen in patients receiving 6-mercaptopurine or azathioprine. He will measure levels of these enzymes in preparations made from lymphocytes from the patients to determine if there is a correlation between the patients' response and the level of these enzymes.

• JAMES R. MATSON, M.D., Fellow, Pediatric Clinical Pharmacology/Nephrology, Departments of Pediatrics and Pharmacology, University of Iowa, College of Medicine. The research to be done in chronically prepared fetal lambs will study the effect of fetal hypoxemia on fetal glomerula filtration rate, renal blood flow, intracortical distribution of flow, and the excretion of electrolytes and water. These will be studied simultaneously, prior to, during, and in recovery from fetal hypoxemia. Those fetal renal phenomena will be further studied under the influence of alpha and beta blockers, prostaglandin inhibitors, and angiotensin II inhibitors. The goal is to delineate fetal renal response to hypoxia and the impact of pharmacologic agents on that response.

• DOUGLAS K. REILLY, M.D., Fellow in Clinical Pharmacology, Department of Pharmacology and Toxicology, University of Rochester, School of Medicine and Dentistry. Dr. Reilly will engage in research dealing with the correlation between *in vitro* and *in vivo* measures of metabolism with emphasis on finding new applications of *in vitro* tests as possible predictors of clinical response, non-response or adverse reactions to drug therapy. A specific area of interest concerns genetically determined differences in catecholamine metabolism which may predispose some patients to be responders and others, non-responders. The initial work will focus on certain antiparkinsonian agents with the intention of also studying selected antihypertensives and antipsychotic medications.

Those individuals whose fellowships began July, 1977 are:

• THOMAS P. GREEN, M.D., Postdoctoral Fellow, Department of Pharmacology, and Medical Fellow, Department of Pediatrics, University of Minnesota.

• STANLEY J. SZEFLER, M.D., Fellow in Clinical Pharmacology, Department of Pharmacology, State University of New York, School of Medicine.

• WALTER M. WILLIAMS, M.D., Ph.D., Fellow in Clinical Pharmacology, Departments of Pharmacology and Medicine, University of Chicago, School of Medicine.

The individual who entered the second year of his award in July, 1977 is:

• WILLIAM P. ARNOLD, III, M.D., Fellow in Medicine and Anesthesiology, Departments of Medicine and Anesthesiology, University of Virginia, School of Medicine.



Geographical distribution of Foundation ''Fellowships for Careers in Clinical Pharmacology'' program, 1973-1978

• One

• More than One

Medical Student Research Fellowships in Pharmacology-Clinical Pharmacology

The third program is the Medical Student Research Fellowships in Pharmacology-Clinical Pharmacology. This program, which began in 1974, provides students an opportunity to spend one year full-time in an investigative project in pharmacology-clinical pharmacology. To meet the fill-time requirement, the student must interrupt his formal medical training, but he must also intend to continue his schooling at the conclusion of the fellowship. It is hoped that by having students become involved extensively in investigative projects at a point when career choices are still relatively flexible, that they will opt for research careers in clinical pharmacology. Twenty-two awards have been made since 1974.

The PMA Foundation has had a medical student support program since 1968. The earlier program offered three month traineeships to enable students to become acquainted with the techniques used in clinical pharmacology.

The six students who received fellowships which began July 1, 1977 are:

• STEVEN D. AVERBUCH, third year medical student at the University of Illinois. Mr. Averbuch is taking the fellowship at Northwestern University. Dr. Steven D. Reich was his principal advisor until the end of 1977. Upon Dr. Reich's departure from Northwestern University, Dr. Arthur Atkinson has agreed to serve as Mr. Averbuch's principal advisor. The objective of his investigation is to study the disposition and biotransformation of adriamycin by pharmacolgic methods. He intends to identify metabolites and study their relationship to the toxicity and efficacy of the drug. Then the pharmacokinetics of this drug will be altered by modifications in the methods of adminstration and in metabolic pathways such that active agents are in optimal concentration. Ultimately, the information gained from this research may suggest clinical protocols which will utilize adriamycin to its fullest and will achieve maximum benefit to cancer patients.

