CELEBRATING 25 YEARS

25 Years of Dedication to
Careers Biomedical Research

1992 Annual Report

Pharmaceutical Manufacturers Association Foundation

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Careers Biomedical Research

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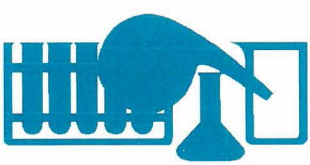


Pharmaceutical Manufacturers Association Foundation

Dedicated To

Irwin Clinton (I.C.) Winter

1910 - 1991

Long-time friend and mentor of the PMA Foundation, I. C. Winter, died on July 15, 1991—almost 83 years to the day. I. C. played a major role in the development of the PMA Foundation, giving it scientific credibility and direction. His counsel, experience and insights were invaluable to the PMA Foundation over the years. With the passing of this good friend, the Foundation has suffered an enormous loss.

Irwin Clinton Winter was born in Clinton, Oklahoma, on July 17, 1910. He received a B.S. degree from Allegheny College in Pennsylvania (1931), M.S. and Ph.D. degrees from Northwestern University (1933 and 1934) and an M.D. degree from the University of Tennessee (1941). He served on active duty in the military 1942-46, after which he joined Searle.

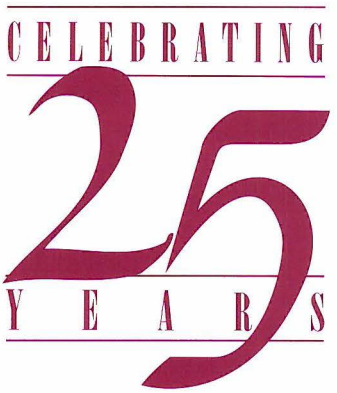
Starting as Director of Clinical Research at Searle in 1946, he became Medical Director and later Vice President for Medical Affairs in 1962. In 1966, during the launching of the PMA Foundation, I. C. became a member of the Scientific Advisory Committee (SAC). He served the Foundation's SAC until 1975, the last five years as Chairman.

In 1975, I. C. retired from Searle but continued his activities with the Foundation, serving as Scientific Consultant until 1988.

For his many contributions to the PMA Foundation over twenty-five years, the PMA Foundation would like to dedicate the 1992 Annual Report to Irwin Clinton (I. C.) Winter, M.D., Ph.D.

A memorial fund has been established by the American Society of Pharmacology and Experimental Therapeutics in Dr. Winter's name for his dedicated service:

I. C. Winter Memorial Fund
c/o Ms. Kay Croker
Executive Director
American Society for Pharmacology
and Experimental Therapeutics
9650 Rockville Pike
Bethesda, Maryland 20814-3995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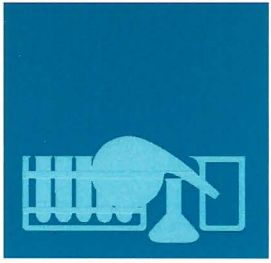

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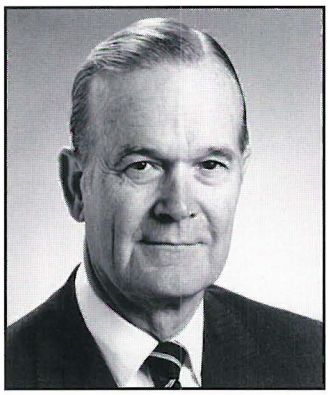
Report of the Chairman



Charles A. Sanders, M.D.
Chairman, PMA Foundation

This is my first opportunity to report to the constituencies of the Pharmaceutical Manufacturers Association Foundation as Chairman of the PMA Foundation Board of Directors. It is a source of pride to be able to do so through this 1992 Annual Report—a period during which we are commemorating the twenty-fifth year of the Foundation.

Since I just assumed the Chairmanship in May, 1992, it is only appropriate to recognize the remarkable leadership of my predecessor, Sheldon G. Gilgore, M.D., during the previous two years.

The smooth succession from one Board Chairman to another can occur only if the administrative and managerial base can accommodate such change. Fortunately, the Foundation's President, Treasurer, and Board of Directors are all dedicated, capable professionals and the Foundation's activities continue unabated. I am proud to have them as part of my administration's "team" and I have asked President Maurice Q. Bectel, D.Sc., and Secretary-Treasurer Joseph A. Mollica, Ph.D., to present annual reports on administrative and financial affairs, respectively, in the 1992 Annual Report.

But it is both my obligation and my pleasure to present, as its Chairman, the Annual Report of the PMA Foundation's Board of Directors.

Let me first express appreciation to my predecessor as Chairman, Sheldon G. Gilgore, M.D. For two years, Dr. Gilgore, Chairman and Chief Executive Officer of Searle, devoted his time and talents to the Foundation's activities. Through two press conferences, held to publicize the need for greater support for biomedical research scientists, Dr. Gilgore both served to advance the cause for careers in biomedical research and simultaneously enhanced visibility of the Foundation. I am pleased to note that Dr. Gilgore continues to serve on the Board; his insights and contributions will continue to advance the Foundation and its programs.

Also continuing on the Board is newly-elected Vice Chairman Theodore Cooper, M.D., Ph.D., Chairman and Chief Executive Officer of The Upjohn Company. Secretary-Treasurer

Joseph A. Mollica, Ph.D., President and Chief Executive Officer of DuPont Merck Pharmaceutical Company, has served in that capacity since 1989, so his experience and familiarity with the Foundation's finances are invaluable.

New Board members, all elected at the May Board meeting, are:

- Robert C. Black, President of ICI Pharmaceuticals Group, ICI Americas Inc.
- G. Gilbert Cloyd, Vice President, Pharmaceuticals, Procter & Gamble Company
- Jan Leschly, Chairman of SmithKline Beecham Pharmaceuticals
- Philip R. Tracy, President and Chief Executive Officer of Burroughs Wellcome Co.

But the election of new Board members means the end of terms for others. Especially missed will be Irwin Lerner, President and Chief Executive Officer of Hoffmann-La Roche Inc. Mr. Lerner has served the Foundation with great distinction, having served on the Board for 11 years, including four as Chairman of the Board. Of particular note is the fact that he was Chairman during the selection of Maurice Q. Bectel as Foundation President and his wisdom and efforts facilitated the transition to the new administration.

Also concluding their terms on the Foundation Board were:

- Paul E. Freiman, Chairman and Chief Executive Officer of Syntex Corporation
- Hubert E. Huckel, M.D., Chairman of the Board, Hoechst-Roussel Pharmaceuticals Inc.
- Klaus Heinz Risse, Ph.D., Vice Chairman of Miles, Inc.

As was mentioned previously, this is the silver anniversary—the twenty-fifth year —of the Foundation. We are all proud of the Foundation's accomplishments, most appropriately exemplified by the 1992 *Scholars* publication listing the 88 PMAF Award Recipients in 1992. While the Award Recipients represent the focus of the Foundation's careers in biomedical research effort, the real work of the Foundation is done by the Scientific Advisory Committee and its Program Advisory Committees.

Indeed, the members of the various committees are the unsung heroes of the Foundation's programs. I would like, therefore, to express our appreciation to the many industry and academic scientists who have contributed so generously of their expertise and insights into development of the awards criteria, review of applications, and selection of recipients over the twenty five years of the Foundation's activities. Without their contributions, the history of the Foundation would have been much different. If you served the Foundation in this capacity, please know that you have our gratitude for a job very well done.

Acknowledgement must also be made of the more than 100 research-intensive member companies, associate members, and research affiliates of the Pharmaceutical Manufacturers Association whose financial contributions enable the Foundation to support the development of those bright young scientists who are pursuing careers in biomedical research.

Charles A. Sanders, M.D.
Chairman, PMA Foundation
Chairman and Chief Executive Officer
Glaxo Inc.

Report of the President

Maurice Q. Bectel
President

The pace of the PMA Foundation continues to set records and we continue to celebrate twenty-five years of achievement.

Again in 1992, for the 1991 review cycle, 88 bright young scientists were named recipients of PMA Foundation grants to assist them in initiating their biomedical science careers. Once again, the grant awards totalled over two million dollars, the third year in which that level of support for careers in biomedical research has been achieved. In addition to the Annual Report, a detailed listing of award recipients, stipend amounts, and research project descriptions is provided in the 1992 issue of *Scholars*, the Foundation's annual publication which publicizes the awards. Copies of *Scholars* and other publications, including grant brochures and application forms, are available through the Foundation office.

The 1992 *Scholars* also commemorates the twenty-fifth anniversary of the Foundation, a milestone of which all of us associated with the Foundation are justifiably proud. While 1992 saw well over $2 million in awards being granted, the twenty-five year aggregate totals show that over 1,500 deserving award recipients have received nearly $32 million through Foundation grants. Such a record places the PMA Foundation high among all philanthropic foundations.

We're proud of the Foundation's past achievements and look forward to the future with confidence and optimism, bringing reality to the axiom of "what is past is prologue." A recent study, commissioned by the Foundation, predicts that pharmaceuticals will provide more than half of all future medical advances, including both control and cure of a variety of disease states. We believe the Foundation is positioned to contribute substantially to those efforts, assisting academic institutions, the pharmaceutical industry, and society in general by advancing the careers of health researchers.

The reason for such confidence is that the Foundation continues to grow. The continuing upward growth of award applications, award recipient numbers, and grant totals show that the Foundation is on the right track and the future looks bright. That's not to say that more funds contributed to the Foundation could not be put to good use—merely that the trends give us assurance that the Foundation will be able to fulfill its continuing commitment to furthering careers in biomedical research. Sometimes that takes different directions. For example, this year the Foundation provided the American Society for Pharmacology and Experimental Therapeutics (ASPET) with a grant with which the Society published a handsome brochure promoting careers in pharmacology.

But the Foundation doesn't rest on its laurels or resist change. Management is always measuring today's resources with tomorrow's anticipated needs. In that vein, the grant programs are under continuous review, to assure the Foundation that limited dollars are wisely distributed. As a result of such review, the Foundation is terminating the Faculty Award in Toxicologic-Pathology. The Foundation began that award in 1983 at a time when there were few such departments and scientists. Subsequently, the numbers of departments and scientists have been increased, many with the assistance of Foundation grants and funds from other sources, to the point where the program's objectives have been achieved. The Foundation is indebted to James W. Newberne, D.V.M., M.Sc., Ph.D., as Chairman of the Toxicologic-Pathology Advisory Committee, and his committee members, who conclude their service on this committee this year. The committee will be given recognition for their services at the 1993 Annual Awardee Meeting.

Again this year, the *Annual Report, Scholars,* and *Tracking 25* serve as the Foundation's means of communicating to its constituencies and to the public at large. They also serve as a means of documenting the ongoing, living history of the Foundation and turn up in a variety of locations, ranging from health science center libraries to congressional offices.

Administratively, the officers in place were unchanged during 1991, but 1992 elections have brought the administration of Charles A. Sanders, M.D., and Theodore Cooper, M.D., Ph.D. as Chairman and Vice Chairman, respectively, into the Foundation's Board of Directors. The transition was smooth and we welcome these new officials. I am pleased that Joseph A. Mollica, Ph.D., continues as Secretary-Treasurer; his Treasurer's Report and Audit appear elsewhere in this Annual Report.

With a welcome to new officers and Board members, with appreciation for the dedication of those who preceded them, with a sense of pride for the accomplishments of 1991-92, and with a sense of optimism for the next twenty-five years, we are pleased to present this Annual Report of the Pharmaceutical Manufacturers Association Foundation.

Maurice Q. Bectel, D.Sc.
President

Activities

Established in 1965 by the Pharmaceutical Manufacturers Association, the PMA Foundation promotes public health through encouraging scientific and medical research. The research-intensive pharmaceutical companies of the PMA are the original and continuing source of support for PMA Foundation funds. Also of significance, is the income received from earnings on reserves. Since its beginning, the Foundation has disbursed nearly $32 million in grants to over 1,500 scientists. Some $6 million has gone to support research, with the bulk of the balance going into educational awards.

