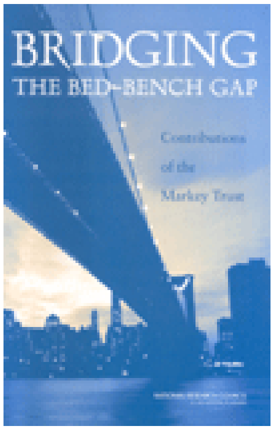

Bridging the Bed-Bench Gap: Contributions of the Markey Trust

Committee on the Evaluation of the Lucille P. Markey Charitable Trust Programs in Biomedical Sciences, Board on Higher Education and Workforce, National Research Council

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Committee on the Evaluation of the Lucille P. Markey Charitable Trust
Programs in Biomedical Sciences

Board on Higher Education and Workforce
Policy and Global Affairs Division

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Preface

In 1997, as the 15-year term of the Lucille P. Markey Charitable Trust neared its end, the Trust asked the National Research Council (NRC) of the National Academies to evaluate the Trust's approach to supporting programs in biomedical science. The National Academies agreed to undertake a project to study the Markey Trust as a model of philanthropy.

To commence this project the National Academies established a Committee on the Evaluation of the Lucille P. Markey Charitable Trust. The Committee was charged with addressing two questions: "Were the Trust's funds well spent?" and "What can others learn from the programs of the Markey Trust both as an approach to funding biomedical research and as a model of philanthropy?"

The five reports of the Committee will

1. examine the General Organizational Grants program that was intended to catalyze new ways to train students in translational research;
2. evaluate the program for Markey scholars and visiting fellows, which supported young biomedical investigators in their early careers;
3. report on a conference of Markey scholars and visiting fellows that was organized by The National Academies in 2002;
4. review the Research Programs Grants, which provided funding to institutions to support the work of senior investigators; and
5. report on methods used to evaluate funding of biomedical science by philanthropic donors.

Since it was established in 1998, the Committee has collected data, conducted site visits, convened workshops, and interviewed grantees to determine the answers to the questions that the Trust posed about its impact on biomedical research. The study will be completed in 2005.

This first report of the Committee presents findings concerning the Markey General Organizational Grants. This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

We wish to thank the following individuals for their review of this report: Jules Hirsch, Rockefeller University; Richard McGee, Mayo Medical School; Joel Oppenheim, New York University; Gary Pasternack, Johns Hopkins University; Deborah Powell, University of Minnesota; and Gayle R. Slaughter, Baylor College of Medicine.

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by Paula Stephan, Georgia State University. Appointed by the National Research Council, she was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

The production of this report was the result of work over a sustained period of time by the study Committee. George Reinhart, study director, Elaine Lawson, program officer, and Elizabeth Briggs Huthnance, administrative assistant, ably assisted the Committee in this study. Virginia Weldon, M.D., who earlier served as chair of the Committee, was instrumental in the early development of both the study and this report.

Enriqueta Bond
Chair
Committee on the Evaluation of the
Lucille P. Markey Charitable Trust
Programs in Biomedical Sciences

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Executive Summary

The Lucille P. Markey Charitable Trust was created as a 15-year, limited-term philanthropy to support basic medical research in compliance with the will of Lucille P. Markey, who died on July 24, 1982. Mrs. Markey wished that a trust be established "for the purposes of supporting and encouraging basic medical research." The trustees, who provided governance for the Markey Trust, directed the Trust's programs to specific needs in the biomedical sciences, where funding could make the biggest difference. These areas, which emerged over the life of the Trust, covered

- support of young researchers in the biomedical sciences;
- establishment, reorganization, or expansion under able investigators of major biomedical research programs or centers; and
- training opportunities in translational research for graduate and medical students.

The Markey trustees were also aware that their mode of philanthropy could provide a model of philanthropy that others could follow, for example,

- distributing all the assets of the Trust over a limited period of time, thereby allowing more funds to be distributed in a given year and larger awards to be offered;
- operating with a small core staff, thereby reducing administrative costs and allowing for a higher proportion of funds to be awarded to grantees; and

- providing funds with a minimum of required reporting, thus freeing recipients from burdensome paperwork often associated with grants.

These three mechanisms of operating a grant-making program may inform others in the philanthropic community about approaches for funding research and training programs in the sciences. However, future funders of graduate training programs should ensure that a comprehensive program evaluation and prospective monitoring of outcomes is an integral part of the overall design of the project.

During the 15 years following its creation the Lucille P. Markey Charitable Trust spent over $500 million on three grant programs in the basic biomedical sciences to support the education and research of predoctoral students, postdoctoral fellows, junior faculty, and senior researchers. In response to a request by the Markey trustees the Committee on the Evaluation of the Lucille P. Markey Charitable Trust is evaluating the Markey Trust's grant programs in the biomedical sciences. This evaluation addresses two questions: "Were the Trust's funds well spent?" and "What can others learn from the programs of the Markey Trust both as an approach to funding biomedical research and as a model of philanthropy?"

MARKEY GRANT PROGRAMS

The Markey Trust awards reflect the main stages of a biomedical research career: basic training, development of young faculty, and research by experienced scientists. The three categories of grants are (1) General Organizational Grants, (2) Markey Scholars and Visiting Fellows Awards, and (3) Research Program Grants. Some grants overlap two or more categories, and for evaluation purposes have been somewhat arbitrarily assigned.

General Organizational Grants

A growing gap between biomedical research and its clinical application has been recognized. The Markey Trust funded the following types of awards to provide training in translational research to diminish this gap: (1) programs that provided significant opportunities for M.D.s to engage in basic research during and immediately following medical school and residency and (2) programs that provided significant clinical exposure for Ph.D.s while they were predoctoral or postdoctoral students. General Organizational Grants were funded for approximately five years and were not renewable.

Markey Scholars and Visiting Fellows Awards

The Trust adopted several mechanisms to fund selected scholars early in their careers. The two most important were (1) the Scholar Awards in Biomedical Sciences with which 113 Markey scholars were supported for up to three years of postdoctoral training followed by five years of support as a junior faculty with both salary and research funding provided and (2) the United Kingdom and Australian Visiting Fellows awards, which supported outstanding young scientists from the United Kingdom and Australia who spent two years as postdoctoral fellows at U.S. research institutions.

Research Program Grants

Research Program Grants were designed to enable established investigators to address important issues in the biomedical sciences through development of new approaches or expansion of continuing approaches to the study of basic biomedical research questions. In some instances the awards permitted new program development or the complete reorganization of existing programs. In other cases the awards enhanced existing programs and research endeavors.

Assessing the General Organizational Grants Program

This report assesses only the General Organizational Grants program. Future reports will assess the Markey Scholars and Visiting Fellows program and the Research Program Grants. Unfortunately only the Markey Scholars program lends itself to a data-driven comparison with another group. Formal evaluation was not built into the planning for the heterogeneous awards that constitute the Markey Trust programs. The Committee is well aware, therefore, of the limitations that are intrinsic to rendering judgments based on information that can be collected by such activities as site visits and workshops.

The Committee used several approaches to assess the General Organizational Grants Program: (1) a workshop titled "Training Programs in Patient-Oriented Pathobiology for Basic Scientists," which brought together six awardees who had provided translational training to Ph.D. scientists; (2) site visits to grant recipients who had provided training in basic research to young physicians; and (3) Committee-commissioned papers by Irwin Arias and by Leon Rosenberg and Tim Ley to provide context to the issue of training in translational research. This report is based on information that emerged from the workshop, site visits, commissioned papers, as well as other sources.

The Committee's Conclusions and Observations

The Committee finds that expert review is the only feasible approach to assessment of the General Organizational Grants program. Strong General Organizational Grants funded by the Markey Trust had six characteristics in common.

1. Leadership and collaboration that bridge the basic and clinical sciences among academic departments;
2. Mentoring, including dual mentors, to bridge clinical and basic sciences;
3. Identification of competitive candidates to recruit the best trainees;
4. A defined, carefully structured program with attention to elements of training, defined course work, mentorship, networking opportunities, and research experience;
5. Protected time for the physician trainees; and
6. Sustainability of some programs with either internal or external funding.

Based on these observations the Committee drew several conclusions about the impact of the Markey Trust's method of operation.