• DONALD C. HARPER, University of Texas (Dallas), was a senior medical student when applying for the award. His principal advisor is Dr. Parkhurst Shore, Professor, Department of Pharmacology. His research deals with the physiological effects of anti-psychotic drugs. Mr. Harper will study the synthesis and metabolism of brain dopamine, a neurotransmitter, in rats to find out what biochemical changes occur in the brain after long-term use of the drugs.

• R. ALAN HOCK, Johns Hopkins University, is into his thesis work toward his M.D./Ph.D. Principal advisor is Dr. Morley D. Hollenberg, Assistant Professor of Medicine and Pharmacology. It is the aim of his research to characterize the nature and evaluate the function of the cell-surface receptor for epidermal growth factor/urogastrone in the growth and development of fetal tissue.

• STEVEN C. SCHLITT, University of Oregon, was a third year medical student at the time of the award. His principal advisor is Dr. George D. Olsen, Assistant Professor, Department of Pharmacology. His research will investigate the respiratory effects of the natural female sex steroids and the synthetic female sex hormones such as those used in oral contraceptive preparations. Oxygen consumption, carbon dioxide production and ventilatory response to hypercapnia and hypoxia will be measured in female Labrador retrievers with chronic tracheostomy. These respiratory effects will be correlated with plasma concentrations of progesterone, and estradiol-17B as measured by radio-immunoassay. These hormones will be studied to determine if they are able to reverse methadone-induced respiratory depression.

• GEORGE M. SHAW, a first year medical student at the Ohio State University, will research and characterize the cerebrospinal fluid from patients with Parkinson's disease treated with L-dopa using the computer guided gas chromatograph-mass spectrometer. Dr. Joseph R. Bianchine, Chairman and Professor, Department of Pharmacology, and Professor, Department of Medicine, will supervise the project.

Previous studies examining the relationship between cerebrospinal fluid (CSF) homovanillic acid (HVA) levels and clinical status of Parkinsonian patients are conflicting. Likewise, the effect of levodopa therapy on CSF-HVA concentration is unresolved. Part of this confusion is undoubtedly caused by the low concentrations of HVA in CSF and the inadequate sensitivity of earlier analytic technology.

This investigation has two main objectives: First, to establish more clearly the relationship between CSF-HVA concentration and clinical status of the Parkinsonian patient. Secondly, to search for other CSF parameters which may reflect neurotransmitter action important in the neuropharmacology of Parkinsonism. The first of these two goals is far more likely to be solved during the fellowship.

• DAVID K. WAYS, enrolled in a M.D./Ph.D. program as a second year medical student at the University of North Carolina. His principal advisor is Dr. David A. Ontjes, Chief, Division of Endocrinology and Professor of Medicine and Pharmacology. His research involves an evaluation of structure-activity relationships of ACTH analogues using an *in vitro* normal adrenal cell suspension as a testing system. Agonistic or antagonistic activity of an analogue would be defined using steroidogenesis, cAMP accumulation, and binding to cell membrane receptors as parameters of ACTH activity. Various adrenal tumor cell lines could be evaluated with ACTH analogues to delineate any differences between these and normal cells with respect to their interaction with ACTH. To synthesize and characterize ACTH analogues containing an alkylating group for their ability to cause irreversible activation or inhibition of steroidogenesis using an *in vitro* normal adrenal cell suspension.



Geographical distribution of Foundation ''Medical Student Research Fellowships in Pharmacology-Clinical Pharmacology'' program, 1974-1977

· More than One

[•] One

BASIC PHARMACOLOGY

Faculty Development Awards in Basic Pharmacology

The purpose of these Faculty Development Awards is to strengthen basic pharmacology by helping maintain existing academic capability and, ultimately, to expand it by enlarging the faculty base. To accomplish these goals, support is provided to full-time junior faculty members committed to careers in pharmacology who give promise of outstanding accomplishments.

The first awards, which are for a two-year period, were made in 1973. They provide salary and fringe benefits at levels which are expected to be consistent within the applicant university. The total number of awards made to date is fifteen.

Those who received awards beginning July 1, 1978 are:



Yvonne C. Clement-Cormier, Ph.D.



Linda F. Quenzer, Ph.D.

• YVONNE C. CLEMENT-CORMIER, Ph.D., Assistant Professor, Department of Pharmacology and Department of Neurobiology, University of Texas, Medical School.