Meetings and Other Activities

PMA Foundation 1991 Program Held During ASPET Annual Meeting, San Diego

Speaking at the fifteenth PMA Foundation program during ASPET's Annual meeting in San Diego on August 19, 1991, was Bob Dillan, Director of the Speaker's Bureau for the Zoological Society of San Diego—operators of the famed San Diego Zoo. The subject of this year's presentation was a departure from the traditional subject format of pharmacology/toxicology or therapeutics, and was well received by the over 100 attendees. Mr. Dillon gave an exciting and informative presentation on "Zoo Babies and the Center for Reproduction of Endangered Species (CRES)" and was accompanied by several residents of the San Diego Zoo—some small, live animals—and, of course, animal trainers.

As Mr. Dillon explained, the CRES program, initiated in 1975, is the most diverse and intensive research program in any zoo in the world with seven separate divisions: animal behavior, comparative physiology, endocrinology, genetics, infectious diseases, reproductive physiology and virology/immunology.

The PMA Foundation program, which has become a tradition at the ASPET Annual Meeting, is held to give Foundation Committee Members, current and former awardees, ASPET Council Members, and Chairmen of Departments of Pharmacology an opportunity to discuss their current activities.

Addressing the 1992 PMA Foundation press conference is PMA Senior Vice President for Science and Technology John F. Beary, III, M.D.

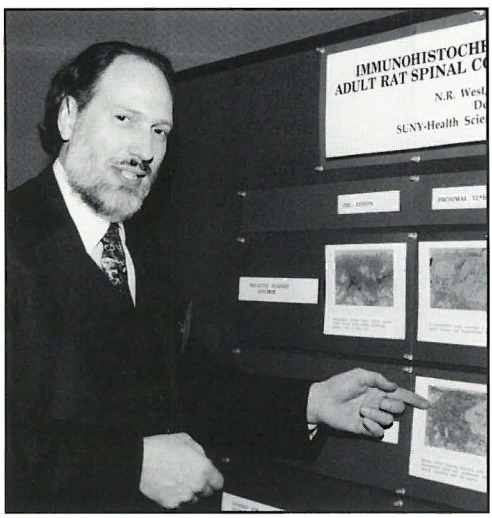
The 1992 Thomas E. Hanrahan Memorial Lecture was presented at the Annual Awardee Meeting by Steven A. Rosenberg, M.D., Chief of Surgery of the National Cancer Institute of the National Institutes of Health. Dr. Rosenberg spoke on "Immunotherapy and Gene Therapy of Cancer".

Twenty-First Annual Awardee Meeting

On January 22 and 23, 1992, the PMA Foundation held its 21st Annual Awardee Meeting at the Vista International Hotel in Washington, D.C. On January 23, over 130 PMA Foundation current and former awardees, committee members and PMA staff heard Steven A. Rosenberg, Chief of Surgery of the National Cancer Institute, National Institutes of Health, speak on "Immunotherapy and Gene Therapy of Cancer." Dr. Rosenberg delivered the Thomas E. Hanrahan Memorial Lecture. Another integral part of the Awardee Meeting is the Poster Session which gave 30+ scientists an opportunity to display their work and exchange ideas. As is customary, the three afternoon subgroup sessions in clinical pharmacology, basic pharmacolgy and pharmacology-morphology allowed attendees to hear presentations regarding their specific discipline. On the evening before the meeting, members of the PMA Board of Directors attended our Annual Awardee Banquet, which provided an opportunity for them to interact with PMA Foundation awardees and committee members, as well as PMA Foundation staff.

PMA Foundation Board of Directors—New Members

At its May 9 meeting at The Greenbrier, White Sulphur Springs, West Virginia, the PMA Foundation Board of Directors elected officers, installed new Board members and bid adieu to retiring Board members. Charles A. Sanders, M.D., Chairman and Chief Executive Officer of Glaxo Inc., was elected Chairman. Theodore Cooper, M.D., Ph.D., Chairman and Chief Executive Officer of The Upjohn Company, was elected Vice-Chairman. Joseph A. Mollica, Ph.D., President and Chief Executive Officer, Du Pont Merck Pharmaceutical Company, was re-elected Secretary-Treasurer. Newly elected to the PMA Foundation Board of Directors are: Robert C. Black, President, ICI Pharmaceuticals Group, ICI Americas Inc.; G. Gilbert Cloyd, Vice President, Pharmaceuticals, Procter & Gamble Company; Jan Leschly, Chairman, SmithKline Beecham Pharmaceuticals; and Philip R. Tracy, President and Chief Executive Officer, Burroughs Wellcome Co.



Considerable interest was demonstrated at the Poster Session held during the Annual Awardee Meeting, with researchers explaining their projects to other recipients, Foundation Board members, and SAC members.

Ten pharmaceutical company executives serve on the current Foundation Board of Directors along with Gerald J. Mossinghoff, President of the PMA, who is an *ex-officio* member. In addition to Sanders, Cooper, Mollica and new Board members Black, Cloyd, Leschly and Tracy, Board members serving are: Sheldon G. Gilgore, M.D., Chairman and Chief Executive Officer, Searle, and George J. Sella, Jr., Chairman and Chief Executive Officer, American Cyanamid Company.

Retiring from the PMA Foundation Board as of May, 1992, are: Paul E. Freiman, Chairman and Chief Executive Officer, Syntex Corporation. (Mr. Freiman currently serves as Chairman of the PMA Board); Hubert E. Huckel, M.D., Chairman of the Board, Hoechst-Roussel Pharmaceuticals Inc.; Irwin Lerner, President and Chief Executive Officer, Hoffmann-La Roche Inc.; and Klaus Heinz Risse, Ph.D., Vice Chairman, Miles Inc.

Faculty Awards in Toxicologic-Pathology

Initiated in 1983, this award was developed to attract scientists in toxicology. As a result of several factors—increased numbers of scientists and departments, and the advent of other sources of support among them—the Scientific Advisory Committee recommended discontinuation of this award program after the 1992 cycle. Acknowledging that the program's objectives had been achieved, the Board of Directors adopted the SAC recommendation.

Accordingly, one award was made in 1992 for the 1991 review cycle, bringing this program's total to eighteen awards. No such awards will be offered or made after 1992.

SAC Chairman Frederick M. Radzialowski, Ph.D., addresses the Annual Awardee Meeting, held in Washington, D.C.

PMA Foundation Chairman Sheldon G. Gilgore, M.D. (seated) confers with press conference panelist Louis M. Lasagna, M.D.,Ph.D. Dr. Lasagna is Dean of the Sacker School of Graduate Biomedical Sciences, Academic Dean of the Medical School, and Director of the Center for the Study of Drug Development at Tufts University. He spoke on the value of research and development to future medical progress.

Education and Training Programs

In order to accomplish its goals in education and research, the PMA Foundation is proud to administer twelve funding programs—four in clinical pharmacology, one in the combined field of pharmacology-morphology, one in pharmacology/toxicology, one in basic pharmacology, one in toxicologic-pathology which will be phased out after 1992, and three in pharmaceutics. The Research Starter Grant provides starter funds in pharmacology, clinical pharmacology, drug toxicology and pharmaceutics. The Foundation also accepts applications in all program areas for research on drugs for rare diseases.

The PMA Foundation Board of Directors, at the recommendation of the Scientific Advisory Committee, agreed to phase out the Faculty Development Award in Toxicologic-Pathology after 1992, due to the success of its mission in recruiting more individuals to this field. The Foundation looks upon this action as a milestone and a credit to the work of the Foundation and foresight of the Foundation's Toxicologic-Pathology Advisory Committee in seeing a need and assisting in fulfilling that need.

Clinical Pharmacology

Faculty Awards in Clinical Pharmacology

The four clinical pharmacology programs provide assistance at the student, fellow and faculty levels. Through the Faculty Development Awards in Clinical Pharmacology program, the Foundation makes three-year awards to medical schools for salary and fringe benefits support of full-time junior faculty members. The Foundation has set a ceiling of $40,000 on the amount of its participation in total yearly salary and fringe benefits for any candidate.

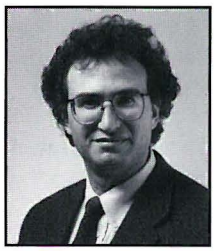
With the awards scheduled to begin July 1, 1992, 95 individuals have been supported under this program since 1967.

Recipients of the awards which began July 1992 are:

Joshua Olajide Atiba, M.B., Assistant Professor of Medicine and Pharmacology, University of California, Irvine—"Modulation of Cytotoxic Chemotherapeutic Agents." This research involves three projects: (l) There is increasing use in clinical cancer therapy of non-cytotoxic compounds in combination with cytotoxic chemotherapeutic agents. These modulation strategies have been successful to varying extents, but there is need to explore the underlying mechanism of the effects seen. This research explores the interaction between levamisole and 5-FU, and that between cyclosporine, VP-16 and cisplatin, in colon and lung cancer patients respectively. It is now well recognized that a large number of human cancers display recurring chromosome abnormalities. What

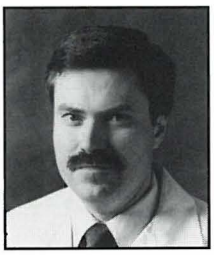
has not been clear is the biological and clinical significance of the cytogentic abnormalities. The enzyme MeSAdo phosphorylase (methylthioadenosine: orthophosphate methyltyioribosyl–transferase), designated MTAP has been mapped to the short arm of chromosome 9. In a recent study 75% of human gliomas from fresh biopsies and glioma cell lines were completely MTAP deficient. MTAP is a normal mammalian tissue enzyme which plays a role in recycling of purines and methionine during polyamine synthesis. The deficiency of this enzyme thus represents a specific metabolic abnormality which distinguishes a common and usually incurable human tumor from normal cells, which can be exploited for chemotherapeutic purposes. This research will study a high dose methotrexate regimen as treatment for patients with MTAP deficient malignant gliomas. In the last project Dr. Atiba plans to study the clinical pharmacokinetics of the novel chemoprevention agent Bowman-Birk Inhibitor (BBI) in patients with oral leukoplakia.

Margaret Ann Smith Dordal, M.D., Ph.D., Assistant Professor of Medicine, Northwestern University Medical School—"Reversal of Transport-mediated Resistance to Doxorubicin." Cancers which are treated with chemotherapy develop resistance not only to the drugs with which they are treated, but to most other drugs also. The best characterized mechanism for resistance is the presence of a cell surface pump, P-glycoprotein, which removes drugs from inside the cell; other resistant cancers show decreased drug influx. A variety of drugs inhibit P-glycoprotein, including calcium channel blockers and dipyridamole. Dipyridamole also increases the influx of vinblastine. Dr. Dordal has developed a kinetic analysis of uptake that separates influx and afflux processes. She will use this technique to study the mechanism of action of drugs that increase uptake. Initial clinical studies with verapamil suggest that it is possible to reverse drug resistance in patients. Verapamil has negative inotropic properties that make it unsuitable for some cancer patients. Dr. Dordol will use dipyridamole together with doxorubicin to treat patients with drug-resistant tumors. Recent advances in flow cytometry permit measurement of intracellular doxorubicin levels and P-glycoprotein levels in each cell from a needle aspirate. With this powerful technology, she will study doxorubicin flux in patients' cancer cells sampled during therapy, and correlate P-glycoprotein function during therapy with the response to therapy.



Leslie A. Lenert, M.D., Assistant Professor, Department of Medicine, Stanford University—"Computer Methods for Decision Support in Clinical Pharmacology." An important part of the discipline of Clinical Pharmacology is research in improvement of clinical decision-making for drug therapy. The spectrum for clinical decision-making for pharmacotherapy includes: (1) indiv–idualization of therapeutic strategies on the basis of patient and disease related factors; (2) development of practice guidelines for the administration of drug therapies on the basis of assessment of effectiveness, risk of side effects, and costs; and (3) periodic reevaluation of the effectiveness of existing drug therapies on the basis of the observed outcomes and complications in large populations of patients. Dr. Lenert's research will focus on the development and enhancement of computer methods to aid with therapeutic decision-making. These methods will include: (1) the application of natural language processing to develop large, inexpensive yet highly detailed databases for post-marketing surveillance; (2) the application of decision analysis in assessment of the appropriateness and cost-effectiveness of medical therapies and the integration of personal preferences for

health outcomes into policy decisions; (3) the automation of decision analysis for individual therapeutic decision-making; and (4) the application of Bayesian forecasting to incorporate information from therapeutic trials in decision-making for long-term drug therapy.