- The terms of Mrs. Markey's will have been fulfilled through the vision and focus of the trustees. Over $500 million was distributed to fund biomedical research in a 15-year period.
- The funds were distributed appropriately for training and organizational change.
- The Markey Trust took funding risks with potential rewards, and many of them paid off through institutional changes and better training opportunities.

In addition, the Committee was able to generalize about the effect of the General Organizational Grants.

- The Committee simply could not evaluate the General Organizational Grants program quantitatively because of the heterogeneity of its central theme and the absence of more stringent data reporting. In the future, funders should build such evaluation processes into their grants.
- Despite the above limitations the Committee strongly felt that this program was an invaluable asset to participating institutions.

About half of the General Organizational Grants awardees continued to operate Markey-supported programs after external support was completed. These large, up-front, and flexible funds provided the "venture capital" that was critical to long-term success. Moreover, these programs were able to use Markey funds to leverage other sources of funding.

There is still a strong national need to "bridge the bed-bench gap" between biomedical research and its clinical application. The Markey awards contributed importantly to this effort and helped maintain an awareness of the problem over the past two decades. In the long run, however, a larger effort, funded by the federal government and philanthropies in partnership, will be required to address the critical issue more fully. Fortunately such initiatives are now under way.

Introduction

Assessment and evaluation in the world of philanthropy often take a back seat to ongoing programs. Funders may argue that money spent on evaluation is money taken from grants that could be distributed. Indeed, philanthropic and charitable organizations can maintain the status quo quite comfortably because in the eyes of their trustees current operations appear to be working well, and there is no need to fix something that is not broken. On the other hand, when programs and award structures of philanthropy are evaluated, useful information can be generated to guide future decision making.

The Markey Trust distributed over $500 million in support of basic biomedical research in just 15 years. At the end of its existence the Trust has asked whether its grants were well spent and whether its mode of philanthropy could be an effective model for other organizations. The Markey trustees asked the National Research Council of the National Academies for such an evaluation. The Committee for the Evaluation of the Lucille P. Markey Charitable Trust Programs in Biomedical Science,[1] with the assistance of the staff of the Board on Higher Education and Workforce, is evaluating the results of the Trust's philanthropy: General Organizational Grants, Markey Scholars and Visiting Fellows Awards

[1]The Committee for the Evaluation of the Lucille P. Markey Program in Biomedical Sciences is the proper name of the NRC committee that will assess the Markey Trust's activities. Hereafter it will be referred to as the "Markey Committee" or the "Committee."

program, and Research Program Grants. To do this the Committee used multiple approaches that varied according to the program being examined. For example, the Markey Scholars program lends itself to in-depth evaluation, but other programs could not be rigorously studied because of the lack of outcome data, the variety and differences of programs supported, and the long-term horizon for basic research.

This is the first of a series of reports that will document the activities of the Markey Trust. Additional reports will assess the Markey Scholars and Visiting Fellows Awards programs and Research Program Grants. Just as each of the Markey programs varied in terms of goals and focus, so will the Committee's approach to assessment and evaluation. For example, the evaluation of the Markey Scholars program will be prospective and will be conducted with greater methodological rigor than this assessment of the General Organizational Grants programs and the Research Program Grants. This report on General Organizational Grants programs (as well as the future report on Research Program Grants) relies on expert judgments and the information gathered in site visits and a workshop, which do not allow for analytical approaches. This report is organized into several sections and a set of appendixes, beginning with a history of the Markey Trust and its grant programs. It continues with a discussion of the methodological issues related to evaluating the Markey Trust programs as a whole and its General Organizational Grants in particular. It presents descriptions of the 22 General Organizational Grants programs. The report concludes with potential lessons-learned for funding organizations and individual philanthropists. Two appendixes contain commissioned papers on the biomedical research environment, descriptions of training programs in clinical research sites visited by the Committee, descriptions of the training programs in translational research at six universities invited to the Workshop on Training Programs on Patient-Oriented Pathobiology for Basic Scientists, and the workshop agenda and associated materials.

History of the Markey Trust

Lucille P. Markey executed her will creating the Lucille P. Markey Charitable Trust[2] in 1975. Mrs. Markey's wealth, which later endowed the Trust, was derived from the family of her first husband, Warren Wright. In 1888 with an initial investment of $3,500 Warren's father William Wright founded the Calumet Baking Powder Company, which he built over the ensuing decades into the leading company in the industry. In the late 1920s Warren sold Calumet to Postum (later General Foods) for about $32 million. This fortune, along with Calumet Farm purchased by the elder Wright in 1924, was the foundation of the Wrights' wealth, the bulk of which passed to Warren. When Warren Wright died in 1950, his estate was valued at approximately $20 million, with about half in securities and a quarter in oil and gas interests, which would appreciate significantly in later years (Auerbach, 1994).

One of the valuable Wright-owned oil fields was the Waddell Ranch located outside Odessa, Texas. Under typical oil lease arrangements the lessor—in this case Gulf Oil Company—paid all costs and received seven-eighths of the proceeds, while the property owner received one-eighth. In 1925 Gulf Oil leased the Waddell Ranch for 50 years, which was unusual because most oil leases are for perpetuity or as long as the land is productive. The leases expired in 1975 following the oil embargo and consequent

[2]The Lucille P. Markey Charitable Trust is the institution's official name. In this report it will be referred to as "the Markey Trust" or "the Trust."

rapid increase in oil prices. Through a series of court cases Gulf fought to have the leases extended at the old 1925 rate, but eventually Wright heirs and the other Waddell Ranch owners were victorious, and the income from the new leases, which were then part of Mrs. Markey's estate, increased dramatically. Before his death Warren Wright amply addressed the needs of his children through a trust arrangement. Mrs. Markey, subsequently married to Eugene Markey, decided that her estate would go either to charity or to taxes. She chose charities, but she was not interested in leaving her money to charity as broadly defined; she wanted something whose effects would be immediate and specific (Auerbach, 1994).

Mrs. Markey's decision to leave her estate to medical research evolved slowly. Her illnesses and those of Gene Markey caused her to be interested in research that could affect human health. Realizing that health research was a broad field, she asked Louis Hector, her attorney, to explore whether something more specific could be identified to guide the work of the charity. To learn more about charitable activities Hector visited the Robert Wood Johnson Foundation, which seeks to improve the health and health care of all Americans, and the Rockefeller University, which focuses on medical research. After hearing about the work of both institutions Mrs. Markey decided that the clinical aspects of health care were covered by other institutions, and that her estate should be dedicated to the promotion of biomedical research. Because of this decision the term "basic medical research" was inserted into her will.

> "It took her quite a while to wrap her mind around the idea of basic medical research," says Hector, "but once she did, that was it." The money, she decided, should go for square-one stuff, to solve the most elemental and perplexing puzzles (Fichtner, 1990).

Mrs. Markey began to respond to solicitations from a variety of local institutions. The following anecdote reveals how her giving began with the University of Kentucky:

> When Dr. Roach first approached Lucille Markey in the late 1970s for a contribution toward the construction of a cancer center on the campus of the University of Kentucky, she said graciously, "Of course, Ben, we'll help. We'll give you $1,000." In response, Gene Markey chimed in, "Dear, he doesn't want a thousand dollars, he wants a million." The next morning Mrs. Markey called Dr. Roach and said, "We're going to give you one million in cash for your center" (Auerbach, 1994, pp. 95-96).

She subsequently gave a number of gifts totaling $5.25 million to the Ephraim McDowell Research Foundation to build a cancer center at the University of Kentucky. In the years 1984 and 1985 the Markey Trust gave nearly $8.1 million to the University of Kentucky to continue programs she initiated before her death (Lucille P. Markey Charitable Trust, 1996).

After settling on a substantive focus for her trust Mrs. Markey determined that she did not want to create a permanent foundation that might change or drift away from her own mission. Rather, she wanted to disperse her estate quickly so that the work of the Trust would not change over time, particularly as trustees changed. Louis J. Hector, who became chairman of the Trust, once told *The Chronicle of Higher Education* that when he and Mrs. Markey were working out the details of the Trust, the heiress told him, "I want the money out there doing a job, and I think what the trustees ought to do is spend it in a reasonable amount of time and then shut down" (Nicklin, 1997).