Dr. Clement-Cormier's research is directed towards a better understanding of the biochemical mechanisms underlying receptor responses in the central nervous system. The objective of her present project is to clarify the relationship between the dopamine receptor and the closely associated dopamine-sensitive adenylate cyclase. Biochemical and pharmacological techniques are being used to characterize the receptor and to study the mechanisms by which neuroleptic drugs effect receptor response. Other studies will attempt to biochemically and pharmacologically characterize dopamine receptors outside the CNS for comparative purposes. The results from this work will provide a better understanding of the dopamine system in the brain and contribute to the design of better and more specific drugs.

• LINDA F. QUENZER, Ph.D., Assistant Professor, Department of Pharmacology, University of Connecticut Health Center. Dr. Quenzer's research is aimed at determining the behavioral and biochemical changes in the brain after chronic activation of the dopaminergic nigro-striatal pathway by the injection of cholera enterotoxin. The behaviors of interest are locomotor activity, circling behavior and compulsive stereotypy. Biochemically the plan is to study the effects of long term nigro-striatal activation on (1) the cAMP generating system including synthesis by the DA-sensitive adenylate cyclase and degradation by cAMP phosphodiesterase; (2) the rate of neurotransmitter synthesis by tyrosine hydroxylase, and (3) the changes in cholinergic neuronal activity as reflected by altered choline uptake. In addition to studying the time course of the toxin-induced changes, the effect of DA-receptor blockade by various neuroleptic drugs on the biochemical and behavioral measures will be studied.

Those who began their award in July, 1977 are:

• R. ADRON HARRIS, Ph.D., Assistant Professor, Department of Pharmacology, University of Missouri, School of Medicine.

• MICHAEL E. MAGUIRE, Ph.D., Assistant Professor, Department of Pharmacology, Case Western Reserve University, School of Medicine.

Those who entered the second year of their award in July, 1977 are:

• SUE PIPER DUCKLES, Ph.D., Assistant Professor, Department of Pharmacology, University of California, School of Medicine.

• GARRETT J. GROSS, Ph.D., Associate Professor, Department of Pharmacology, Medical College of Wisconsin.

• DANIEL A. KOECHEL, Ph.D., Assistant Professor, Department of Pharmacology and Therapeutics, Medical College of Ohio.

Those who ended their award in June, 1977 are:

• CARL L. JOHNSON, Ph.D., Associate Professor, Department of Pharmacology and Therapeutics, University of Cincinnati Medical Center.

• CLAIRE M. LATHERS, Ph.D., Assistant Professor, Department of Pharmacology, Medical College of Pennsylvania.



Geographical distribution of Foundation "Faculty Development Awards in Pharmacology," 1973-1978

• One

More than One

Fellowships for Advanced Predoctoral Training in Pharmacology or Toxicology

The program is designed to assist those candidates who have one or two years remaining in their predoctoral training, during the time they are engaged in their thesis research.

The fellowship program provides a stipend of \$3,900 a year, payment of tuition and \$500 for incidentals directly associated with the thesis research preparation. The program has been funded to provide seven fellowships each year. However, three extra fellowships were authorized in 1978, the initial year of awards.

Those who received fellowships which begin between January—August, 1978 are:

• GALE L. CRAVISO, Department of Pharmacology, New York University. Ms. Craviso's thesis advisor is Jose M. Musacchio, M.D., Professor of Pharmacology. The thesis deals with the study of the enzymes in the guinea pig brain which degrade both leucine and methionine enkephalin. Their distribution in different subcellular fractions will be investigated. In order to determine which peptidases are physiologically significant in terminating enkephalin activity, the regional distribution of the brain peptidases and their associations with regions rich in opiate receptors and/or enkephalins will be explored. Any enzyme which is suspected of being physiologically important will be fully characterized and purified. Specific enzyme inhibitors will be sought since they may provide a new class of agents.