Raymond J. Hohl, M.D., Ph.D., Assistant Professor, Department of Internal Medicine, University of Iowa—"Isoprenylated Proteins in Malignant Cell Growth; Strategies for Impairing Their *In Vivo* Isoprenylation and Function." To critically examine whether *in vivo* competitive inhibition of hydro–xymethylglutaryl coenzyme A (HMG CoA) reductase alters the levels of isoprenylated growth regulating proteins in peripheral blood mononuclear cells (PBMNCs) and in the malignant cells of patients with acute myeloid leukemia. We have observed that the *in vitro* incubation of cells with HMG CoA reductase inhibitors alters cell proliferative capacity and affects the isopreny–lation of the RAS protein. RAS is an isoprenylated (farnesylated) growth-promoting protein; KREV1 is also isoprenylated (geranyl–geranylated) but is growth-suppressing. Dr. Hohl hypothesizes that the competitive inhibition of HMG CoA reductase alters cell growth because of changes in the levels of intracellular isoprenylated growth regulating proteins. Clinical application of this hypothesis requires an understanding of whether isoprenylation reactions can be affected by the in vivo administration of the HMG CoA reductase inhibitors. Dr. Hohl will measure the RAS and KREV1 protein levels in PBMNCs and leukemia cells from volunteers after the administration of HMG CoA reductase inhibitor. The cells' proliferation capacity will be measured in an ex vivo system. Finally, Dr. Hohl will develop methods to selectively impair the isoprenylation of growth-regulating proteins. The results obtained from these studies may provide further rationale to support the development of new drugs that selectively inhibit isoprenylation reactions.

Recipients of the three awards which began July 1991 are:

Daniel David Gretler, M.D., Instructor, University of Chicago School of Medicine

Michael J. Jamieson, M.B.Ch.B., M.R.C.P., Assistant Professor, University of Texas Health Science Center.

Theresa A. Shapiro, M.D., Ph.D., Assistant Professor of Medicine, Johns Hopkins University School of Medicine.

Individuals who entered the second year of their award in 1991 are:

Joseph J. Crowley, M.D., Assistant Professor, Division of Geriatric Medicine, University of Washington.

Paolo B. DePetrillo, M.D., Instructor, Department of Medicine, Brown University.

Charles W. Flexner, M.D., Assistant Professor, Department of Medicine and Department of Pharmacology, The Johns Hopkins University School of Medicine.

Joseph F. Foss, M.D., Assistant Professor, Department of Anesthesia and Critical Care, Committee on Clinical Pharmacology, University of Chicago.

Individuals who entered the third year of their awards in July 1991 are:

Patrick Taylor Horn, M.D., Ph.D., Assistant Professor, Committee on Clinical Pharmacology, University of Chicago.

Ralph A Kelly, M.D., Assistant Professor, Harvard Medical School.

Lawrence G. Miller, M.D., Assistant Professor, Tufts University School of Medicine.

Individuals who ended their awards in 1991 are:

Thomas C. Shea, M.D., Assistant Professor, Department of Medicine and Oncology, University of California, San Diego.

John Tangney Sullivan, M.D., Assistant Professor, Johns Hopkins University.

Fellowships for Careers in Clinical Pharmacology

The second program in clinical pharmacology 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 study in the basic pharmacologic sciences needed to complement his or her clinical skills.

The program allows an individual to apply for a fellowship two years in advance of the activation date of the award. For example, those applying for a fellowship in the fall of 1992 may request that the fellowship begin July 1993 or July 1994.

The program began in 1973. Since that time, 55 fellowships have been awarded.

Recipient of the award beginning July 1, 1992:

Gene R. Pesola, M.D., Postdoctoral Fellow, Department of Pharmacology, Medical University of South Carolina—"Stereospecific Sulfate Conjugation of B_2-Agonist Drugs in Man"—The hypothesis to be tested in this proposal is that chiral B_2-agonist drugs in humans are metabolized by sulfoconjugation in a stereoselective fashion, thus changing their enantiomeric composition in the body and therefore pharmacologic activity. This will be investigated for the model drug isoproterenol and the clinically most important B_2-agonist albuterol, using an *in vitro/in vivo* approach. In AIM 1 sulfation will initially be studied in fresh human liver with the human hepatoma cell line Hep G2 as a critically important synthetic tool. These studies will then be extended to intestinal metabolism, important for many of these drugs, and the platelet as an *in vitro/in vivo* model. In AIM 2 studies will be performed using the purified human phenolsulfotransferases to determine enzyme/substrate specificities as a basis for future studies of the regulation of the various enzyme forms. In Aim 3 the findings and technology of AIMS 1 and 2, together with newly developed immuno–affinity isolation techniques, will be applied to *in vivo* studies, determining the enantiospecific clearances of the B_2-agonist albuterol through sulfation. Findings from the proposed studies should provide a cellular and enzymatic basis for the first evaluation of the pharmacokinetic/pharmacodynamic relationships for the B_2-agonist class of drugs.

Individuals who began their awards in July 1991 are:

Nabil S. Andrawis, M.D., Ph.D., Program in Clinical Pharmacology, Department of Medicine, Brown University School of Medicine.

Halina S. Darling, M.D., Loyola University of Chicago School of Medicine.

Andre Terzic, M.D., Ph.D., Thomas Jefferson University, Jefferson Medical College. Dr. Terzic transferred his fellowship to Mayo in February 1992.

Individuals who ended their awards in July 1991 are:

David Michael Kerins, M.R.C.P.I., Division of Clinical Pharmacology, Vanderbilt University.

Therese K. Schmalbach, M.D., Ph.D., Department of Biology, Chemistry and Molecular Pharmacology, Harvard Medical School.

David W. Rudy, M.D., Indiana University.

Daniel Ward, D.V.M., University of Georgia.

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, offers students an opportunity to spend up to two years full-time conducting an investigative project in pharmacology-clinical pharmacology. The minimum period of the award is three months and maximum is two years. It is hoped that by having students become involved in investigative projects at a point when career choices are still relatively flexible, they will eventually choose research careers in clinical pharmacology. One-hundred seven awards have been made since 1974.

Individuals whose awards began in July 1992 are:

Michael S. Conners, New York Medical College (one year). Mr. Conner's research is entitled "Injury Induced Corneal Angio–genesis: Role of 12(R) HETrE." His principal advisor is Michael L. Schwartzman, Ph.D., Associate Professor, Pharmacology.

Reza Goharderakhshan, Louisiana State University School of Medicine (one year). Mr. Goharderakhshan will be studying the "Regulation of the Hip Vascular Bed by Calcium Regulating Peptides." His principal advisor is Howard Lippton, M.D., Pulmonary Medicine.

Frederic S. Leeds, Case Western Reserve University Medical School (one year). Mr. Leeds will focus on "Regulation of Mitochondrial Biogenesis by Coenzyme A Metabolism." His fellowship supervisor is Eric P. Brass, M.D., Ph.D., Associate Professor of Medicine and Pharmacology.

Svetomir N. Markovic, Medical College of Pennsylvania (four months). He will be studying the "Effects of Halothane and Isoflurane on Human Peripheral Blood Natural Killer Cytotoxicity." His principal advisor is J. Roberts, Ph.D., Professor and Chairman of the Department of Pharmacology.

Ronald Medley, Texas Tech University Health Science Center (three months). Mr. Medley will study "The Biology of Alcoholism." His fellowship advisor is Peter J. Syapin, Ph.D., Assistant Professor of Pharmacology.

Betty D. Moore, Meharry Medical College (one year). Ms. Moore's research will focus on "Plasma Protein Binding of Drugs in Blacks and Caucasians." Her fellowship supervisor is Timi Edeki, M.D., Ph.D., Assistant Professor of Pharmacology.

Philip K. Wu, University of Vermont College of Medicine (one year). Mr. Wu will be studying "Structure-Activity Relationships of Novel Anti-Neoplastic BIS (Platinum) Compounds." His advisor will be Nicholas P. Farrell, Ph.D., Research Associate Professor, Department of Chemistry.

Enjoying a relaxed moment are Foundation President Maurice Q. Bectel and Irwin Lerner, former Board Chairman and longstanding member of the Foundation Board.

Clinical Pharmacology Unit Support

This program assists directors of clinical pharmacology units established within a two-year period preceding the award, or units that have acquired a new director during that period. In 1991, the Clinical Pharmacology Advisory Committee recommended and the PMA Foundation Board approved an increase in this award from $50,000 per award to $100,000, effective for 1992 awards. The purpose of the program is to provide supplementary funds to assist the unit's research efforts until other research grants are obtained. The first grants were made in 1978 and the total number of awards made to date is twenty-three.

Timi I. Edeki, M.D., Ph.D., Director, Clinical Pharmacology Unit, Meharry Medical College. Dr. Edeki's unit will research: (l) inter-ethnic differences between Blacks and Caucasians in the metabolism of drugs and their response. This will include studies on the response to propranolol and its stereoselective metabolism and on the respiratory depressant effects of morphine. A population study will be conducted in Blacks using a pharmacogenetic probe drug, debrisoquine, to determine the prevalence of different genetic phenotypes in this population. (2) The possibility of sickle cell disease, in view of its multiple organ pathology, altering the pharmacokinetics of drugs will be investigated for morphine, a drug widely used to control the pain crisis in this hematologic disorder. (3) Studies will be conducted on the possibility of drug interaction following ocular administration of ophthalmic timolol with such cardiovascular drugs like verapamil, and on the effect of felodipine, a new calcium channel blocker, on cytochrome P-450 enzyme system, using antipyrine as a probe drug.

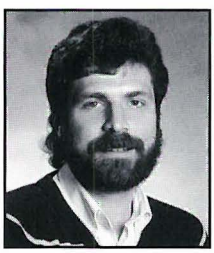
Basic Pharmacology

Faculty Development Awards in Basic Pharmacology

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

The first awards were made in 1973 and are for a two-year period. The program provides salary and fringe benefits. The Foundation has set a ceiling of $30,000 on the amount of its participation in the total yearly salary and fringe benefits for awardees. The total number of awards made to date is 56.

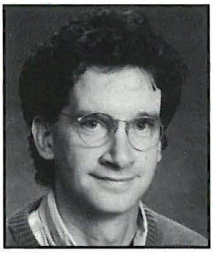
Recipients of the 1992 Faculty Development Awards in Pharmacology are:



Todd A. Verdoorn, Ph.D., Assistant Professor, Department of Pharmacology, Vanderbilt University School of Medicine—"Exploring the Structural Basis of GABA/Benzodiazipine Receptor Heterogeneity Using Recombinant GABA receptor Subunits." Combinations of recombinant GABA receptor subunits will be transiently expressed in fibroblasts and the functional properties of the resulting receptors measured with patch clamp techniques. The focus will be on the $\alpha_1\beta_2\Psi_2$ and a $\alpha_3B_2\Psi_2$ subunit combinations because these GABA receptor isoforms show differences in benzodiazipine binding pharmacology and electrophysiological properties. The structural basis of channel gating and benzodiazipine action will be probed by testing the function of chimeric α_1/α_3 subunits or a subunits carry specific mutations. These studies will hopefully lead to a better understanding of channel

gating mechanisms, and the modulation of channel gating by benzodiazipines. It is anticipated that these studies will provide findings that ultimately will result in the design of drugs that are selective for various isoforms of the GABA/benzodiazipine receptor complex and thus have improved therapeutic potential.

Roseann L. Vorce, Ph.D., Assistant Professor, Department of Pharmacology, University of Nebraska Medical Center—"Regulation of GTPase Activating Protein (GAP) in Response to Increased ras p21 Activity." An increase in ras p21 protein activity is associated with cell proliferation and transformation. Apparently, the ras p21 protein is functional when bound to GTP and is inactivated by GTP hydrolysis. It has been found that GAP can increase the rate of p21 hydrolysis, thus contributing to ras inactivation. The hypothesis for this study is that increased ras p21 activity is accompanied by an increase in the activity of GAP, its functional antagonist. To address this possibility, the biochemical activity of GAP and its expression level in WB-F344 cells will be compared to these parameters in cells stably transfected with the normal Ha-ras gene or its mutated (activated) form. If GAP expression is elevated in ras-overexpressing cells, it will be determined whether this increase is due to increased synthesis or decreased degradation. Finally, the 5' regulatory region of the GAP gene will be cloned and analyzed to identify regions for baseline expression and for ras-stimulated induction. It is anticipated that elucidation of the mechanisms by which GAP activity is controlled will contribute to the rational design of therapies for the treatment of hepatocellular carcinoma, possibly through a gene therapy approach using a mutated ras-specific GAP gene.