Mrs. Markey limited the term of the Trust to 15 years and the number of trustees to five. Her decision was based on four guiding principles (Dickason and Neuhauser, 2000, p. 2).

1. She felt it was important to apply as much money as possible to achieving the Trust's purpose in as short a time as possible.
2. She wanted to know who would be involved in the management of the assets and distribution of her largess. She named five trustees, all of whom she knew well. Four of them were alive at her death and three continued to serve throughout the life of the Trust.
3. She wanted her money applied to grants, not to support a permanent bureaucracy.
4. She believed that the purpose and goals of any foundation could become obsolete over time; a time limit could help to prevent such obsolescence.

When Mrs. Markey died on July 24, 1982, the Lucille P. Markey Charitable Trust was incorporated as a Florida nonprofit organization with 501(c)(3) status. The initial meeting of the Board of Trustees occurred in October 1983, and the Trust's Miami office opened on January 1, 1984. The trust completed all activities on June 15, 1997.

Four trustees attended the initial 1983 meeting (Dickason and Neuhauser, 2000).

1. Laurette Heraty, who had served Mrs. Markey and her first husband, Warren Wright, in their Chicago office as a secretary since 1937. She retired from the board in 1989.
2. Louis Hector, who was Mrs. Markey's attorney and who drafted her will. He served as a trustee of the University of Miami, Rockefeller University, Lincoln Center, and is a member of the American Academy of Arts and Sciences.
3. William Sutter, an attorney and expert in oil- and gas-leasing

issues, who worked for Mr. Wright and Mrs. Markey from his Chicago office in the law firm of Hopkins and Sutter.

4. Margaret Glass of Lexington, Kentucky, who had worked so closely with Mrs. Markey over the years that she was seen as an effective custodian and interpreter of her wishes.

Two additional trustees were named during the life of the Trust.

1. George Shinn, a financial expert (elected to fill the position left vacant by the death in 1980 of Gene Markey) was president of Merrill Lynch & Co., chief executive officer of First Boston Corporation, and a member of the Board of Governors of the New York Stock Exchange; and
2. Robert Glaser, a physician with experience in both academic medicine and philanthropy (elected in 1989 following the retirement of Laurette Heraty), was director of medical sciences from 1984 until 1989. He was a past president of the Henry J. Kaiser Family Foundation and dean of the University of Colorado Medical School and Stanford University School of Medicine.

The structure and the function of the Markey Trust were guided from its inception by Louis Hector's vision of supporting and encouraging basic medical research. This vision was consistent and unwavering throughout the duration of the trust, and it guided the selection of grantees, advisors, reviewers, and funding mechanisms.

Dr. Glaser also played an important role in guiding the implementation of the Markey Trust programs. In 1984 he was asked to become the director of medical sciences for the Trust. Some of his initial recommendations included the idea of supporting basic (as opposed to targeted) research. "Medicine was going through an exciting period," Glaser recalled. "There were new fields like structural biology and developmental biology coming along and with substantial resources such as the Trust enjoyed, they could do a very important thing by offering support that was flexible to people and/or programs over a period of time" (R. Glaser, personal communication, 2002). Dr. Glaser also recommended that the Trust provide enough support to bright young people to allow them to have protected time to establish their research careers. His expertise and vision were to become the major force in the foundation.

The Trust began distributing funds in 1984 to institutions Mrs. Markey had supported during her lifetime. At the same time, the Trust began to plan a long-term strategy for its programs. In 1984 the Trust held a series of three "think tank" meetings with distinguished biomedical researchers in California, New York, and London. These sessions produced a number of recommendations, the most important of which was the idea of long-term financial support for postdoctoral fellows and young faculty members. In 1984 the Trust announced the creation of the Markey Scholars Awards in Biomedical Sciences, which became the Trust's best-known program. The initial cohort of Markey Scholars was appointed in February 1985. In the fall of 1985 the initial Research Program Grants were awarded. Later, in 1988, the Trust began making what would later be known as General Organizational Grants. Each of these award mechanisms will be discussed in greater detail later.

In 1985 most Trust activity ceased because of complicated litigation involving the pricing of natural gas. The litigation involved the Federal Energy Regulatory Commission, the California Public Service Commission, and a number of major oil and gas companies. The case was eventually settled in the Texas courts. During the two years of court proceedings the Trust funded no new research grants and was able to continue funding only the Markey Scholars program and a few small miscellaneous and related grants. During this hiatus the trustees continued to receive new grant proposals and were able to conduct selected site visits. The value of the Markey estate and trust grew substantially, benefiting from investment income as well as the continued oil and gas income. In the fall of 1987 the litigation was resolved and the Trust resumed awarding Research Program Grants.

During its 15-year lifetime the Markey Trust gave a total $507,151,000 to basic medical research and research training. Administrative costs amounted to $29,087,000 or approximately 5 percent of the total Trust. Additional expenses included $10,529,000 for direct investment costs and mineral depletion costs. The total value of the Trust was $549,520,000, which included $149,565,000 in investment income (Dickason and Neuhauser, 2000).

Grant Programs

The Markey Trust made awards in the three stages of a biomedical research career in which "supporting and encouraging basic medical research" can occur.

1. The General Organizational Grants sought to improve the education and training of Ph.D.s and M.D.s who were planning careers in biomedical research to better prepare them for basic clinical research and research in molecular medicine.
2. The Markey Scholars and Fellows awards supported outstanding younger researchers in the biomedical sciences and provided them with long-term financial assistance early in their careers.
3. The Research Program Grants provided funding opportunities for established scientists with proven records of excellence in biomedical research.

A few grants fell outside the above stages and are categorized as miscellaneous. The distribution of funding for all four programs is shown in Figure 1.

The Markey Scholars and Visiting Fellows awards and the Research Program Grants are briefly described below. They will be the subjects of later full-length evaluative reports.

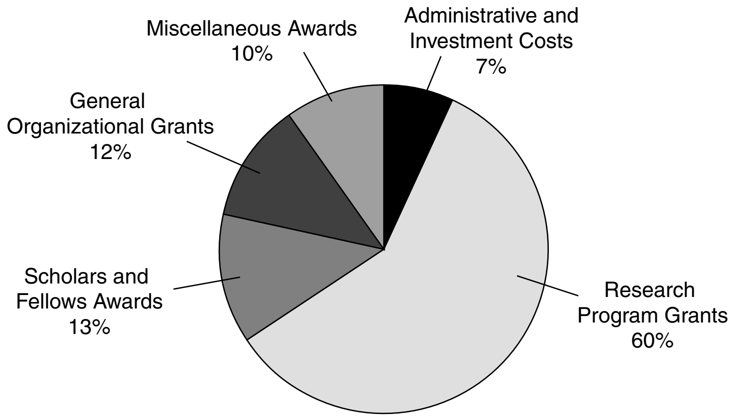

FIGURE 1 Distribution of Markey Trust programs and grant making.

MARKEY SCHOLARS AND FELLOWS

The Markey trustees recognized the importance of providing funding to young biomedical scientists as they launch their careers. The Trust dedicated $63,093,900 to fund the Scholar Awards in Biomedical Sciences and the United Kingdom and Australian Visiting Fellows.

Scholar Awards in Biomedical Sciences

By establishing the Markey Scholars program in 1984 the trustees recognized that top priority should be given to support young researchers as they moved from postdoctorate into junior faculty positions. The goal was to enable the scholars to conduct independent research early in their careers. Between 1985 and 1991, 113 Markey scholars were supported for up to three years of postdoctoral training, followed by five years as beginning faculty members. This support included both salary and research funding. Scholar awards ranged from $570,000 to $711,000, depending on the length of their postdoctoral experience. The Markey Trust was unique in providing support for young scientists for up to eight years. The total funding for Markey scholars was $59,795,900.

United Kingdom and Australian Visiting Fellows

The trustees also supported outstanding young scientists from the United Kingdom and Australia by enabling them to spend two years as postdoctoral fellows at U.S. research institutions. Thirty-six visiting fellows—26 from the United Kingdom and 10 from Australia—were selected between 1986 through 1994, and support amounted to $3,298,000.