• PAUL E. DRIEDGER, Department of Pharmacology, Harvard Medical School. Mr. Driedger's thesis advisor is Dr. Peter M. Blumberg, Assistant Professor. The thesis deals with the further elucidation of the phenotypic effects of phorbol myristate acetate (PMA) on chicken embryo fibroblasts (CEF) and comparison of these effects with changes seen in CEF after oncogenic transformation. Experiments are in progress on (RSV-sensitive) actin cable arrangements, serum requirements, and ornithine decarboxylase activity in PMA-treated CEF. The thesis will also involve identification of the CEF receptor(s) for the phorbol esters. This work will involve the acquisition or synthesis and radioactive labeling of a suitably potent phorbol derivative. Then CEF will be treated with the labeled compound either as whole cells or as cell extracts or sonicates. Specific binding will be that binding which is blocked by addition of excess unlabeled ligand. A variety of techniques common to the study of pharmacological receptors may be employed.

• CLIFFORD C. HALL, Department of Pharmacology, University of Wisconsin. Mr. Hall's thesis advisor is Dr. Arnold F. Ruoho, Assistant Professor. The thesis deals with the maping of the cardiotonic steroid binding site of sodium-potassium activated adenosine-triphosphatase (Na-KATPase), the putative cardiotonic steroid receptor, using photolabels.

Various photolabels are being developed in order to obtain structural information. The structural probes will be used to covalently derivatize the subunits of the enzyme with a radioactive species. By developing compounds of suitable binding specificity, such an approach should reveal those peptides which are immediately adjacent to the binding site. It will also be possible to characterize the labelled portions of the peptides. This constitutes an important approach for obtaining structural information which is presently difficult to obtain for this integral membrane protein by other methods.

• DENNIS M. HIGGINS, Department of Pharmacology, University of Connecticut Health Center. Mr. Higgins' thesis advisor is Dr. Achilles Pappano, Associate Professor. The thesis deals with the investigation of the normal development of the adrenergic innervation of the chick embryo right ventricle by measuring: the density of histochemically demonstrable adrenergic nerves; the activity of tyrosine hydroxylase; and the onset of neuroeffector transmission. Also, two possible neurotrophic effects will be studied; the influence which pregaglionic cholinergic neurons may have on the development of postgaglionic adrenergic neurons, and the influence which these postgaglionic neurons may exert on the development of the ventricular muscle.

• VIVIAN Y. Ho HOOK, Department of Pharmacology, University of California. Ms. Hook's thesis advisor is Dr. Horace H. Loh, Professor. Numerous studies strongly indicate that CA++ and cAMP are critical factors involved in morphine tolerance and dependence development. Because adenylate cyclase and CA++ have been found to affect one another's activities, it is likely that there is a close interaction between these two systems for regulation of various cellular activities which may be involved in morphine action. To elucidate the mechanism of Ca++ and cAMP involvement in morphine action, the thesis will study brain adenylate cyclase. An understanding of the control mechanisms involved in adjusting adenylate cyclase activity will help determine how morphine affects this enzyme, and thus lead to further knowledge about morphine action.

• STANLEY R. JOLLY, Department of Pharmacology, Medical College of Wisconsin. Mr. Jolly's thesis advisor is Dr. Harold F. Hardman, Professor and Chairman. Mr. Jolly will examine the possible beneficial effects of increased oxygen delivery through decreased hemoglobin-oxygen affinity in the ischemic heart and brain. This study will determine whether or not it is feasible to treat conditions of ischemic hypoxia by manipulating the oxy-hemoglobin disassociation curve with pharmacological agents. A major effort will also be made to describe the determinants of oxygen transport and oxygen extraction under conditions of ischemic hypoxia. Orthoiodo sodium benzoate (OISB), a prototype agents, decreases the affinity of hemoglobin for oxygen. Data indicate that the isolated dog heart can utilize this extra available oxygen. An animal model will also be employed to evaluate the functional integrity of the brain subjected to graded ischemic hypoxia. Electrophysiological recordings of cortical and subcortical structures will be made during ischemic lypoxia and OISB will be evaluated for its ability to reverse or prevents signs of ischemic hypoxia.

• MICHAEL R. PALMER, Department of Pharmacology, University of Colorado. Mr. Palmer's thesis advisor is Dr. Barry J. Hoffer, Professor of Pharmacology. The thesis deals with the role of enkephalins as neurotransmitters or neuromodulators in the rat somatosensory cerebral cortex and in other brain areas which may be enkephalinergic. The technique of microiontophoresis will be used to compare the effects of enkephalins on firing frequencies of functionally different neuronal types, to correlate the structure-activity electrophysiological relationships of various enkephalin anlogs within their stimulation of the opiate receptors, to determine the interaction of enkephalins with other transmitters or neuromodulators, and finally to

describe changes in the above parameters which occur during the development of tolerance and dependence to opiate narcotics. Specificity of opiate effects will be defined by naloxone reversibility.