William Frederick Wonderlin, Ph.D., Assistant Professor, Department of Pharmacology and Toxicology, West Virginia University—"Non-genetic Regulation of Ion Channel Expression in Neurons." Voltage-gated ion channels in the plasma membrane of neurons are the molecular basis of neuronal excitable properties. These properties require a precise regulation of the expression of different classes of voltage-gated ion channels to maintain an appropriate balance between channels that exert excitatory versus inhibitory actions. Our understanding of the regulation of channel expression is limited by our lack of knowledge of the full range of regulatory processes. With attention focused on gene transcription, other intracellular processes of potential regulatory importance have been ignored. The goal of this project is to identify non genetic factors that might regulate the expression of transit of voltage-gated ion channels, focusing on ion channels and the transport vesicles in which they are carried during their transit from the Golgi to the plasma membrane. Experiments will use transport vesicles released by perforation of cultured embryonic rat brain neurons. Several psychological recording techniques will be used to examine: (1) the ionic perme–abilities of transport vesicles; (2) the sorting and packaging of different classes of channels into single transport vesicles; and (3) the insertion or removal of channels from the plasma membrane by vesicle fusion and endocytic processes, respectively. These experiments should enable identification or elimination of several potential regulatory processes in the control of expression of voltage-gated ion channels.

Individuals who began their awards in July 1991 are:

Stewart N. Abramson, Ph.D., Assistant Professor, University of Pittsburgh, School of Medicine.

Rodney Kawahara, Ph.D., Assistant Professor, University of Nebraska Medical Center.

Scott A. Waldman, M.D., Ph.D., Assistant Professor, Thomas Jefferson University, Jefferson Medical College.

Those who entered the second year of their awards in 1991 are:

James J. Galligan, Ph.D, Assistant Professor, Department of Pharmacology and Toxicology, Michigan State University.

Anna T. Riegel, Ph.D., Assistant Professor, Department of Pharmacology, Georgetown University, School of Medicine.

Philip C. Smith, Ph.D., Assistant Professor of Pharmacy, College of Pharmacy, University of Texas at Austin. Dr. Smith transferred his award in July 1992 to his University of North Carolina, Chapel Hill.

Those who ended their awards in 1991 are:

Peter J. R. Cobbett, Ph.D., Assistant Professor, Department of Pharmacology, Michigan State University.

Robert A. Nicholas, Ph.D., Assistant Professor, University of North Carolina at Chapel Hill.

Fellowships for Advanced Predoctoral Training in Pharmacology or Toxicology

This program is designed to assist those candidates who expect to complete the research for their doctoral dissertations.

In 1992, the fellowship program provided a stipend of $10,000 a year and $500 a year for incidentals directly associated with preparation of the dissertation. The Basic Pharmacology Advisory Committee has decided to raise the stipend to $12,000 for 1993 awards and give ten instead of twelve fellowships, maintaining the $500 per year expense money. The program, in its 15th year, has awarded a total of 184 fellowships.

Those who have been awarded 1992 fellowships beginning between January and July are:

Janet E. Clark, Yale University School of Medicine. Ms. Clark's research is entitled "Molecular Cloning and Characterization of a Novel Na+-Dependent GABA Transport Protein." Her principal advisor is Susan G. Amara, Ph.D., Associate Professor/Scientist.

Cathleen Peterson Duncan, Duke University School of Medicine. Ms. Duncan will investigate the "Regulation of Electrically-Evoked Release of Glutamate and Aspartate by Neuromodulators." Her principal advisor is J. Victor Nader, Ph.D., Professor of Pharmacology.

Pictured at the Annual Awardee Meeting reception are (l. to r.) William R. Darrow, M.D.,Ph.D., of the Scientific Advisory Committee and Senior Vice President for Medical Operations, Schering-Plough Corporation; Lodewijk de Vink, President and Chief Operating Officer, Warner-Lambert Company; Harvey E. Bale, Jr., Ph.D., PMA Senior Vice President , International Affairs; and Gerald J. Mossinghoff, PMA President.

Dawn Louise Duval, University of Nevada School of Medicine. Ms. Duval will study Leukocyte Mediated Liver Toxicity." Her principal advisor is Dr. Ruth E. Billings, Associate Professor of Pharmacology/ Surgery.

Bonnie Lynne Firestein, University of California, San Diego. Ms. Firestein's research focuses on the "Role of Phospholipases and Protein Kinase C in Interactions between Adrenergic and Purinergic Receptors on MDCK-D1 Cells." Her advisor is Paul A. Insel, M.D., Professor of Pharmacology.

Annette Elizabeth Fleckenstein, Michigan State University. Ms. Fleckenstein will examine the "Influence of Histaminergic Neurons on Dopaminergic Neuronal Systems in the Rat Brain." Her principal advisor is Kenneth E. Moore, Ph.D., Professor and Chairman, Department of Pharmacology/Toxicology.

Tanmoy C. Ganguly, University of Kentucky School of Medicine. Mr. Ganguly will focus on the "Role of Prolactin in Regulation of Hepatic Na+ Dependent Taurocholate Transport." His advisor is Mary Vore, Ph.D., Professor and Vice Chairman, Department of Pharmacology.

Richard D. Griner, Jr., University of Georgia, College of Veterinary Medicine. Mr. Griner's research will explore how "Aerobic Metabolism and Growth Factors Regulate Differentiated Functions." His thesis advisor is Dr. Rick Schnellmann, Associate Professor.

Diane F. Kelly, University of Massachusetts Medical Center. Ms. Kelly will investigate the "Characterization of the Primary Structure of Staphylococcus Aureus DNA Polymerase III and Its Response to Enzyme-Selective Inhibitors." Her principal advisor is Neal C. Brown, D.V.M., Ph.D., Professor and Chairman, Department of Pharmacology.

Margy S. Lambert, University of California, Berkeley. Ms. Lambert will study the "Alterations in DNA Fingerprints as a Method to Detect Somatic Mutations." Her thesis advisor is Martyn T. Smith, Ph.D., Associate Professor, Biomedical and Environmental Health Science.

Suk-Kyeong Lee, Northwestern University Medical School. Ms. Lee's research focuses on "Parathyroid Hormone and Calcitonin Signalling: Mechanism of Desensitization." Her advisor is Paula H. Stern, Ph.D., Department of Pharmacology.

Elizabeth A. O'Donnell, University of Pennsylvania. Ms. O'Donnell will focus on "Inhibition of Viral Receptor Interactions Utilizing Antibody Derived Biologically Active Peptides." Her principal advisor is David B. Weiner, Assistant Professor, Department of Medicine.

Kristien J. Piron, Texas Tech University Health Sciences Center (one year). Ms. Piron will analyze the "Developmental Aspects of Mono-ADP-Ribosylation in the Rat Brain." Her thesis advisor is Kathryn K. McMahon, Ph.D., Assistant Professor.

Derk Schultz, University of North Carolina at Chapel Hill (one year). Mr. Schultz will explore the "Crystallization of Soluble Penicillin-Binding Protein 2 from Neisseria Gonorrhea and Soluble Penicillin-Binding Protein 3 from E. Coli." His primary advisor is Dr. Robert A. Nicholas, Assistant Professor, Department of Pharmacology.

Robert D. Traver, University of Southern California (one year). Mr. Traver will study "Regulatory Changes in NAD(P)H:Quinone Oxidoreductase in Human Carcinoma Cells." His principal advisor is Dr. Neil Gibson.

Leonidas Tsiokas, New Jersey Medical School, University of Medicine and Dentistry of New Jersey. Mr. Tsiokas will investigate the "Expression of Muscarinic Receptor Subtypes and Activation-Transcription Coupling as Molecular Substrates for Initial Sensitivity and Tolerance to Ethanol." His advisor is Mark Watson, Ph.D., Assistant Professor of Pharmacology.

John Stephen Verbanac, Wayne State University College of Pharmacy and AHP. Mr. Verbanac will analyze the "Electrophysiological Characteristics of Locus Ceruleus Neurons in Genetically-Inbred Anxious and Non-Anxious Rat Strains." His advisor is Dr. Randall L. Commissaris, Associate Professor of Pharmacology.

Karen A. Woodfork, West Virginia University School of Medicine (one year). Ms. Woodfork's research will focus on the "Mitogenic Signal Transduction in Breast Cancer." Her primary advisor is Jeannine Strobl, Ph.D., Professor, Department of Pharmacology/Toxicology.

Those who received fellowships in 1991 which are continued in 1992 are:

Michael A. Barry, Dartmouth Medical School.

Cynthia Cheng, Thomas Jefferson University, Jefferson Medical College.

Alison F. Dobrenski, Georgetown University School of Medicine.

Carrie Teresa Drake, University of Washington School of Medicine.

Jeffrey Keefer, Vanderbilt University School of Medicine.

Kristine A. Kimball, University of Arkansas for Medical Sciences.

Galina Kuznetsov, Robert Wood Johnson Medical School, UNDNJ.

Barbara W. LeDuc, Tufts University School of Medicine.

Matthew V. Lorenzi, University of Miami School of Medicine.

Lisa Ellen Rubin, Cornell University Graduate School of Medical Sciences.

Thomas Riley Shannon, University of Missouri-Columbia, School of Medicine.

Grace A. Stafford, Cornell University, New York State College of Veterinary Medicine.

Marilyn Eileen Thompson, University of South Alabama.

Richard Regis Vaillancourt, University of Wisconsin Medical School-Madison.

David E. Wildman, Yale University School of Medicine.

Barbara Y.R.H. Williams, University of Texas Medical School.

Pharmacology/ Morphology

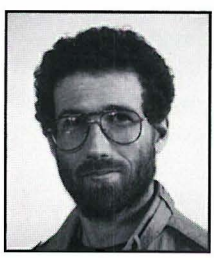
Fellowship Awards in Pharmacology-Morphology

The purpose of this program is to increase our knowledge about the actions of drugs by direct study of their effects on cells and tissues; to correlate the morphological changes; and, concurrently, to uncover associations observed with functional parameters of cells and tissues.

The awards are 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. First offered in 1968, 86 awards have been made to date.

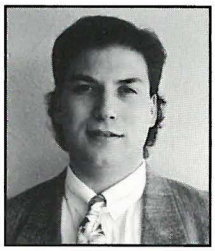
In order to be eligible for an award, the candidate must possess formal training in a morphologic specialty or in pharmacology. However, subsequent training in the complementary discipline, during the period of the fellowship, may be informal. On completion of the program, the fellow should be able to use the tools and concepts of both disciplines.

Recipients of the fellowship beginning July 1992 are:



Eran Blaugrund, Ph.D., Columbia University, College of Physicians and Surgeons—"Effects of Cocaine and Amphetamines on Developing Enteric Neurons *In-Vitro*" Some of the psycho–stimulating effects of cocaine are mediated by its

inhibition of the re-uptake of monoaminergic neurotransmitters by nerve terminals. In addition, both cocaine and amphetamine are weak bases and it has been proposed that this property contributes to the effects of these compounds. Amine storage organelles are normally acidic because of a H^+ translocating ATPase creates transmembrane H^+ (DpH) and potential (Dy) gradients; the proton-motive force established by these gradients provides the drive for amine uptake into the vesicles. Weak bases are trapped in acidic compartments and tend to dissipate the proton-motive force, leading to a translocation of amine from vesicle to cytosol or, in the case of amphetamines, to the extracellular space. While information exists about the effects of cocaine and amphetamines on the mature nervous system, little information is available as to the actions of these compounds on the developing nervous system. Indirect evidence that cocaine may have deleterious effects on neuronal development come from the observations that the children of mothers that have taken "crack" cocaine during pregnancy ("crack babies") have personality and learning defects later in life. The aim of this research is to investigate the hypothesis that cocaine and amphetamines are neurotoxic to developing neurons, in part because of their action as weak bases and, especially in the case of cocaine, because of inhibition of the re-uptake of secreted amines. These studies will be carried out in the developing enteric nervous system (ENS) of the rat, a model system that has been well characterized, is accessible, and which is simpler than the brain. Assessing the effects of drugs on enteric neurons in-vitro may elucidate some of the cellular mechanisms that are responsible for the long-term toxicity of these drugs to the developing nervous system. What is learned about the interaction of cocaine and amphetamines with the monoaminergic neurons of the ENS are likely to be applicable to the development of the CNS as well.