Research Program Grants

The largest Markey awards in terms of funding amount and number of projects were the Research Program Grants. These grants were designed to enable investigators to address important issues in the biomedical sciences by developing new approaches or expanding continuing approaches to the study of basic biomedical fields.

A wide range of activities was funded through Research Program Grants, which could be used to fund predoctoral and postdoctoral stipends, renovation of laboratories, purchase of major equipment, and recruitment of additional staff.

Generally, grants were awarded for five years. Because of the limited term of the Trust, awardees were advised that the grants were not renewable. The Trust made 92 Research Program Grants between the years of 1986 and 1995 amounting to over $322,248,175. In 1996 the Trust made supplementary awards of $3,090,000.

MISCELLANEOUS AWARDS

During its tenure the Markey Trust made a number of awards that did not fit into the three major award categories. These awards continued the support provided by Mrs. Markey during her lifetime, funded endowed chairs, afforded scholarships to biomedical researchers, and funded related research support. These award programs, totaling $53,606,232, are listed below.

Lucille P. Markey Basic Medical Research Funds

To memorialize the Trust's support for the training of biomedical scientists, endowments totaling $14 million were made to seven institutions. These institutions established permanent endowments, known as the Lucille P. Markey Basic Medical Research Funds, to provide support for promising predoctorals, postdoctorals, and junior faculty.[3]

[3]These seven institutions were Harvard University; Johns Hopkins University; Rockefeller University; Stanford University; University of California, San Francisco; University of Michigan; and University of Texas Southwestern Medical Center.

Markey Predoctoral Fellows

In its early years the Trust provided $9.4 million to 15 academic institutions to assist predoctoral students in biomedical science programs. These graduate students were known as Markey fellows.

Other Grants for Career Development

The Trust provided $3,030,000 to six research institutes to fund summer seminars and short courses for potential scientists in basic medical research.

Continuation of Programs Initiated by Mrs. Markey

These awards were made in 1984 and 1985 to the University of Kentucky and University of Miami and totaled $8.7 million.

Endowed Chairs

Between 1985 and 1996 the Markey Trust provided $11.5 million to fund endowed chairs at seven universities.

Research Support and Related Grants

Between 1985 and 1997 the Trust provided $6,976,232 to fund 56 miscellaneous grants for support of smaller research projects and to encourage or facilitate basic medical research.

GENERAL ORGANIZATIONAL GRANTS

By the end of the 1970s a serious gap between fundamental biological research and clinical research had developed (Wyngaarden, 1979). The nation was no longer producing as many clinical researchers as it needed to translate the discoveries of biomedical science into practical medical practice, a problem experts referred to as the "bed-bench gap." These experts urged that more students be encouraged to pursue translational research. Trustee Louis Hector recognized this problem in the early stages of the Markey Trust. He had read seminal articles about this issue, including the James Wyngaarden article [1979]. The Markey Trust as it began operations confirmed the gap as it reviewed applications for scholarships and other research assistance.

In 1987 the University of California, San Francisco, proposed an extensive reorganization of its graduate programs in biomedical sciences.

Under this proposal the programs in biochemistry and molecular biology, cell biology, immunology, neurobiology, and genetics would be merged into a new Program in Biological Sciences. This was followed by an application from the Rockefeller University for a program to fund university fellows in developmental biology. Neither of these proposals was for biomedical research projects that the Trust normally funded; however, the Trust was interested in funding such proposals, and these two became the first of what were to become General Organizational Grants.

In 1989 the Trust held another "think tank" session during which input was sought from a number of biomedical scientists on directions for Trust funding during its remaining term. Workshop participants advised that there was general concern in medical schools about the bed-bench gap and that plans were emerging in many universities to develop new curricula and teaching techniques to close the gap.

The Trust decided to be responsive to proposals that sought to develop training programs designed to bridge the bed-bench gap. The Trust received a number of proposals that fell into two categories: (1) those that provided significant opportunities for M.D.s to engage in basic research during and immediately following medical school and residency and (2) those that provided significant clinical exposure for Ph.D.s while predoctoral or postdoctoral students. The first of these awards, also known as General Organizational Grants, was made in 1992. These grants were intended to close the widening gap between rapid advances in our understanding of biological process and the translation of that knowledge into techniques for preventing diseases (Lucille P. Markey Charitable Trust, 1995).

General Organizational Grants were funded for approximately five years, although many grant recipients were able to extend the grant's duration because of the flexibility of the Markey grants. Because of the limited term of the Trust, General Organizational Grants could not be renewed. Between 1988 and 1995 twenty-two General Organizational Grants were awarded, amounting to $62,121,700 as seen in Table 1. The average amount awarded was about $2.8 million, but award amounts ranged from $50,000 to $13,750,000.

General Organizational Grants were awarded using a tiered peer review process. It was not an open competitive process; instead institutions selected on the basis of their track record in biomedical research and training were identified by the trustees and were asked to submit applications. These applications were reviewed by the trustees and a committee of experts consisting of James E. Darnell, M.D., Gordon N. Gill, M.D., and James B. Wyngaarden, M.D. Applications were received from 45 institutions. Of these, 22 received awards. The trustees and selection committee

TABLE 1 Number and Value of General Organizational Grants Awards by Year

Fiscal Year	Number of Awards	Total Funded
1988	1	$13,750,000
1989	2	5,400,000
1992	6	20,371,700
1993	6	11,500,000
1994	6	11,050,000
1995	1	50,000
Total	22	$62,121,700

SOURCE: Data compiled from Lucille P. Markey Charitable Trust (1996).

requested that applicants prepare major revisions of nearly every proposal that was accepted, some extensively. For example, of the 22 award recipients 20 were asked to submit revised proposals. The funding level was reduced in 18 cases and increased in two cases.

Assessing the Markey General Organizational Grants Program

To assess the Trust's General Organizational Grants program the Committee examined separately those programs that provided (1) clinical research exposure to Ph.D.s trained in basic biomedical research and (2) training in basic research to medical school students or young physicians.

The training of Ph.D.s was the more innovative of the two approaches in terms of translational research; the Committee thus decided to concentrate on these training models. A workshop of program directors titled "Training Programs in Patient-Oriented Pathobiology for Basic Scientists" was convened to learn more about the successes and problems of these programs. This workshop, conducted in October 1999, brought together program directors from six institutions: Johns Hopkins University; Harvard University; University of California, San Diego; Washington University; University of Virginia; and University of Chicago. Irwin Arias of Tufts University made the keynote presentation (Arias, 2003). A description of all programs for training Ph.D.s is in a subsequent section of this report.

In addition, the Committee conducted a series of site visits to grant recipients who provided training in basic research to young physicians. These sites were selected because they represented a wide range of the types of programs that introduced physicians to basic research. The institutions—College of Physicians and Surgeons of Columbia University, Children's Hospital of Boston/Harvard University, and the University of California, San Francisco—highlight the rich variation in approaches taken by the institutions funded by Markey. A description of all programs for training physician-scientists is in a subsequent section of this report.

This report is based on information that emerged from the workshop and site visits as well as other sources. The Committee obtained detailed information on nine of the General Organizational Grants programs. Extant data were used for the remaining programs. The full range of sources includes

- a review of extant data on General Organizational Grants programs provided by the Markey Trust;
- a review of the literature (see References);
- the Workshop on Training Programs on Patient-Oriented Pathobiology for Basic Scientists;
- site visits to programs that provide training in basic research to physicians;
- oral history interviews of Markey trustees and executive staff;
- a commissioned paper, "Bridge Building Between Medicine and Basic Science," by Irwin Arias; and
- a commissioned paper, "The Endangered Physician-Scientists: Opportunities for Revitalization Emerge," by Leon E. Rosenberg and Timothy J. Ley.

Detailed information on the workshop and site visits, the two commissioned papers, and the membership of the Markey Committee is presented in the appendixes to this report.