• TODD M. SAVARESE, Section of Biochemical Pharmacology, Brown University. Mr. Savarese's thesis advisor is Dr. Robert E. Parks, Jr., Professor of Medical Science. The thesis will investigate the biochemical basis for the potentiation of the antineoplastic action of selected adenosine analogs in the presence of ADA/AMP deaminane inhibitors. The results obtained could be of value in the design of combination chemotherapy regimens for the treatment of cancer as well as in elucidating the mechanisms of immunosuppression in adenosine deaminase-associated severe combined immunodeficiency.

• WILLIAM L. STRAUSS, Department of Pharmacology and Therapeutics, State University of New York (Buffalo). Mr. Strauss' thesis advisor is Dr. J. Craig Venter, Assistant Professor. The primary objectives of the proposed research are to isolate, purify, and characterize the *B*-adrenergic receptor from a homogenous line of cells in tissue culture. A protocol of gel exclusion, affinity, and ion exchange chromotography will be employed in the purification procedure. The physical parameters as well as the drug-binding kinetics of the purified receptor will be examined. This study will provide information basic to an understanding of the molecular basis of adrenergic effects.

• LARRY A. WALKER, Department of Pharmacology, Vanderbilt University. Mr. Walker's thesis advisor is Dr. Jurgen C. Frolich, Associate Professor of Medicine and Pharmacology. The thesis deals with the role of prostaglandins (PGs) in renal water excretion. The plan is to investigate the relationship between antidiuretic hormone (ADA) and renal PGs in rats with hereditary hypothalamic diabetes insipidus. Recent studies in the department indicate a lower renal PGE₂ synthesis in these animals than in normal Long-Evans rats, and treatment with exogenous ADH increases this PG synthesis to the normal range. Studies are planned to determine the mechanism of this stimulation; to examine the effects of inhibition of PG synthesis on water excertion; and to investigate in dogs the possible role of the PGs in the redistribution of renal cortical blood flow by ADH. The study will also be interested in the role of PGs in the diabetes insipidus encountered as a side effect of lithium therapy.



Geographical distribution of Foundation awards under the "Fellowships for Advanced Predoctoral Training in Pharmacology/Toxicology, 1978

• One

More than One

The aim of this program of fellowship awards is to advance understanding of drug action through the 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. The level of support varies and is aimed at keeping within the existing stipends for similarly trained individuals within the applicant university. Since 1968, when the first fellowships were offered, 37 awards have been made.

The program requires that a candidate be qualified primarily either in a morpholgic speciality or in pharmacology. However, training to be achieved under the fellowship in the complementary discipline need not be formal. The candidate's program should result in a familiarity with a new disciplinary approach by using his primary discipline as a medium for acquiring the second.

The recipients of fellowships which began in July, 1977 are:

Douglas E. Chandler, Ph.D.



Carole L. Jelsema, Ph.D.

 DOUGLAS E. CHANDLER, Ph.D., Postdoctoral Fellow, Department of Physiology, University of California (San Francisco), School of Medicine. Dr. Chandler will collaborate with Dr. Heuser in using a quick freezing technique developed by Dr. Heuser to halt exocytosis-the extremely rapid process in which the membrane-bound, histamine-containing granules within the mast cell, fuse with the plasma membrane and release their contents into the medium outside the cell. The new freezing technique is capable of stopping cellular processes within several milliseconds and of preserving cell ultrastructure without the use of chemical fixatives. This will allow Drs. Chandler and Heuser to study the histamine secretion from mast cells which are immobilized but still alive. They anticipate that new facets of the exocytosis process visualized by these techniques will have widespread significance since this release process is thought to be used by secretory tissues that store their products in membrane-bound granules.

• CAROLE L. JELSEMA, Ph.D., Postdoctoral Staff Scientist, Section of Cytology, Yale University, School of Medicine. Dr. Jesema's project deals with membrane biogenesis in both rapidly-dividing malignant and normal cells and the effect of cancer chemotherapeutic agents on the specific metabolic processes concerned with the synthesis and assembly of membrane components. Aspects of training necessary to conduct this work involves phospholipid biochemistry, enzyme biochemistry, enzyme cytochemistry, electron microscopy and elucidation of the effects of tumor chemotherapeutic agents on these processes.