David A. Jones, Ph.D., University of Utah School of Medicine—"Endothelial Cell Expression and Function of Platelet-Endothelial Cell Adhesion Molecule-1." Dysregulation or inappropriate activation of neutrophils underlies numerous pathologic events ranging from reperfusion injury to hemorrhagic shock. A model of such dysregulated neutrophil function is the neutrophil-dependent necrosis resulting from envenomation by the brown recluse spider. They have discovered that the venom of Loxosceles reclusa (the brown recluse spider) potently induces endothelial cell-dependent neutrophil adhesion. This induced adhesion is dependent on de novo protein synthesis, but is due to none of the currently defined adhesion molecules expressed by stimulated endothelial cells (P-selectin, E-selectin, ICAM-1, or PAF). Their preliminary data suggests that this endothelial cell adhesive protein may be PECAM-1 (CD31). Since PECAM-1 is thought to mediate endothelial cell-endothelial cell binding through homotypic interaction, it is possible that Loxosceles-treated endothelial cells express newly-synthesized PECAM-1 on their surface and it is this mis-localized molecule that mediates neutrophil adhesion. Dr. Jones will examine the mechanism for this induced adhesion and its role in EC-PMN interactions under other circumstances.

Sarath Kanekal, Ph.D., University of Texas School of Pharmacy—"Peroxidase-mediated Metabolism of Cyclophosphamide." Lung and bladder injury are side-effects of cyclophosphamide (CP) chemotherapy. Although, the mixed function oxygenases are known to metabolize CP to reactive species, inhibitors of these enzymes have no effect on therapeutic

activity or lung toxicity. In contrast, inhibitors of prostaglandin H synthase (PHS) can prevent CP-induced lung injury. In contrast, inhibitors of prostaglandin H synthase (PHS) can prevent CP-induced lung injury. The overall objective of these studies is to examine whether PHS can bioactivate CP *in vitro.* Ability of CP to act as a cosubstrate to purified peroxidases will be assessed by incubating $^{14}C/^{3}H$-CP with horseradish peroxidase, soybean lipoxidase or PHS using H_2O_2 or arachidonate (AA) as substrates. Covalent binding of reactive CP metabolites to exogenously added proteins and generation of polar metabolites will be examined. The capacity of lung and bladder microsomes, isolated from mice sensitive to CP-induced lung and bladder injury, to metabolize CP by this alternate pathway also will be assessed. Finally, the significance of cooxidation of CP will be studied by examining metabolism and cytotoxicty in human lung cancer cell line rich in PHS activity (NCI H358). The results of the proposed studies could potentially provide definitive evidence on bioactivation of CP by PHS and will reveal the relative importance of cooxidation in CP metabolism and toxicity. Understanding mechanisms of metabolic activation of CP could potentially lead to better therapeutic strategies and synthesis of drugs with lesser side effects.

Stefan Strack, Ph.D., Vanderbilt University School of Medicine—"Identification of a Neurona/Glial Growth Factor Receptor." S100β is a glial-derived protein that may play important roles in nervous system development and maintenance, as suggested by these key findings: First, S100β has neurotrophic activity on select populations of central and peripheral neurons. Second, S100β is a growth factor for glial cells, stimulating proliferation of primary astrocytes and glioma cells. Third, S100β can rescue embryonic motoneurons from normal cell death in vivo and from injury-induced cell death following spinal transection. Little is known, however, about the molecular mechanisms by which S100β exerts its diverse effects. Dr. Strack's research proposes to fill this void in our knowledge by identifying and characterizing the receptor for S100β on target cells. They plan to conduct the following sets of studies: optimize receptor binding assays, determine the features of the S100β receptor on neuronal vs glial cells, identify and characterize the S100β receptor protein, and isolate the receptor cDNA. Encouraged by initial feasibility data, Dr. Strack believes his laboratory's studies will provide fundamental new insights into the mechanism of action of a new neurotrophic/growth factor.

Cynthia J. Ziegra, V.M.D., Ph.D., Cornell University College of Veterinary Medicine—"Cloning and Functional Characterization of Canine Keratinocyte Cell Adhesion Molecule." Pemphigus vulgaris is a serious and often fatal autoimmune skin disease of man and animals. Recent evidence indicates that the antigenic protein against which the autoantibodies react is a member of the cadherin family of cell adhesion molecules. In this study, Dr. Ziegra proposes to clone and sequence the pemphigus vulgaris antigen cDNA of canine keratinocytes. Then she will investigate the function and regulation of this protein in cultured COS monkey kidney cells and keratinocytes stably transfected with the cloned pemphigus cDNA. She will then try to determine the specific binding domain of this homophilic binding protein. She will have synthesized polypeptides derived from the predicted extracellular domain. She will use these peptides to compete with the binding of transfected COS cells to monolayers of keratinocytes. Polyclonal antibodies will be developed to use as specific probes to investigate the pathogenesis of this disease and to study the role of this cell adhesion molecule in the normal migration and differentiation of keratinocytes.

Individuals who began their awards in July 1991 are:

Charles Allan Fox, Ph.D., Mental Health Research Institute, University of Michigan.

Laura J. Sim, Ph.D., Department of Physiology and Pharmacology, Bowman Gray School of Medicine, Wake Forest University.

Marie Vivien St-Pierre, Ph.D., Department of Physiology, Tufts University School of Medicine.

Those individuals entering the second year of their fellowship in 1991 are:

Andrew Bean, Ph.D., Departments of Histology and Neurobiology, Karolinska Institute.

Ellen B. Cornbrooks, Ph.D., Department of Anatomy and Neurobiology, College of Medicine, University of Vermont. Dr. Cornbrooks delayed the start of her second year and will be entering her second year in 1992.

Kathleen Gogas, Ph.D., Department of Anatomy, University of California, San Francisco.

Ending their awards in 1991 are:

Karen J. Axt, Ph.D., The Johns Hopkins University, Department of Neuroscience.

Meredith Mason Garcia, Ph.D., Department of Anatomy, Tulane University School of Medicine.

Bruno C. Jubelin, M.Sc., Ph.D., Department of Anatomy and Cell Biology, College of Physicians and Surgeons of Columbia University.

Melissa Rogers, Ph.D., Dana-Farber Cancer Institute, Harvard University.

Paul R. Wade, Ph.D., Columbia University, College of Physicians and Surgeons, Department of Anatomy & Cell Biology.

Toxicology-Pathology

Faculty Awards in Toxicologic Pathology

Initiated in 1983, this award was developed to attract scientists interested in analyzing, reviewing and questioning, where appropriate, the present state of the art in the field of toxicology. As indicated earlier in the President's Report, with the concurrence of the Board, the Scientific Advisory Committee has decided to phase out this program after 1992 due to its success in bringing talented individuals to the field of toxicologic-pathology. The goal of this program had been to support veterinary and comparative pathologists who would devote two years to research with drugs. In 1992 this program offered $30,000 per year for two years' salary and fringe benefits. One award was made which will be the last award given by the PMA Foundation in this program. This brings the total number of these awards to 18.

Beginning her award in July 1992 is:

Jan L. VanSteenhouse, D.V.M., Ph.D., Assistant Professor, Veterinary Clinical Pathology, Louisiana State University, School of Veterinary Medicine—"Toxicity of a Naturally Occurring Nitrile and the Role of Glutathione Metabolism in Toxicity." Dr. VanSteenhouse's research is directed toward dietary modification of xenobiotic metabolism. Specifically, this research revolves around the metabolism of a naturally occurring nitrile, 1-cyano-3, 4-epithiobutane (CEB) derived from cruciferous plants present in our diets as cabbage, broccoli, kale and Brussel's sprouts. To date, CEB has been shown to conjugate with glutathione (GSH) resulting in a depletion of hepatic GSH with a rebound increase and an increase in renal GSH with no observed depletion phase in rats. In addition to the

altered GSH metabolism, CEB also induces a mild renal tubular necrosis and degeneration after a single dose. Previous studies with buthionine sulfoximine suggest that the GSH conjugate may itself play a role in these effects. These studies will further investigate the possible role and source of the conjugate by administration of a variety of inhibitors of GSH metabolism and transport prior to administration of CEB. Additional metabolism of CEB, or effects on other xenobiotic metabolizing enzyme activities, will be determined by identification of urinary metabolites and determination of the activity of a battery of xenobiotic enzymes after administration of CEB. These and future studies are driven by the potential for CEB as a significant chemoprotective agent due to its propensity to increase renal GSH.

Individuals who began their awards in July 1991 are:

Renate Reimschuessel, V.M.D., Ph.D., Assistant Professor, Department of Pathology, School of Medicine, University of Maryland.

Thomas J. Rosol, Assistant Professor, Department of Veterinary Pathobiology, The Ohio State University.

Individuals who entered the second year of their awards in July 1991 are:

Dale C. Baker, D.V.M., Ph.D., Assistant Professor, Department of Pathology, Colorado State University.

Mary K. Reinhard, M.S., D.V.M., Assistant Professor and Director of Clinical Medicine, Department of Comparative Medicine, Medical University of South Carolina.

Ending their awards in 1991 are:

Deborah Gillette, D.V.M., Ph.D., Assistant Professor of Pathology, School of Veterinary Medicine, University of Pennsylvania.

Matthew A. Wallig, D.V.M., Ph.D., Assistant Professor of Pathology, College of Veterinary Medicine, Department of Pathobiology, University of Illinois at Urbana-Champaign.

PHARMACEUTICS

Undergraduate Research Fellowships in Pharmaceutics

This fellowship is designed to offer support to undergraduate students in pharmaceutics and gives the undergraduate student an opportunity to participate in a meaningful research project with a motivated, inspiring and research-active pharmaceutics faculty member. Initiated in 1990, the award provides a selected pharmaceutics faculty member with a one-year fellowship for $5,000 which the faculty member can provide to a qualified undergraduate of his/her choosing. Twelve awards are budgeted for this award, however, due to the outstanding quality of these applications, thirteen awards were made for 1992.

Faculty and their undergraduate students who will receive fellowships between January and August 1992 are:

Jane P. F. Bai, Ph.D., Assistant Professor, Pharmaceutics Department, University of Minnesota, College of Pharmacy.
Student: Tryn T. Stimart—"Distribution of Brush Border Membrane Peptidases Along the Intestine of the Rabbit and Rat."

Jane P. F. Bai, Ph.D., Assistant Professor, Pharmaceutics Department, University of Minnesota College of Pharmacy.
Student: Nahid Kowsar —"Structural Requirements for the Intestinal Mucosal Cell Peptide Transporter: The Need for a Free C-Terminal Carboxyl Group."

Robin Humcke Bogner, Ph.D., Assistant Professor, University of Connecticut, School of Pharmacy.
Student: Sherry Lynn LaPorte—"Microviscosity at the Surface of a Dissolving Polymer Film."

Diane J. Burgess, Ph.D., Assistant Professor, Department of Pharmaceutics, University of Illinois at Chicago, College of Pharmacy.
Student: Nelly Milman—"Interfacial Tension Studies on Mixed Emulsifier Systems."

M. J. Cho, Ph.D., Associate Professor, University of North Carolina at Chapel Hill, School of Pharmacy.
Student: Mei Chuan Lai—"Citric Acid as an Adjuvant for Transepithelial Transport of Fluid-Phase Markers."

David J. W. Grant, D.Sc., Professor, Department of Pharmaceutics, University of Minnesota, College of Pharmacy.
Student: Flora Kit Ying Fung—"Implications of Chiral Purity in Solid State Pharmaceutics."

Vincent H. L. Lee, Ph.D., Professor of Pharmaceutical Sciences, University of Southern California, School of Pharmacy.
Student: Jennifer Yuan-Fung Yih—"Oral Delivery of Polar and Labile Peptides."

Steven L. Nail, Ph.D., Associate Professor, IPPH Department, Purdue University, School of Pharmacy.
Student: Brent Sinclair—"The Relationship Between Viscoelastic Properties and Chemical Stability of an Amorphous Freeze-Dried Drug."