LIMITATIONS TO THIS ASSESSMENT

This report does not attempt to evaluate the programs of the 22 General Organizational Grant recipients. First, the goals of the General Organizational Grants program remained relatively broad; for example, there was no request for application against which program activities could be judged. Second, the Trust allowed considerable latitude for funded institutions to modify program activities. Because many of the grants ended well before the beginning of this assessment and key training personnel had moved to other institutions, it was difficult to track these changes and their implications for expected outcomes. Third, because no explicit requirements were systematically imposed by the Trust for evaluation, the outcome data collected by grantees were limited and not systematically collected; in addition, for more recently funded programs an insufficient amount of time had passed for expected outcomes to occur. Fourth, institutions were selected for General Organizational Grants partially because of their track record in biomedical research and training. These institutions already had substantial extramural funding in biomedical research at the time of the Markey award. Therefore, it was difficult if not impossible to differentiate the impact of the Markey award from other funding. Not surprisingly these limitations helped to preclude the use of those evaluation designs needed to confidently link outcomes to the General Organizational Grants program (e.g., the appropriate use of comparison groups).

The Committee considered the possibility of identifying all students who participated in Markey-funded training programs and contacting them in order to monitor their careers. The Committee ultimately decided against that strategy for a number of reasons.

- The student selection criteria varied among the programs as did the goals of each of the programs. Consequently aggregating these data was not appropriate.
- Record keeping at host institutions was uneven, in some cases spotty and in other cases almost nonexistent, making it difficult if not impossible to identify and contact a significant number of trainees.
- No appropriate comparison group could be identified.

Consequently the Committee concluded that trying to identify trainees would tax resources and would not be productive. It decided that a general programmatic estimation by experts would be the only feasible approach to the assessment of the General Organizational Grants program. The one program funded by the Markey Trust that lends itself to a data-driven evaluation is the Markey Scholars program. This program had a clear goal that was defined by the Markey Trust in advance, so that a proactive outcome assessment of seven cohorts of Markey scholars with an appropriate comparison group is possible. The scholars were selected through a consistent, transparent system and were all at the same career stage at the time of funding. The Committee believes intensive tracking, monitoring, and data collection and analysis for the Scholars program is both feasible and the best use of the Committee's limited resources.

This report does provide an explanation of the Markey Trust's funding mechanism for the General Organizational Grants, a description of some of the best practices of the recipient organizations, and a summary of Committee insights to help guide other philanthropic funders.

The Biomedical Research Environment in the 1980s

Throughout the 1980s and 1990s many investigators continued sounding the alarm about the state of translational research. Like Wyngaarden, Gill (1984), Arias (1989), Hartwell (1992), Bunn and Casey (1995), Goldstein and Brown (1997), Shine (1998), and Nathan (1998), among others, expressed marked concern that a shortage of clinical researchers was endangering our nation's leading role in today's biomedical revolution. A shortage of clinical researchers was clearly contributing to a widening gap between those discoveries made in the basic science laboratories and the application of discoveries to conquer human diseases. Physician-scientists are key to bridging the gap since they relate to both human patients and laboratory research (Rosenberg and Ley, 2003).

In 1988 the National Institutes of Health (NIH) commissioned the Institute of Medicine (IOM) to assess the availability of resources for performing clinical research. That study committee found that the number of highly talented young medical school graduates pursuing careers as clinical investigators was declining. As many as 20 percent of clinical traineeships and fellowships were filled by individuals with the Ph.D. degree rather than the M.D. degree (Institute of Medicine, 1988). Following the release of the committee's report, *Resources for Clinical Investigation* (Institute of Medicine, 1988), the IOM convened a planning meeting to develop a strategy for exploring problems associated with clinical research training.

In the second half of the twentieth century the production of Ph.D.s in the life sciences increased substantially. In 1960 there were 1,160 doctorates awarded in the biological sciences (National Research Council, 1969); by 1999 that number had increased to 5,600 (Sanderson et al., 2000). In the past 20 years the advance of Ph.D.s into disease-oriented research has increased dramatically. In 1997 "the majority of principal investigators for clinical research projects supported by the NIH and the Agency for Healthcare Research and Quality held Ph.D.s (1,449) rather than M.D.s or M.D.-Ph.D.s (1,061)" (National Research Council, 2000, p. 42).

Despite the impressive numbers of Ph.D. scientists available to perform clinical research, the development of training programs that specifically prepare basic scientists for clinical research has been sporadic. Before 1980 there was practically no systematic instruction of basic scientists in disease-oriented research. In 1980 Harvard Medical School began offering a one-semester course in organismal physiology and disease mechanism to basic science students (Arias, 2003). During the 15 years between 1984 and 1998, 214 predoctoral students, and postdoctoral fellows, and faculty participated in the one-semester course. In 1984 Irwin Arias began training basic scientists at Tufts University in pathobiology as part of an effort to bridge the gap between basic science and its application to medicine (Arias, 1989).

Closing the Bed-Bench Gap

Against this background the Markey Trust began to dedicate some of its grants to programs offering innovative ways of training physicians to enable them to engage in basic biomedical and translational research and to expose Ph.D. scientists to disease-oriented research. Through the General Organizational Grants program the Trust requested proposals for two types of grants from selected institutions for training programs: (1) programs that offered significant clinical exposure for Ph.D.s during their student years and (2) programs that permitted M.D.s to engage in research during their years in medical school and residency.

The Trust's support of organizational grants began with two large awards to the University of California, San Francisco, and Rockefeller University that were intended to stimulate organizational change. A lawsuit interrupted dispersal of funds (see Introduction). When the Trust resumed its grant making the intention of the grants had changed from stimulating organizational change to supporting the training of physician-scientists. Grants changed from supporting the training of Ph.D. students to training both types of students.

The Trust funded a wide variety of training programs for M.D.s. These programs provided for intense research integrated into medical school curricula, offered protected time for research during residency, and developed refresher courses in basic science for M.D.s. In addition, the Trust funded several programs to provide basic clinical training for Ph.D.s. For both physician and scientist training programs the Markey trustees wanted to aim for the best candidates at the best institutions, but institutions differed in how they selected trainees.

General Organizational Grants programs were funded for approximately five years, although many grant recipients were able to extend the grant's duration. This section describes the kinds of programs supported by the Trust to enhance the workforce needed to address bed-bench gaps.

TRAINING PROGRAMS FOR PHYSICIANS

The Markey Trust provided funding to seven institutions that provided training in basic research to medical students or young physicians. These programs identified physicians at various stages of medical training and provided opportunities for them to receive intensive training in basic research.

The eight programs provided training and support to 132 physician-scientists during the 1990s. The total cost of these eight programs was $14.9 million and the average cost per program per year was about $317,000. There was a great deal of variation among the programs. One provided five years of protected time. Other programs provided stipends for a two- or three-year postdoctoral fellowship. One program offered an intensive summer program. Programs also varied in terms of the career stage of participants, duration of funding, and training strategies. The average cost was about $113, 000 per physician-scientist.

Descriptions of programs that provided training in basic science to physicians are presented below.

• **Children's Hospital Boston/Harvard University ($2,250,000 • 1993-1998).** The Markey Child Health Research Center program, co-directed by Philip Pizzo and Stephen Harrison, was aimed at providing research training for pediatricians. Pizzo believed that pediatricians were the most endangered group of physician-scientists. A total of 17 young pediatric investigators received fellowships for one or two years, depending on the availability of independent funding after the first year. Each fellow was assigned to a senior faculty mentor to assist in the training process. The focus of the program was on providing protected time for immersion into research.

• **The Rockefeller University ($2,500,000 • 1993-1998).** This grant, developed by Jules Hirsch, provided support for the Clinical Scholars program in molecular medicine to allow research experiences for physician faculty. The program established independent laboratories and training opportunities in research techniques and concepts of modern biology. Salaries and startup costs for two assistant professors and two medical fellows were funded.

• **College of Physicians and Surgeons of Columbia University ($2 million • 1993-1998).** The Career Tracks Program in Postgraduate Medical Education, codirected by Sharon Wardlaw and Christopher Schindler, received a $2 million award. The program was modeled after the successful Johns Hopkins National Research Service Awards program. Its goal was to provide research training and experience to talented medical school graduates early in their residency training. Fifteen fellows were selected for the two-year program after the second or third year of their house staff residency. During the research-training period residents continued to follow their own patients in the general medicine outpatient clinic in order to maintain their clinical skills.