Michael P Marietta, Ph.D.



Mark F Nelson, Ph.D.

• MICHAEL P. MARIETTA, Ph.D., Postdoctoral Fellow, Department of Pharmacology, Pennsylvania State University, Milton S. Hershey Medical Center. Dr. Marietta will be trained in quantitative cytochemistry and its application. Dr. Marietta will use new methods to localize cytochrome P-450 dependent microsomal enzyme system in the rat brain and to examine hepatic drug metabolizing enzymes of the simian fetus.

• MARK F. NELSON, Ph.D., Postdoctoral Fellow, Department of Pharmacology, The Johns Hopkins University, School of Medicine. Dr. Nelson's research will cover three sections: (1) Synaptogenesis: Tissues will be collected from fetuses and offspring of treated and controlled females on gestational days 18, 19, 20 and postnatal days 0, 5, 15, and 30. Two methods for observing synaptic profiles will be used, both of which began with tissue preparation by glutaraldehyde fixation and post-fixing which allows for easy counting of synapses and the determination of pre- and post-synaptic projections. (2) Neuron-Target Cell Interaction: The second stage of the proposed research concerns the possible effects of altering synaptic development on target tissue differentiation. (3) Neurochemical Synaptic Markers: Changes in the differentiation of target cell groups could result from alterations in synapse formation or from a direct effect of the drugs on the tissues. In order to separate these causes, the third stage of the planned research will consider changes in the normal development of pre- and post-synaptic neurochemical markers in the straitum.



Geographical distribution of Foundation "Fellowship Awards in Pharmacology-Morphology,"

• More than One

Those individuals who entered the second year of their fellowships in July, 1977 are:

• CHERYL F. DREYFUS, Ph.D., Staff Associate, Department of Anatomy, Columbia University, College of Physicians and Surgeons.

• SUSAN B. STEARNS, Ph.D., Postdoctoral Fellow, Department of Pharmacology, State University of New York, Upstate Medical Center.

Those individuals whose fellowships concluded in June, 1977 are:

• CLARA F. ASNES, Ph.D., Senior Fellow, Department of Zoology, University of Washington, Friday Harbor Laboratories.

• RAYMOND J. DINGLEDINE, Ph.D., Postdoctoral Fellow, Addiction Research Foundation, Palo Alto, California. Dr. Dingledine conducted his research at the MRC Neurochemical Pharmacology Unit, University of Cambridge.

• JOHN W. MILLS, Ph.D., Assistant in Biology, Department of Renal Biophysics, Massachusetts General Hospital.

• R. WILLIAM SOLLER, Ph.D., Instructor in Pharmacology, Department of Pharmacology, University of Pennsylvania, School of Medicine.

RESEARCH GRANTS

An important aspect of PMA Foundation effort has been the support of fundamental research in drug toxicology. Between 1966 and the end of 1971, 26 research grants of relatively large amounts for two to five years were awarded, principally to established investigators to either extend existing research or to provide "seed" monies to follow a promising lead. In 1971 a change in emphasis within the Foundation's programs shifted the bulk of the funds into educational support programs, and, therefore, into less research. The foundation does, however, continue to accept requests for support and suggestions for pertinent research projects, since it is important that the potential for helping that particularly promising effort within the Foundation be maintained.



Geographical distribution of Foundation general research grants, 1966-1978

- One
- More than One
- Outside U.S.

As part of the change of emphasis in 1971 which sought to direct monies more toward the development of the individual, a program of Research Starter Grants was initiated. These grants are intended to provide financial support for beginning investigators. The program currently offers \$6,000 a year for two years, with the second year contingent upon a continuing need for the funds. The research areas of interest within this program are in pharmacology, clinical pharmacology and drug toxicology. The program allows for approximately 20 research grants each year. The first awards were made in 1972. A total of 168 research starter grants have been made, including the 26 awards beginning January 1, 1978.