Ronald J. Sawchuk, Ph.D., Professor of Pharmaceutics, University of Minnesota, College of Pharmacy.
Student: Chad Gednalske—"*In Situ* Absorption of Selected Antiviral Nucleosides from Rabbit Intestine."

Ronald J. Sawchuk, Ph.D., Professor of Pharmaceutics, University of Minnesota, College of Pharmacy.
Student: Belinda W. Cheung—"Studies of the Comparative Uptake of Three Antiepileptic Agents into Rabbit Brain."

Philip C. Smith, Ph.D., Assistant Professor, Department of Pharmaceutics, University of Texas at Austin.
Student: Hollie Stallings—"Toxicokinetics of Salicyl Acyl Glucuronide: Stability and Covalent Binding to Proteins In Vitro and *In Vivo*."

Raj G. Suryanarayanan, Ph.D., Assistant Professor, Department of Pharmaceutics, University of Minnesota, College of Pharmacy.
Student: Aye Khin Khin—"Quantitative X-Ray Diffractometry of Complex Pharmaceutical Systems."

Francis C. Szoka, Jr., Ph.D., Professor, Department of Pharmacy, University of California at San Francisco, School of Pharmacy.
Student: Winnie M. Yu—"Peptide-Bile Salt Conjugates-Potential Prodrugs with Increased Absorption."

Fellowship for Advanced Predoctoral Training in Pharmaceutics

Initiated in 1987, this program's purpose is to assist candidates who have one or two years remaining in their predoctoral training—the time during which they are engaged in dissertation research.

In 1992, the fellowship program provided a stipend of $10,000 a year and $500 a year for incidentals directly associated with the preparation of the dissertation. In 1993, with the concurrence of the Board and the Scientific Advisory Committee, the Pharmaceutics Advisory Committee agreed that the stipend should be raised to $12,000 and that seven awards be given instead of eight. The expense money of $500 per year will remain the same. Four fellowships were awarded for 1992 bringing the total number of awards to 33.

Those who received fellowships beginning between January and August 1992 are:

Shyue-fang Hsu, Department of Pharmaceutics, University of Wisconsin-Madison School of Pharmacy. Ms. Hsu will investigate "The Use of Amphotericin B as a Model to Study the Role of Membrane Perturbants in Transmembrane Drug Delivery." Her advisor is Ronald R. Burnette, Professor of Pharmaceutics.

Two award recipients Gary Mawe and James Galligan, discuss a poster exhibit held during the Annual Awardee Meeting with Michael D. Gershon, M.D. (right). Dr. Gershon is Chairman of the Pharmacology Morphology Advisory Committee and a member of the SAC.

Michelle T. Marra, Department of Pharmaceutics, University of Utah College of Pharmacy. Ms. Marra's will investigate the "Barrier Mechanism of Model Lipid Bilayer Systems." Her advisor is Kristine Knutson, Ph.D., Associate Professor of Pharmaceutics.

Paul B. Myrdal, Department of Pharmaceutics, University of Arizona College of Pharmacy. Mr. Myrdal will evaluate the "Estimation of Aqueous Activity Coefficients of Organic Compounds." His advisor is Dr. Samuel H. Yalkowsky.

Robert G. Strickley, Department of Pharmaceutics, University of Utah College of Pharmacy. Mr. Strickley's research involves the "Mechanism of Thiocarbamate Decomposition and Stabilization in Pharmaceutical Systems." His advisor is Bradley D. Anderson.

Continuing their 1991 fellowships into 1992 are:

Christine Gentry, Department of Pharmaceutics, University of Utah School of Pharmacy.

Kathleen M. Hillgren, Department of Pharmaceutical Chemistry, University of Kansas College of Pharmacy.

Patrick M. Hughes, Department of Industrial and Physical Pharmacy, Purdue University, School of Pharmacy and Pharmacal Sciences.

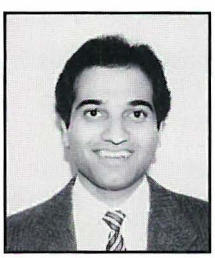
Michael Mulski, Department of Pharmaceutics, University of Wisconsin School of Pharmacy.

Susanne M. Peck, Department of Pharmaceutics, University of Maryland School of Pharmacy.

Postdoctoral Research Fellowships in Pharmaceutics

Complementing the other two pharmaceutics programs offered by the PMA Foundation, a new program was initiated in 1992 for Postdoctoral Research Fellowships in Pharmaceutics. The purpose of this program is to encourage more qualified graduates to obtain the postdoctoral research training so vitally needed in the area of pharmaceutics. The PMA Foundation and its Pharmaceutics Advisory Committee, in recognizing the critical need for such well-trained scientific investigators, gave three such awards in 1992 in the amount of $25,000 per award per year.

In 1992, the following individuals received awards:



Prashant J. Chikhale, Ph.D., University of Kansas, School of Pharmacy—"A Redox-Sensitive Prodrug Approach Toward Optimizing Delivery of Acivicin to Solid Tumors and Minimizing its Toxicity to the Central Nervous System."

Dr. Chikhale proposes that redox-sensitive prodrugs for acivicin based upon the bioreversible quinone propionic acid promoiety will be synthesized. The prodrug approach described is an attempt to optimize the therapeutic effectiveness of acivicin by: (a) decreasing its large neutral amino acid (LNAA) carrier-mediated transport

across the blood-brain barrier (BBB), thus decreasing its central nervous system (CNS) toxicity; (b) exploiting the redox potential of the hypoxic tumor site to achieve target specificity; and (c) enhancing the release and therefore the delivery of acivicin at the tumor site due to the unique structural configuration of the "trimethyl lock". The designed and synthesized redox-sensitive prodrugs for acivicin will undergo appropriate tests in order to ascertain that: (a) reduction of the prodrugs occur prior to hydrolysis; (b) there exist differences in susceptibility of the prodrugs toward reduction; (c) derivatization at the N-terminal end of the primary amino group of acivicin reduces its BBB carrier-mediated transport; and d) the designed redox-sensitive prodrugs exhibit *in vitro* cytotoxic potency and target specificity toward solid tumors *in vivo*.

Michael Mulski, University of Minnesota, School of Pharmacy, Department of Chemical Engineering—"Water Vapour Transport in Semi-Crystalline Polymer Films - A Model Based on Percolation Theory." This project will study water vapour transport across polyethylene and poly(4-methyl-1-pentene) semi-crystalline films. these polymers were chosen because of the difference in the transport behavior of their crystalline regions. The crystalline phase of polyethylene is generally regarded as impermeable to vapor transport. The crystalline phase of poly(4-methyl-1-pentene) has been shown to be permeable to small gas molecules. The primary objective is to construct experimentally verifiable models based on percolation theory which accurately predict diffusion of water vapour across and water vapour sorption into semi-crystalline polymer films. A secondary objective is to seek a fundamental physical understanding of the relationship of structure to transport in order to achieve predictability and control of transport behavior in these systems. Semi-crystalline polyethylene and poly(4-methyl-1-pentene) films ranging in crystallinity from 0%, 70%-100% will be used for the studies. Diffusion and solubility coefficients will be determined by a radiotracer technique. Raman spectroscopy will be used to determine the volume fraction of the three phases in semi-crystalline polyethylene films. DSC will be used to determine the crystalline and amorphous phase contributions for semi-crystalline poly(4-methyl-1-pentene) films. Transmission electron micrographs will be obtained for a number of the films to verify the consistency of crystal habit and random nature of the distribution of the amorphous phase within the semi-crystalline matrix.

Raymond D. Skwierczynski, University of Wisconsin-Madison, School of Pharmacy—"The Influence of Nonhydrogen-Bonded Bipole-Dipole Interactions on the Solid-State Organization of Organic Molecules." The interior of a protein is a highly ordered compact structure resulting from many weak noncovalent interactions. Studying the origin of these weak forces is difficult because the locations of atoms in the protein cannot be determined precisely. Therefore, organic crystals are often used as model systems to examine these interactions. This project will examine the role of nonhydrogen-bonded dipole-dipole interactions on the crystal packing of four model tertiary amide systems: (1)N,N-disubstituted amides, (2) N,N,N′,N′-tetramethyldiamides, (3) cyclic oligomers of sarcosine (N-methylglycine), and (4) linear oligomers of sarcosine. From the positions and orientations of the dipole moments in the crystal, the dipole-dipole interaction energy will be calculated using a model derived from classical electrostatics. These values will be refined using molecular mechanics. Thermodynamic parameters will also be measured. A systematic statistical analysis will be performed to

Scientific Advisory Committee Chairman Frederick M. Radzialowski, Ph.D., Vice President, Product Safety and Metabolism, Searle, spoke informally at a luncheon meeting of the SAC.

determine the importance of the nonhydrogen-bonded dipole-dipole interactions on the packing of organic crystals. This systematic exploration of nonhydrogen-bonded dipolar interactions in the solid-state that we propose should also provide insights on the role of nonhydrogen-bonded dipole-dipole interactions in determining the secondary and tertiary structures of proteins.

Research Grants

An important aspect of the PMA Foundation effort has been the support of fundamental research. However, since 1971 a change in emphasis within the Foundation shifted the bulk of the funds into educational support programs and, consequently, less into research. It is understood that these educational programs place high emphasis on the research programs of the applicants for each award. In this sense, educational support programs are in fact also supporting research. The Foundation continues to accept requests for research support and suggestions for pertinent research projects since it is important that the potential within the Foundation for helping that particularly promising effort be maintained.

The Foundation will continue to review research applications that do not fall within the scope of its formal programs, but will not fund them unless they are deemed to be exceptional and novel approaches that have not generated support from conventional sources.

Ethical Considerations

The Scientific Advisory Committee as well as the program advisory committees of the PMA Foundation are sensitive to the appropriate use of experimental subjects, animals and humans, in research. In their deliberations, they consider all aspects of a proposal and may deny support for many reasons. Careful consideration is given to humane use and care of animal subjects. For human and animal research, the project review committee requires, in writing, a statement of adherence to prevailing standards of ethical research practices, including Institutional Review Board approval before initiation of any research project. In addition, for human research, assurance of informed consent will be required.

Research Starter Grants

Active since 1971, the Research Starter Grants are intended to provide financial support for beginning investigators. The program allows for approximately 20 research starter grants each year. The first awards were made in 1972. A total of 440 research starter grants have been made, including the 17 awards beginning January 1, 1992.

Recipients of the grants beginning January 1992 are:

Michael Babich, Ph.D.
University of Illinois
College of Medicine

Jane P. F. Bai, Ph.D.
University of Minnesota
College of Pharmacy

Michael Balazy, Ph.D.
New York Medical College

James K. Bashkin, Ph.D.
Washington University
Graduate School of Arts & Sciences

Michael J. Blake, Ph.D.
University of North Dakota
School of Medicine

Ralph C. Dornburg, Ph.D.
University of Medicine and
Dentistry of New Jersey
Robert Wood Johnson Medical School

Stanley W. Halvorsen, Ph.D.
State University of New York at Buffalo

Charles Ward Luetje, Ph.D.
University of Miami (Florida)
School of Medicine

A. Leslie Morrow, Ph.D.
University of North Carolina at Chapel Hill
School of Medicine

Sunday Edet Ohia, Ph.D.
Creighton University
School of Pharmacy

Scott Warren Rogers, Ph.D.
University of Colorado
Health Science Center

Mary Beth St. Clair, Ph.D.
North Carolina State University

David C. Thompson, Ph.D.
Texas A&M University
College of Medicine

Todd A. Verdoorn, Ph.D.
Vanderbilt University
School of Medicine

Roseann L. Vorce, Ph.D.
University of Nebraska
Medical Center

Donald E. Walters, Ph.D.
Auburn University
School of Pharmacy

William Frederick Wonderlin, Ph.D.
West Virginia University
Health Sciences Center

Based on need for funds, a review of the 20 research starter grantees whose awards began January 1, 1991, for a second year of the awards resulted in 10 of them having their awards continued. These are:

Nicholas R. Ferreri, Ph.D.
New York Medical College

Michael James Jamieson, M.B.Ch.B, M.R.C.P.
University of Texas Health Science Center

Rodney Kawahara, Ph.D.
University of Nebraska Medical Center

Stephen Korn, Ph.D.
University of Connecticut

Kenneth J. Mack, M.D., Ph.D.
University of Wisconsin
School of Medicine

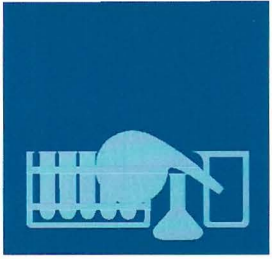
Chris R. Ross, D.V.M., Ph.D.
Kansas State University
College of Veterinary Medicine

Bryan L. Roth, M.D., Ph.D.
Case Western Reserve University
School of Medicine

Theresa A. Shepard, Ph.D.
Rutgers University College of Pharmacy

Thomas E. Smithgall, Ph.D.
Eppley Cancer Center
University of Nebraska

Mark Jonathan Winn, Ph.D.
University of Alabama at Birmingham
School of Medicine



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 which govern the distribution of funds are in support of fundamental research on drugs and programs for training personnel in basic and clinical pharmacology, toxicology and pharmaceutics.