• **Four Schools' Physician-Scientists Program in Internal Medicine ($3.5 million • 1991-2001).** Alfred Fishman was the coordinator of this program to develop physician-scientists in the departments of internal medicine at the University of Pennsylvania, Duke University, Washington University, and Johns Hopkins University. The four schools program introduced physicians to basic research in three phases. Phase 1 was a year of research following the third year of medical education. Phase 2 consisted of clinical research experience during residency. Phase 3 was two years of postgraduate research experience. Forty-six physicians completed the program.

• **Yale University ($2.1 million • 1993-1998).** This grant supported the physician-scientist training program in which physicians retooled over a three-year period. Training consisted of a six-month period of laboratory courses and 2.5 years of in-depth research supervised by mentors from both clinical and basic research departments. Developed by J. D. Jamison, the program provided exposure to basic research for 12 practicing physicians. Each summer the program conducted a two-week integrated lecture and laboratory program in molecular and cellular biology designed to reacquaint physicians with the basic science necessary to submit grant applications. This program attracted 20 to 30 participants annually.

• **University of California, San Francisco ($2.5 million • 1992-1999).** The Molecular Medicine program, directed by Marc Shuman, enabled 31 physicians who were just completing their residency to spend three years in laboratories of molecular medicine in the university's Program in Biomedical Sciences. In addition to research experience fellows also received extensive coursework in biochemistry, cell biology, and molecular genetics, ensuring that the fellows had a theoretical background comparable to that of graduate students in biochemistry.

• **Brigham and Woman's Hospital ($50,000 • 1994-1995).** Under the direction of Thomas Stossel this grant supported development of a summer training program for physicians who were beginning laboratory research training. The program focused on three two-week blocks consisting of biochemistry, molecular biology, and cell biology. Seven students participated full-time, all day for six weeks through lectures, journal clubs, and hands-on laboratory experience.

To gain a better understanding of how these programs worked and their impact on biomedical science training, the Markey Evaluation Committee chose to visit three programs that were representative of this type of General Organizational Grant: University of California, San Francisco; College of Physicians and Surgeons of Columbia University; and Children's Hospital, Boston/Harvard University. Detailed site visit reports for these programs are presented in Appendix F. Unfortunately lack of outcome data on the trainees prevented a deeper evaluation although the Committee believes the support of such training programs is worthy of philanthropic attention. Future funders of graduate training programs should ensure that a comprehensive program evaluation and prospective monitoring of outcomes is an integral part of the overall design of project. The approaches taken in many of the training programs, especially those that provided an extended and in-depth experience in research, are still in use in many academic centers. The value of flexible and generous dollars in resource-constrained times was noted by leaders of these programs during site visits. Summaries of these site visits are in Appendix F.

TRAINING PROGRAMS FOR PH.D. SCIENTISTS

The Markey trustees funded 12 programs that provided clinical experience to basic scientists. These are listed below. These new experiments attempted to determine whether Ph.D.s with a better understanding of clinical problems could better alleviate the ongoing decline of physician-scientists. One program, at Stanford University, subsequently changed its focus from clinical to basic research. Of the remaining 11 programs the programs at Tufts University and Rockefeller University were already under way when they received Markey grants, having been started in 1986 and the 1970s, respectively. The remaining programs were newly created with Markey Trust funds.

These 12 programs provided training in patient-oriented pathobiology to 430 basic scientists during the 1990s. These programs varied greatly in form and content, ranging from highly structured four-year programs to single summer courses. In addition, programs offered training to a wide variety of scientists including undergraduate and graduate students, postdoctoral fellows, and young faculty. The total cost for the 12 programs was \$39.2 million. The average cost was about \$552,000 per program per year and about \$60,000 per participant.

A brief description of each of these programs is presented below.

• **Tufts University School of Medicine ($400,000 • 1989-1996).** This program, built around coursework in pathobiology, has basic scientists at the graduate school and postdoctoral level analyzing 20 major human diseases. The students study gross and microscopic pathology, observe major diagnostic procedures, witness specialized patient care such as renal dialysis and transplantation, and participate in clinical rounds. The Trust provided funding for 105 students. The program at Tufts is ongoing and continues to produce scientists versed in disease-oriented research. Outcome data provided by Arias (2003) show that trainees are working in research jobs, many in clinical departments.

• **Washington University School of Medicine ($4 million • 1992-1999).** This grant, directed by Alan Schwartz and Jeffrey Saffitz, provided support for the establishment of the Special Emphasis Pathway in Human Pathobiology. The program provided clinical exposure to 33 predoctoral and 18 postdoctoral scientists through a series of courses that focused on a specific disease. In addition to participating in three courses each graduate student or postdoctoral fellow had dual mentors. The clinical mentor had the role of integrating students into the culture and practice of the hospital. This program has been maintained through the combined efforts of the 19 departments in the biological sciences that provide support amounting to about $200,000 per year.

• **Harvard Medical School ($4 million • 1992-1996).** This project, directed by Franklin Bunn, emphasized the concept of "New Pathways" and the restructuring of biomedical scientist training. Interaction between biomedical scientists and student physicians was stressed. Ph.D.s received a master's degree in medical science. In addition, the program was concerned with career outcomes of Ph.D.s and focused on placing Ph.D.s into clinical departments. A total of 57 students participated in the program.

• **University of California, San Diego ($2.5 million • 1992-1997).** This program, developed by George Palade, supported the development of graduate studies in cellular and molecular biology. The program focused on inter-institutional training at the UCSD School of Medicine, the Research Institute of Scripps Clinic, the Salk Institute, and the La Jolla Cancer Center (Burnham Institute) for 89 UCSD graduate students.

• **University of Virginia ($800,000 • 1993-1997).** This program, directed by Michael Webber, was designed to prepare scientists to study the molecular basis of human diseases and to facilitate the interaction between clinical and basic scientist researchers. The program, which used a dual-mentor approach for four students per year (a total of 20 students), consisted of one year of course work followed by two years of blended clinical and laboratory experience.

• **Stanford University ($900,000 • 1993-2001).** This grant was intended to enable medical school faculty to develop a new Ph.D. program in molecular mechanisms of disease under the direction of Michael Lieber, a Markey scholar. Because of changes by which graduate student tuition could no longer be reimbursed at universities and the financial difficulties common to all private medical schools, the program as intended became financially untenable. Consequently Stanford received permission from the Markey trustees to use the award to support Ph.D. students in existing interdepartmental programs whose work focused on the studies of human disease. These students were under the direction of Joseph Lipsick and Michael Cleary. Ten students were funded for two years each.

• **University of Chicago ($3.2 million • 1993-1998).** The grant, directed by Nancy Schwartz, provided support for a new Ph.D. program in molecular medicine. The program recruited graduate students to focus on the biology of human disease using a dual mentor approach. The program was part of a new interdisciplinary biological science complex with clinical and basic science components. Thirteen scientists participated in the program that bridged the gap between basic science research and its relevance to human biology and disease processes.

• **Johns Hopkins University ($3.2 million • 1994-2000).** This grant, directed by Thomas Pollard and Peter Agre, developed a cross-departmental program in cellular and molecular medicine. Students took course work in biochemistry, cellular and molecular biology, neuroscience, human genetics, and physiological and pathological basis for human disease. Trainees had access to research opportunities in basic science and access to clinical faculty with joint appointments. There were over 450 applicants to the program and 43 graduate students participated. The Johns Hopkins program was able to redefine its orientation so that it received a training grant from the National Institute of General Medical Sciences of the NIH.

• **Carnegie Mellon University ($1.4 million • 1994-1999).** This grant supplemented National Science Foundation-funded support for the Science and Technology Center. The program provides training in advanced technology and equipment for nine young faculty members in basic sciences, five postdoctoral scientists, four graduate students, one computer engineer, and two technicians. This program anticipated the interdependence of modern medicine and technology. The primary areas of emphasis included structural and developmental biology, computational biology and chemistry, microscopy and imaging technology, and in vivo imaging. Lansing Taylor was the program director.

• **University of Cincinnati ($50,000 • 1995-1996).** The program on pathobiology and molecular medicine was developed to encourage and foster the performance of translational biomedical research by graduate students and was modeled after Irwin Arias's program at Tufts. Gregory Retzinger, a Markey scholar, used funding from the Markey Trust to develop the course in pathobiology of disease taught by the departments of pathology and laboratory medicine (taken by eight graduate students). Intramural funding has allowed this approach to translational research to continue.