DONALD C. BRATER, M.D. RICHARD MCGEE, JR., Ph.D. University of Texas (Dallas) Georgetown University Southwestern Medical School School of Medicine & Dentistry DANIEL E. FURST, M.D. CHANDRA K. MITTAL, Ph.D. University of California (Los Angeles) University of Virginia School of Medicine School of Medicine GERALD GIANUTSOS, Ph.D. MARJORIE MYERS-ROBFOGEL, Ph.D. St. John's University University of Rochester College of Pharmacy & Allied Health Medical School Professions SIDNEY D. NELSON, Ph.D. MARGARET E. GNEGY, Ph.D. University of Washington School of Pharmacy University of Michigan Medical School DONALD E. NERLAND, Ph.D. EDWARD HUA-SENG GOH, Ph.D. University of Louisville Indiana University School of Medicine School of Medicine RUSSELL E. SAVAGE, JR., Ph.D. RONALD HOLZ, M.D., Ph.D. Ohio University University of Michigan College of Osteopathic Medicine Medical School JAMES E. STRONG, Ph.D. ANDREA HUNTER, Ph.D. Baylor College of Medicine East Carolina University DAVID A. TAYLOR, Ph.D. School of Medicine University of Colorado SAMUEL A. JACOBS, M.D. Medical School University of Pittsburgh WILLIAM VEATCH, Ph.D. Medical School Harvard Medical School KENNETH M. JOHNSON, Ph.D. REGIS R. VOLLMER, Ph.D. University of Texas Medical Branch University of Pittsburgh (Galveston) School of Pharmacy PAUL J. KOSTYNIAK, Ph.D. GEORGE L. WILCOX, Ph.D. State University of New York (Buffalo) University of Minnesota School of Medicine Medical School LAN K. WONG, Ph.D. GEORGE L. KRAMER, Ph.D. Vanderbilt University Ohio State University School of Medicine College of Medicine LYMAN T. LAIS, Ph.D. GEORGE F. WOOTEN, JR., M.D. Oregon State University Washington University Medical School School of Pharmacy BILLY R. MARTIN, Ph.D. Medical College of Virginia

The recipients of the grants beginning January, 1978 are:

Review of the need of the 24 research starter grantees whose awards began January 1, 1977 for a second year of the awards resulted in 16 of them having their awards continued. These are:

REBECCA J. ANDERSON, Ph.D. The George Washington University School of Medicine ASA CALVIN BLACK, JR., M.D. University of Iowa College of Medicine ALAN S. BLOOM, Ph.D. The Medical College of Wisconsin DAVID A. BRASE, Ph.D. Eastern Virginia Medical School TIEH H. CHIU, Ph.D. Medical College of Ohio YVONNE C. CLEMENT-CORMIER, Ph.D. University of Texas (Houston) Medical School JOHN W. DIETRICH, Ph.D. University of Illinois Peoria School of Medicine SALVATORE J. ENNA, Ph.D. University of Texas (Houston) Medical School R. ADRON HARRIS, Ph.D. University of Missouri

University of California (San Francisco)

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School of Medicine

CLAIRE M. LATHERS, Ph.D. The Medical College of Pennsylvania MUSTAFA F. LOKHANDWALA, Ph.D. University of Houston College of Pharmacy JOSEF F. NOVAK, Ph.D. Allegheny General Hospital DANIEL G. PACE, Ph.D. Case Western Reserve University School of Medicine JAMES R. POWELL, Ph.D. Emory University School of Medicine MARK JAE REASOR, Ph.D. West Virginia University

Medical Center

Geographical distribution of Foundation awards under the "Research Starter Grants" program, 1972-1978

• One

More than One

OTHER GRANT SUPPORT

A grant of \$3,000 made to William Y. W. Au, M.D., Professor of Pharmacology and Medicine, University of Arkansas for Medical Sciences, to help implement certain programs and services within this newly developed clinical pharmacology unit concluded this year.

FOUNDATION FINANCES

HE TOTAL INCOME OF THE FOUNDATION IN 1977 was \$999,155. Of this amount, \$920,375 came from contributions. The balance of \$78,780 came from investments and refunds of unexpended balances from grants.

Contributions were received from approximately four out of every five PMA Member Firms. Contributions were also received during 1977 from individuals and other groups in the health field.