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 who hold the highest promise of advancing the purposes of the Foundation.

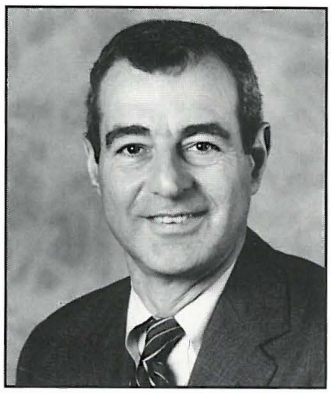
Those areas not supported within the existing guidelines are:

(1) Research on specific drugs, unless the drug is for an orphan disease. 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 (except as otherwise indicated).
(4) Funds to cover entertainment costs.

While Foundation support of research continues, such support is currently primarily available in programs such as the Research Starter Grants as discussed on page 26 and under the Education and Training Programs Section on page 9.

While meetings have never received a large portion of the support dollar, only in very exceptional circumstances will meetings receive support in the future.

Report of the Treasurer



Joseph A. Mollica, Ph.D.
Secretary-Treasurer
PMA Foundation

Since its inception twenty-five years ago, the PMA Foundation has been supported by the generosity of the research-intensive pharmaceutical manufacturers—the PMA member firms, associates, and research affiliates. The total income of the Foundation in 1991 was $2,563,948. Of this amount, $2,303,350 came from contributions. The balance of $260,598 came from investments and refunds of unexpended balances from grants.

Grants, Foundation-sponsored programs, special meetings and other expenses for 1991 amounted to $2,553,509. Of this total, $1,955,174 represents expenditures for grants. The total fund balance as of December 31, 1991, was $5,092,771. 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 disbursed. As of December 31, 1991, the contingency liability for 1992-95 was approximately $3,212,323.

The Foundation's financial position as of December 31, 1991, has been audited by the Washington D.C. accounting firm of Buchanan & Company.

Joseph A. Mollica, Ph.D.
Secretary-Treasurer, PMA Foundation
and
President and Chief Executive Officer
The Du Pont Merck Pharmaceutical Company

Statement of Income and Expenditures For the Year Ended December 31, 1991

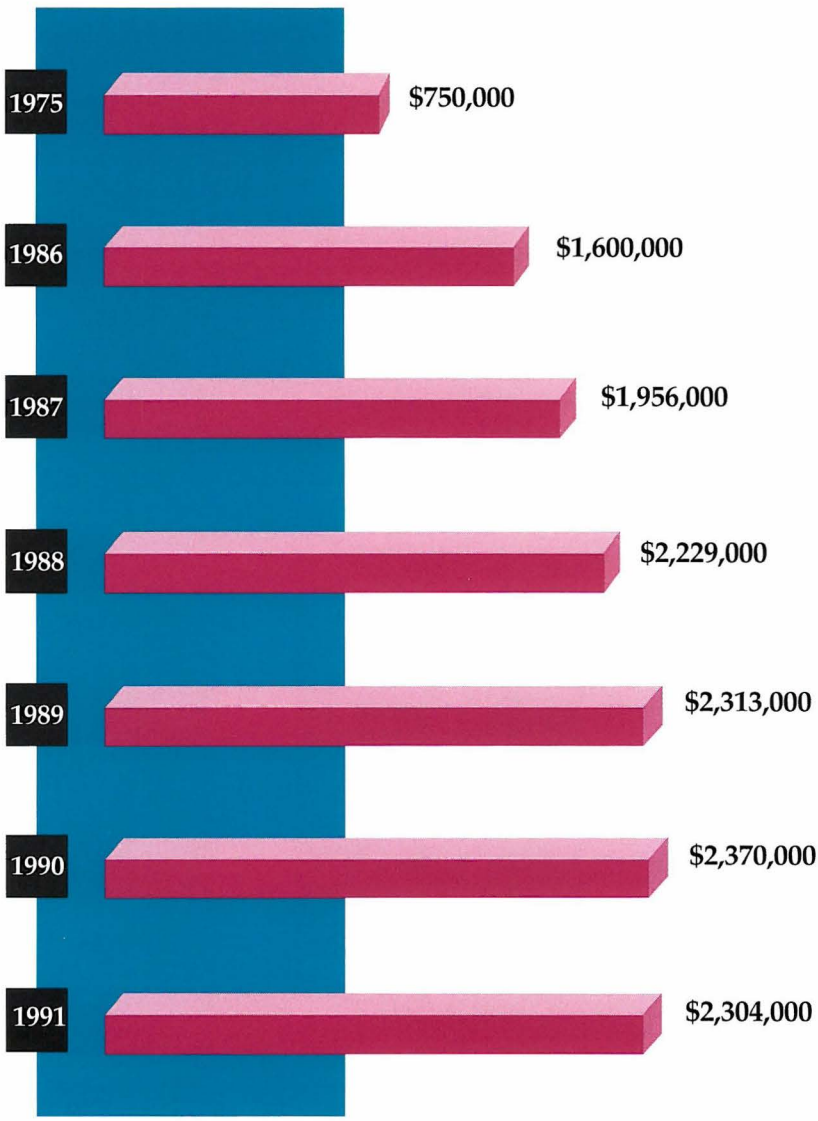
Income	
Contributions	2,303,350
Interest from investments	132,050
Interest Transferred from Future Commitment Fund	109,344
Miscellaneous Income	19,204
Total Income	2,563,948
Expenditures	
Grants (Note A)	
Clinical Pharmacology Unit Award	89,206
Faculty Awards in Clinical Pharmacology	375,000
Faculty Awards in Basic Pharmacology	165,000
Fellowships for Careers in Clinical Pharmacology	83,299
Advanced Predoctoral Fellowships in Pharm/Tox	309,500
Pharmacology-Morphology Fellowships	152,669
Medical Student Research Fellowships	76,000
Research Starter Grants	370,000
Faculty Awards in Toxicologic-Pathology	127,500
Advanced Predoctoral Fellowships in Pharmaceutics	147,000
Undergraduate Fellowships in Pharmaceutics	60,000
Total	1,955,174
Administrative, February Awardee Meeting Annual ASPET Meeting and Other Expenses	598,335
TOTAL EXPENDITURES	2,553,509
Excess of income over expenditures	10,439
Operating fund balance at January 1, 1991	2,932,995
Operating fund balance December 31, 1991	2,943,434
Future Commitment Fund (Reserve Fund) (Note B)	2,149,337
Total fund balance at December 31, 1991	5,092,771

Note A—In addition to the amounts shown, the Foundation is committed, subject to annual review, to make certain grants. At December 31, 1991, the amounts still to be disbursed with respect to these grants amounted to aggregated $3,212,323 with $1,826,990 of this to be disbursed during 1992; $1,009,083 in 1993; $276,250 in 1994; and $100,000 in 1995.

Note B—The Future Commitment Fund is a reserve fund established by the Foundation to ensure the continuation of existing grants.

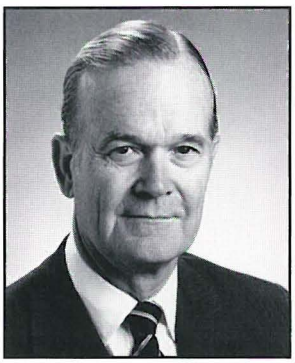
Income from Investments	121,613
Interest Transferred to Operating Fund	(109,344)
Dividend Income	11,192
Gain (Loss) on Sale of Stock	(15,765)
Less: Trust Commission Expense	(15,264)
Excess of expenditures over income:	(7,568)
Future Commitment Fund Balance at January 1, 1991	2,156,905
Future Commitment Fund Balance at December 31, 1991	2,149,337

PMA Foundation Income 1975-1991 (thousands)



Organization and Administration

1992 Officers

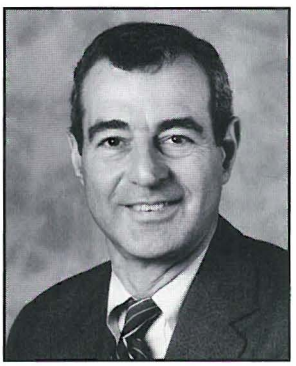


Charles A. Sanders, M.D.
Chairman
PMA Foundation
Chairman and Chief Executive Officer
Glaxo Inc.
Research Triangle Park, North Carolina

The PMA Foundation operates through its officers, Board of Directors and five advisory committees. In May of 1992, Charles A. Sanders, M.D., Chairman and Chief Executive Officer of Glaxo Inc., was elected Chairman. Sheldon G. Gilgore, M.D., Chairman of the Board and Chief Executive Officer of Searle stepped down as Chairman of the Foundation but remains on the Board. Theodore Cooper, M.D., Ph.D., Chairman and Chief Executive Officer of The Upjohn Company, was elected Vice-Chairman. Joseph A. Mollica, Ph.D., President and Chief Executive Officer, Du Pont Merck Pharmaceutical Company, was re-elected Secretary-Treasurer.

Maurice Q. Bectel, D.Sc., again served as the Foundation's President and Donna Moore served as Associate. Edward J. Cafruny, M.D., Ph.D., and C. Joseph Stetler, Esq., continue to serve as Foundation consultants—Dr. Cafruny as scientific consultant and Mr. Stetler as staff counsel.

Theodore Cooper, M.D., Ph.D.
Vice Chairman
PMA Foundation
Chairman and Chief Executive Officer
The Upjohn Company
Kalamazoo, Michigan



Joseph A. Mollica, Ph.D.
Secretary-Treasurer
PMA Foundation
President and Chief Executive Officer
Du Pont Merck Pharmaceutical Company
Wilmington, Delaware

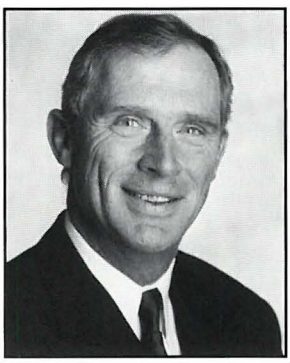
Maurice Q. Bectel, D.Sc.
President
PMA Foundation

1992 Board of Directors

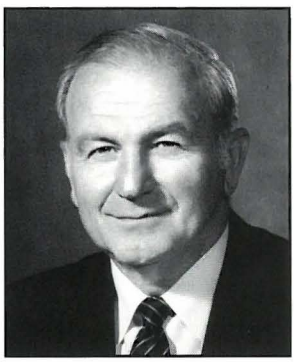
***Robert C. Black**
President
ICI Pharmaceuticals Group
ICI Americas Inc.
Wilmington, Delaware

***G. Gilbert Cloyd**
Vice President, Pharmaceuticals
Procter & Gamble USA
Procter & Gamble Company
Cincinnati, Ohio

Sheldon G. Gilgore, M.D.
Chairman and
Chief Executive Officer
Searle
Skokie, Illinois

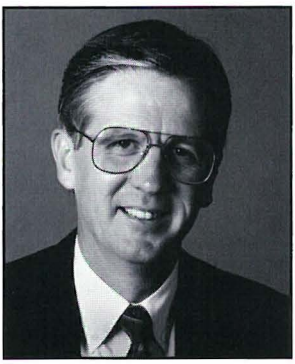


***Jan Leschly**
Chairman
SmithKline Beecham
Pharmaceuticals
Philadelphia, Pennsylvania



George J. Sella, Jr.
Chairman and Chief Executive
Officer
American Cyanamid Company
Wayne, New Jersey