- **University of California, San Francisco ($13,750,000 • 1988-1995).** Under the leadership of Michael Bishop, the Markey award, combined with funds from other sources, was used to fund an extensive reorganization of the graduate programs in biomedical sciences. Under this proposal the programs in biochemistry and molecular biology, cell biology, immunology, neurobiology, and genetics were merged into a new program in biological sciences. Unlike the other General Organizational Grants this award was used primarily to restructure the programs in biomedical research and included a component to provide medical experience for graduate and postdoctoral students. Most of the funds were used for equipment, supplies, and construction.
- **Rockefeller University ($5 million • 1989-1993).** Markey Trust funds supplemented the University Fellows program, originally developed in the 1970s. University fellows were mature scientists with at least three years of postdoctoral experience and established research agendas. Thorsten Wiesel directed the program. Markey Trust funds supported 13 university fellows as assistant professors and included salary support, equipment, supplies, and renovation. Four of the university scholars were also Markey scholars and seven subsequently became Howard Hughes Medical Institute investigators.

The directors of six of these programs participated in the National Research Council-sponsored Workshop on Training Programs in Patient-Oriented Pathobiology for Basic Scientists in October 1999. These directors presented detailed information on the overall description and history of their program, the program's efforts to bridge the bed-bench gap, characteristics of applicants and students in the program, and a summary of program finances. Summaries of the presentations of each of the six programs are presented in Appendix E.

TRAINING PROGRAMS FOR BOTH PH.D. SCIENTISTS AND PHYSICIANS

The Markey Trust funded three programs that provided training in translational research for both physicians and scientists. A wide variety of predoctoral, postdoctoral, and young faculty received funding from these hybrid programs. A total of $6.4 million was expended to cover the stipends of 55 scholars. The cost was $320,000 per program per year, or about $116,000 per fellow. A brief description of these programs follows.

- **University of Utah ($2 million • 1994-1999).** This grant supported an expansion of the program in human molecular biology and genetics, an interdepartmental effort to strengthen the interface between clinical and basic investigators. The goal was to provide protected time, a five-year research experience without interruption for six M.D. and Ph.D. young faculty. While the majority of funding was restricted to faculty salaries, a significant proportion of funding (about 30 percent) was for equipment. Stephen Prescott and Raymond White were the co-principal investigators.
- **Cornell University Medical College and Memorial Sloan-Kettering ($2.4 million • 1994-2000).** This grant supported multidisciplinary training in both institutions. Trainees included 10 Ph.D. candidates, 10 M.D. postdoctoral fellows, and 6 M.D./Ph.D. physician-scientists. The goals of the program were (1) to train a new generation of scientists to be competent to perform modern molecular and cell research and possess the knowledge to identify and address questions related to human disease and (2) to create an environment that enabled laboratory scientists with expertise in basic biology to interact regularly with investigators who approach research from a disease-oriented perspective. This program was delayed due to external factors; the initial cohort of students arrived in 1995. The majority of funding was directed toward salaries. Marvin Gershengorn and Richard Rifkind were the principal investigators and, because of the flexibility of funding, were able to extend the program several years.
- **Emory University ($2 million • 1994-2000).** This program established a new department in neurosciences. While it was more research oriented than the other General Organizational Grants, the focus of funding was on the development of the Center for Neurological Sciences. The grant provided stipend support for M.D./Ph.D., M.D., and Ph.D. postdoctoral fellows, junior faculty, and visiting scientists in neurodegenerative diseases, movement disorders, psychiatric syndromes, and epilepsy and stroke through shared courses, seminars, and grand rounds. Eighteen postdoctoral and two predoctoral fellows, three junior faculty, and one visiting faculty was supported by Markey Trust funds. The co-principal investigators were Donald Humphrey and Jeffrey Houpt.

The Current Biomedical Research Environment

Notwithstanding the efforts of the Markey Trust and other funding entities to bridge the gap between rapid advances in our understanding of biological process and the translation of that knowledge into techniques for preventing diseases, concerns remain about the preparation and numbers of the workforce for conducting clinical research. Leon Rosenberg (1999) in the second annual Shannon Lecture at the NIH called on the NIH, the Howard Hughes Medical Institute, and other organizations concerned with scientific training to create and expand attractive training programs for medical students, M.D./Ph.D. students, postdoctoral fellows, and junior faculty.

The NIH had already begun addressing the systemic and institutional issues surrounding the bed-bench gap before Rosenberg's charge, creating in 1995 the NIH director's Panel on Clinical Research. The Panel, which included 14 physicians from academia and industry, released a report in 1998 (Nathan, 1998) calling for new programs, new resource allocations, and policy changes to encourage physicians to undertake careers in patient-oriented clinical research. Both federal and private funders have responded to the Panel's recommendations. Immediately upon the report's release, the NIH created K-23 awards for mentored patient-oriented research career development and K-24 midcareer investigator awards in patient-oriented research (National Institutes of Health, 1998). In the first two years these award programs attracted 452 research grant applications, the majority from M.D. investigators. In response to the call for new training programs in clinical research, the NIH K-30 awards provide funds for curricular development at 55 institutions across the United States. In late 2001 the NIH announced its Clinical Research Loan Repayment program, which repays educational debts of investigators who are conducting patient-oriented research (National Institutes of Health, 2001).

Concurrently the collective investment in the career development of clinical researchers from the private sector has more than doubled since 1997. The total annual commitment has risen from $37 million to $78.5 million among a group of 11 private foundations and voluntary health agencies (Egan et al., 2002). Most striking is the foundation group's response to the Panel's recommendations at the level of the new investigator, where the annual dollar commitment has tripled since 1997 and now stands at $29.7 million per year. Foundation awards at this level have incorporated features designed to counteract the disincentives for physician-scientists to enter careers in clinical research, such as loan repayment, more generous funding, longer award terms, and portability. The Howard Hughes Medical Institute announcement in June 2001 specified that its next cohort of investigators would include only physician-scientists who were pursuing careers that integrated direct patient contact with biomedical research (Howard Hughes Medical Institute, 2001).

Despite the diversity and magnitude of these efforts, several areas still remain in critical need of support (Rosenberg and Ley, 2003; Zemlo et al., 2000). Examples are additional research fellowships for medical students that involve debt prevention, recruitment of underrepresented minorities into clinical research careers, and training of Ph.D. researchers in translational research (Gray and Bonventure, 2002).

The federal government currently provides the bulk of funding for basic biomedical research at academic institutions. The President's fiscal year 2003 budget for the NIH, the largest source of such dollars, totals $27.3 billion (Government Printing Office, 2003). Research-based pharmaceutical companies invested $30.6 billion in R&D in 2001, but only about 5 percent of those dollars go to basic biomedical research and almost nothing goes into translational training programs. In 1999 about 73 percent of R&D expenditures at universities and colleges came from the federal government, 9 percent came from industry, and 9 percent from philanthropy. Private philanthropists might wonder what can be accomplished with the substantially fewer private-sector dollars, but in fact, as noted by Kenneth Shine (American Cancer Society et al., 1998), "America's leadership in health science research can be greatly attributed to the creative synergism of public and private support of the research enterprise." While industry makes the greatest financial contribution, most of its support goes for the downstream development of products. Federal government funding, while the main source of money for biomedical research in universities, is largely for support of the research of individual investigators, with fewer dollars available for training or infrastructure investments, for risky research, for emerging areas of science often at the interfaces of fields, or for the training of translational researchers. Philanthropic dollars can provide the risk capital for the biomedical enterprise by providing flexible dollars for innovation, for training in translational research, and for supporting undervalued or emerging areas of research. The Markey Trust provides one example of how charitable dollars can support translational research.

Conclusions and Observations for Philanthropic Funders

Private philanthropy has an important role to play in biomedical research. All interviewees at site visits and recipients of Markey Trust awards noted the enormous benefit of flexible and generous philanthropic awards, funds that were not available from other sources.