Grants, Foundation-sponsored programs and other expenses for 1977 amounted to \$882,393. Of this total, \$704,054 represented expenditures for grants and Foundation-sponsored programs. There was a fund balance of \$1,526,170 as of December 31, 1977. This figure, however, does not reflect the tentatively authorized, undisbursed funds 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, 1977, the contingency liability for 1978 was approximately \$687,500.

Financial Report. The Foundation's financial position as of December 31, 1977 has been audited by the accounting firm of Ernst & Ernst. Copies of this statement will be supplied upon request.

Financial statements have been issued to contributors quarterly during 1977. These reports are prepared by Washington, D.C. accounting firm of Buchanan & Company.



PMA Foundation Contribution Income 1965–1977 (Thousands)

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State of Income and Expenditures For the Year Ended December 31, 1977

Income

Contributions—Note a Income from Investments Miscellaneous Income	\$	920,375 74,872 3,908
TOTAL INCOME	\$	999,155
Expenditures		
Grants—Note b Clinical Pharmacology Faculty Awards	\$	202,785
Clinical Pharmacology Fellowships		39,000
Basic Pharmacology Faculty Awards		127,569
Medical Student Research Fellowships		30,000
Pharmacology-Morphology Fellowships		70,558
Research Starter Grants		231,142
University of Arkansas		3,000
	\$	704,054
Administrative and Special Meeting Expenses	\$	170,440
Loss on Sale of Stock		7,899
TOTAL EXPENDITURES	\$	882,393
Excess of income over expenditures	\$	116,762
Fund balance at January 1, 1977	\$1.	409,408
Fund balance at December 31, 1977	\$1,	526,170

Note a—The Foundation received contributions of \$120,000 prior to December 31, 1977 which the Foundation considered applicable to 1978 and, therefore, are not recorded as income in 1977.

Note b—In addition to the amounts shown, the Foundation has committed itself, subject to annual review, to make certain grants. At December 31, 1977 the amounts still to be disbursed with respect to these grants during 1978 amounted to approximately \$687,500.

PURPOSE

he 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 the 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 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 be better served by channeling the Foundation's available resources into other areas.

(3) Funds for travel.

(4) Funds to cover entertainment costs.

In 1971, the Board of Directors authorized a major shift in program emphasis. While Foundation support of research continues, such support is to be primarily available in a redirected fashion such as the Research Starter Grants program discussed on page 20.

In line with this change of emphasis, the Foundation is expanding support within its current educational programs as outlined in the Education and Training Programs Section on page 4. While meetings have never received a large portion of the support dollar, only in very exceptional circumstances will meetings receive support in the future.

ORGANIZATION AND ADMINISTRATION

he PMA Foundation operates through its officers and four advisory committees. The Chairman of the Board is Daniel C. Searle, Chairman of the Board, G. D. Searle & Co., C. Joseph Stetler is President, Thomas E. Hanrahan is Executive Director and I. C. Winter, M.D., Ph.D. serves as staff consultant. In June, 1977 Mr. Searle was reelected Chairman of the Board. W. Clarke Wescoe, M.D., Chairman of the Board and Chief Executive Officer, Sterling Drug Inc. was reelected Vice Chairman and Donald van Roden, President, Smith Kline & French Laboratories, was reelected Secretary, Treasurer.

In reaching decisions on the most worthwhile activities for support, the Board of Directors has had the advice of extremely knowledgeable individuals serving on four advisory committees.



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¹New Member April, 1977 ²Term Expired April, 1977

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⁶New Member December, 1977 ⁷New Member July, 1977

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APPLICATIONS

he Foundation accepts requests for support and suggestions for pertinent research projects from qualified institutions and individuals. However, in 1971 the Foundation underwent a major shift in program direction, now emphasizing education and training support.

To expedite the handling of requests for research support, it is suggested that a brief one or two page letter be directed to the Foundation, outlining the intended project and an estimate of the funds involved. After review of this more informal request by members of the Scientific Advisory Foundation guidelines, a decision can be made as to whether a formal proposal is warranted.

Letters should be addressed to:

Thomas E. Hanrahan Executive Director Pharmaceutical Manufacturers Association Foundation, Inc. 1155 15th Street, N.W. Washington, D.C. 20005

PHARMACEUTICAL MANUFACTURERS ASSOCIATION FOUNDATION, INC. 1155 15th Street, N.W. Washington, D.C. 20005