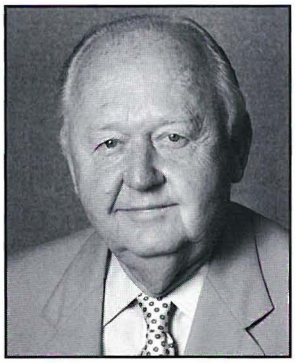
*Elected to the Board May 1992



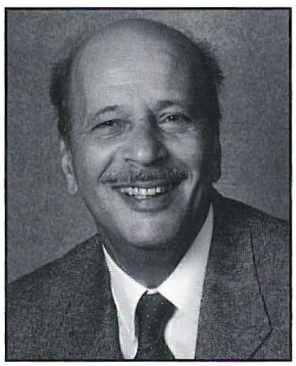
***Philip R. Tracy**
President and Chief Executive Officer
Burroughs Wellcome Co.
Research Triangle Park, North Carolina

Gerald J. Mossinghoff
President
Pharmaceutical Manufacturers Association
Washington, D. C.
(Ex-Officio)

Staff Consultants



C. Joseph Stetler, Esq.
Attorney at Law

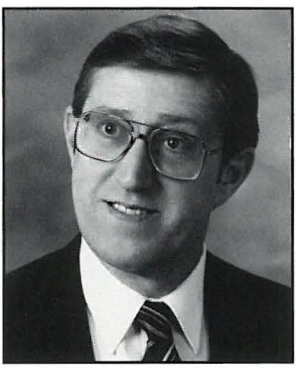


Edward J. Cafruny, M.D., Ph.D.
Emeritus Distinguished University Professor
University of Medicine and Dentistry of New Jersey

*Elected to the Board May 1992

Advisory Committees

Scientific Advisory Committee



Frederick M. Radzialowski, Ph.D.
(Chairman)
Vice President
Product Safety and Metabolism
Searle
Skokie, Illinois

Paul Calabresi, M.D.
Chairman and Professor
Department of Medicine
Brown University
Providence, Rhode Island

Michael D. Gershon, M.D.
Professor and Chairman
Department of Anatomy & Cell Biology
Columbia University
College of Physicians and Surgeons
New York, New York

Jerry R. Mitchell, M.D., Ph.D.
President
Upjohn Laboratories
and
Corporate Vice President
The Upjohn Company
Kalamazoo, Michigan

***James W. Newberne, D.V.M., M.Sc., Ph.D.**
Vice President
Drug Safety Assessment and Oversight
Merrell Dow Research Institute
Marion-Merrell Dow Inc.
Cincinnati, Ohio

William K. Riker, M.D.
Professor and Chairman
Department of Pharmacology
Oregon Health Science University
School of Medicine
Portland, Oregon

Frank G. Standaert, M.D.
Director of Research
The Toledo Hospital
Todelo, Ohio

James Swarbrick, D.Sc., Ph.D.
Professor and Chairman
Division of Pharmaceutics
School of Pharmacy
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

****E. Leong Way, Ph. D.**
Professor Emeritus
of Pharmacology, Toxicology and
Pharmaceutical Chemistry
Schools of Medicine and Pharmacy
University of California, San Francisco

Irwin M. Weiner, M.D.
Dean
College of Medicine
State University of New York, Brooklyn
Health Science Center
Brooklyn, New York

* Retired from Committee May 1992
** Retired from Committee 1991

PMA Section Liaisons to the Scientific Advisory Committee
Representing Medical, R&D, and Biological respectively

William R. Darrow, M.D., Ph.D.
Senior Vice President
Medical Operations
Schering-Plough Corporation
Kenilworth, New Jersey

Gary L. Neil, Ph.D.
Senior Vice President
Research and Development
Wyeth-Ayerst
Philadelphia, Pennsylvania

C. Searle Wadley
Director
Corporate Compliance Assurance
Abbott Laboratories
Abbott Park, Illinois

Clinical Pharmacology Advisory Committee

Paul Calabresi, M.D.
(Chairman)
Chairman and Professor
Department of Medicine
Brown University
Providence, Rhode Island

William B. Abrams, M.D.
Executive Director
Clinical Research
Merck Sharp & Dohme Research Laboratories
West Point, Pennsylvania

Terrence F. Blaschke, M.D.
Chief and Associate Professor
Division of Clinical Pharmacology
Stanford University
School of Medicine
Stanford, California

Edward A. Carr, Jr., M.D.
Professor of Pharmacology and Therapeutics and Professor of Medicine
School of Medicine and Biomedical Sciences
State University of New York at Buffalo
Buffalo, New York

Leo E. Hollister, M.D.
Professor of Psychiatry and Pharmacology
Medical School
University of Texas at Houston and
Medical Director
Harris County Psychiatric Center
University of Texas Medical School
Houston, Texas

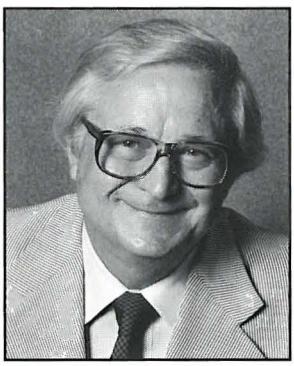
Louis Lemberger, M.D., Ph.D.
Lilly Clinical Research Fellow
Lilly Laboratory for Clinical Research
Eli Lilly and Company
and
Professor of Pharmacology, Medicine and Psychiatry
School of Medicine
Indiana University
Indianapolis, Indiana

Gilbert Mannering, Ph.D.
Professor Emeritus
Department of Pharmacology
University of Minnesota
Medical School
Minneapolis, Minnesota

Albert Sjoerdsma, M.D., Ph.D.
President Emeritus
Merrell Dow Research Institute
Cincinnati, Ohio

Lester E. Soyka, M.D.
Vice-President
Worldwide Medical Development
Bristol-Myers Squibb Co.
Princeton, New Jersey

Toxicologic-Pathology Advisory Committee*



James W. Newberne, D.V.M., M.Sc., Ph.D.
(Chairman)
Vice President
Drug Safety Assessment and Oversight
Merrell Dow Research Institute
Marion Merrell Dow Inc.
Cincinnati, Ohio

William W. Carlton, D.V.M., Ph.D.
Leslie Morton Hutchings Distinguished
Professor of Veterinary Pathology
School of Veterinary Medicine
Purdue University
West Lafayette, Indiana

Felix A. de la Iglesia, M.D.
Vice President
Pathology and Experimental Toxicology
Parke-Davis Pharmaceutical Research
Ann Arbor, Michigan

*Toxicologic-Pathology Program and Committee Phased Out after 1992

Paul M. Newberne, D.V.M., S.M., Ph.D.
Mallory Institute of Pathology
and
Professor of Pathology
School of Medicine
Boston University
Boston, Massachusetts

Walter E. Tucker, Jr., D.V.M.
Director
Toxicology and Experimental Pathology
The Burroughs Wellcome Company
Research Triangle Park, North Carolina

Basic Pharmacology Advisory Committee

Irwin M. Weiner, M.D.
(Chairman)
Dean
College of Medicine
State University of New York, Brooklyn
Brooklyn, New York

****James W. Aiken, Ph.D.**
Associate Director
Metabolic Diseases Research
The Upjohn Company
Kalamazoo, Michigan

**Joined the Committee 1992

Theodore M. Brody, Ph.D.
Professor
Department of Pharmacology and Toxicology
Michigan State University
East Lansing, Michigan

George C. Fuller, Ph.D.
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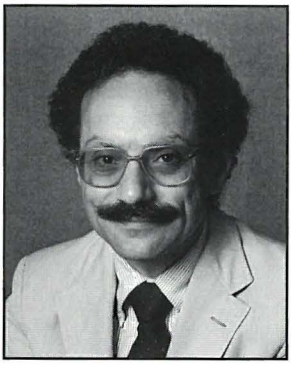

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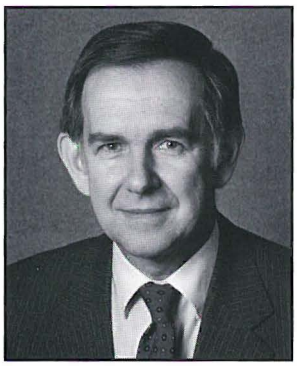

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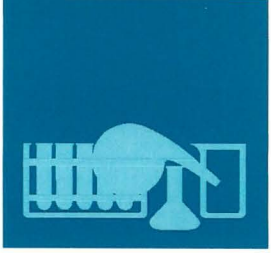
During the Annual Awardee Meeting's reception, Arthur Hull Hayes, Jr., M.D., Mrs. Hayes, and Board Chairman Sheldon G. Gilgore, M.D., share a moment. Dr. Hayes, former FDA Commissioner, is a former PMA Foundation award recipient and has been a longtime supporter of the Foundation.



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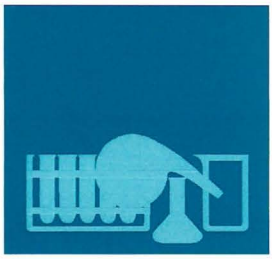
Claire Lathers, Ph.D. reviews the results of a research project during the Poster Session.



APPLICATIONS

Descriptive brochures and application forms for all of the PMA Foundation Grant Programs listed on the opposite page are available by contacting the Foundation offices.

Also, as a part of pursuing its objective of promoting careers in biomedical research, the Foundation accepts requests for support and suggestions for pertinent research projects outside the formal grant programs from qualified institutions and individuals. These grant applications are reviewed by members of the Foundation's Scientific Advisory Committee to ensure that the application falls within Foundation grant program guidelines and to identify qualified individuals and projects.

For more information:

Maurice Q. Bectel, D.Sc.
President
Pharmaceutical Manufacturers Association
Foundation
1100 Fifteenth Street, N.W.
Washington, DC 20005

CELEBRATING 25 YEARS

PMA Foundation Current Programs for 1993

Name of Program/ Year of First Awards	Number of Awards Budgeted Yearly/ Length of Award	Program Budget	Deadline Announcement Date Starting Time
Clinical Pharmacology Advisory Committee			
(1) Faculty Awards in Clinical Pharmacology (1967)	3 budgeted/ 3 years	$ 360,000 total $ 40,000 per award per year	October 1 December 15 July 1
(2) Fellowships for Careers in Clinical Pharmacology (1973)	4 budgeted/ 2 years	$ 192,000 total $ 24,000 per award per year	October 1 December 15 July 1
(3) Medical Student Research Fellowships (1974-Amended 1982)	8 budgeted/ 3 months to 24 months	$ 80,000 total $ 833 per month maximum $ 10,000	January 15 March 15 July 1
(4) Development Grants for Clinical Pharmacology Units (1978)	1 budgeted/ 3 years to use funds	$ 100,000 per award	January 15 March 15 July 1
Basic Pharmacology Advisory Committee			
(5) Faculty Awards in Basic Pharmacology/Toxicology (1973)	3 budgeted/ 2 years	$ 180,000 total $ 30,000 per award per year	September 15 December 15 July 1
(6) Research Starter Grants (1972)	16 budgeted/ 2 years	$ 400,000 total $ 12,500 per award per year	September 1 December 15 January 1
(7) Advanced Predoctoral Fellowships in Pharmacology/Toxicology (1978)	10 budgeted/ 1 or 2 years	$ 250,000 total $ 12,500 per award per year	September 15 December 15 January-August
Pharmacology-Morphology Advisory Committee			
(8) Fellowships in Pharmacology-Morphology including Cell Biology (1968)	3 budgeted/ 2 years	$ 126,000 total $ 21,500 per award per year	January 15 March 15 July 1
Pharmaceutics Advisory Committee			
(9) Advanced Predoctoral Fellowships in Pharmaceutics (1987)	7 budgeted/ 1 or 2 years	$ 175,000 total $ 12,500 per award per year	October 1 December 15 January-August
(10) Undergraduate Research Fellowships in Pharmaceutics (1990)	12 budgeted/ 1 year	$ 60,000 total $ 5,000 per award	October 1 December 15 January-July
(11) Postdoctoral Fellowships in Pharmaceutics (1992)	2 budgeted/ 1 or 2 years	$ 100,000 $ 25,000 per award per year	October 1 December 15 January-December

All of the above programs will accept applications for research on drugs for rare diseases

Pharmaceutical Manufacturers Association Foundation
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