In 2000, 56,582 foundations made grants totaling $27,610,000,000 (Foundation Center, 2002, p. 50). Grant dollars for medical research were in excess of $842 million dollars in that year, but more dollars might be available if a good case could be made for the value of private investments in biomedical research. Wealthy individuals contributed in addition more than $160 billion in charitable giving in 2001 (AAFRC Trust for Philanthropy, 2002), only a fraction of which went to biomedical research. The Markey Trust is a good example that could be used to encourage additional private contributions in this area.

Markey Trust charitable contributions to biomedical research had the following attributes:

- Awards were restricted to biomedical research and training.
- Funds were dispersed over a 15-year period in a limited-term trust.
- Administrative costs were minimized to less than 5 percent of the Trust's total assets, placing most of the dollars into grant making rather than staff monitoring and ongoing program management.
- Awards were not prescriptive and award administration was flexible, leaving institutions and awardees to make such decisions as how to spend funds and the length of time for the award.

- Awards were not open to all institutions but were restricted to a list developed by the trustees based on their view of the research environments in institutions. These institutions were then invited to apply for General Organizational Grants.
- Invited proposals were peer reviewed. The Markey Trust adopted a multilayered system to review the General Organizational Grants. First, Markey administrative staff screened the proposals to ensure that they were within the scope of the request, were complete, and were worthy of further consideration. Second, Robert Glaser, the Trust's medical director, reviewed applications to assess the feasibility of the research and the appropriateness of the proposed budget. Finally a panel of renowned scientists, including members of the National Academy of Sciences or the Institute of Medicine, reviewed the applications.

In general, award amounts were relatively large so as to produce an impact on institutional behavior, facilitate organizational change, and enable training programs to be established. Long-term viability was the goal, and it was often achieved through the leverage of additional funds from other sources once the Markey seed money was in place. For example, the first two General Organizational Grants awards were made to the University of California, San Francisco, for $13,750,000 and to Rockefeller University for $5 million. The training grants awarded to programs to provide research exposure to young physicians were typically $2.5 million. Awards to provide clinical exposure to Ph.D. scientists were somewhat higher, with some awards reaching $5 million.

The most innovative programs went to institutions that created new approaches to providing Ph.D.s with experience in clinical research. In the words of Irwin Arias (2003), "The goal is to have Ph.D. graduates who can function in the interface between basic science and disease and collaborate with physician-investigators who work in the interface between the patient and basic science." The Committee urges that other private funders consider this as an area for grant making.

Evaluation of the projects was complicated by several factors. The Committee found that these programs could not be definitively evaluated because the funded programs did not have similar objectives, approaches, or attributes. Progress reports that were required by the foundation did not have a required format so that the reports were not consistent, varying considerably in length, precision, and amount of detail. Most importantly the programs were not required to track or monitor the progress of trainees beyond the completion of the program so that the lack of outcome data limited the Committee's ability to assess the success of different training approaches. Future funders of graduate training programs should ensure that a comprehensive program evaluation and prospective monitoring of outcomes is part of the overall design of the project. The Committee was, however, able to assess the long-term viability of programs and how the viable programs were funded. Over half of the programs continued operation beyond the five years of Markey funding—three of the six programs that were evaluated at the workshop and two of the three programs whose sites were visited. During these site visits and at the workshop, program staff stressed the importance of large front-end funding to firmly establish the program. Moreover, continuing programs leveraged other sources of funding (e.g., NIH and intramural funds).

Listed below are attributes common to many of the strong programs funded by Markey. Most of these elements were identified through the site visits and the workshop that was convened to consider the training programs for Ph.D. students. These observations represent the Committee's observations following an examination of Markey records, the site visits, the workshop, and Committee members' collective experiences and are not based on objective data. All General Organizational Grants recipients were not visited nor were all participants in the workshop. The Committee's observations emphasize the experiences of the recipients whose sites were visited or who attended the workshop. These elements of successful programs may seem almost self-evident and have been identified by other reports, but the Committee believes it is useful to list them to guide future investments in training or organizational change.

Leadership. Programs that require collaboration among departments and that bridge the basic and clinical sciences must have strong institutional leadership by department chairs and deans to enable organizational change to occur.

Mentoring. Successful training is dependent on the presence of excellent mentors. Dual mentors (one a basic scientist, the other a clinician scientist) may be crucial for both physicians and Ph.D. scientists who train in translational research.

Identification of Candidates. A competitive process and early identification of excellent candidates are essential to recruiting the best trainees.

Defined Program. A carefully structured program with attention to elements of training, defined course work, mentoring, networking opportunities, and research experience was found in programs that the Committee considered to be excellent

Protected Time for the Physician Trainees. Time must be protected from the additional responsibility of patient care if the physician-scientist is to obtain sufficient training to enable him or her to compete with their Ph.D. colleagues in research productivity.

Sustainability. As expected, training programs that have endured were able to obtain funding to continue from other sources or from their institutions. For training grants five years of support may not be sufficient time for outcome data to demonstrate the efficacy of the program. Philanthropies that fund training programs should consider longer periods of support. This could be done by combining large front-end levels of support with partnering with other potential funders from the beginning or by working with the institution on plans for the sustained support of the programs when grant dollars end.

Several Trust training programs have been sustained after Markey funds were depleted (e.g., both programs at the University of California, San Francisco; Washington University in St. Louis; and Columbia University College of Physicians and Surgeons, all of which tailored their programs to emphasize translational research). Johns Hopkins University developed a new degree program that concentrated on translational research and has succeeded in obtaining extramural funding from the NIH. In these four programs the Markey award was a catalyst in changing the focus of training for a cadre of students. Tufts University had established their program in translational research before receiving Markey funding. This program is ongoing and continues to produce scientists versed in disease-oriented research.

Funds to sustain these programs have come from different sources. For example, intramural funding is used at Washington University and the programs at the University of California, San Francisco; endowment funds have been channeled into the program at Columbia University; and extramural funding has been obtained by Johns Hopkins University. The Committee recognized that for many of the recipient institutions the Markey award was one of a number of training grants awarded from a wide range of funding sources. When Markey funds were expended and not renewed, the institution turned to other sources to continue the training of graduate students or physicians, in some cases reflecting the new goals of the follow-on funder.

The NIH and a number of philanthropic organizations have made major new investments in training and sustaining physician-scientists both to develop new investigators and to retain existing investigators in research. Because these are new programs, no outcome data are available. On the other hand, few if any funders have attempted to support training for Ph.D.s to better translate basic science into clinical applications.

Based on the findings above, the Committee can draw several conclusions about the operations of the Markey Trust.

- The terms of Mrs. Markey's will were fulfilled through the vision and focus of the trustees. Over $500 million was distributed to fund biomedical research in a 15-year period.

- The funds were distributed appropriately for training and organizational change.
- The Markey Trust took funding risks with potential rewards, and many of them paid off in the form of institutional changes and better training opportunities.

Concerning the General Organizational Grants program, the Committee simply could not evaluate the General Organizational Grants program quantitatively in view of the heterogeneity in its central theme and the absence of more stringent reporting of the necessary data. In the future, funders should build such evaluation processes into their grants.

Despite the above limitations, the Committee was strongly of the subjective opinion that this program was an invaluable asset to the participating institutions.

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Appendixes

A

Bridge Building Between Medicine and Basic Science[1]

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Vieles ist bekannt, aber leider in verschiedenen Kopfen.
Much is known, but unfortunately in different heads.

W. Kollath

I have been asked to review issues surrounding the gap between basic sciences and their application to human disease, describe the history of and relative success of approaches taken to bridge this gap, and develop scenarios for ways to enhance medical research in light of the changes occurring in training in the biomedical sciences and the provision of health care. These issues will be discussed largely based on my experiences as professor and associate chairman of the Department of Medicine at the Albert Einstein College of Medicine, where I was a physician-scientist for 28 years, followed by what is now my fifteenth year as chairman of the Department of Molecular and Cellular Physiology at Tufts University School of Medicine. Having lived on both sides of the proverbial academic street influences my perspective on the issues to be reviewed.

This is an exciting time to be involved in biomedical research. The opportunities to solve longstanding disease-related problems are greater than at any time in the past due to the amazing conceptual and technical

[1]The author wishes to thank many colleagues, particularly Samuel Silverstein, Ezra Lamdin, and Lyuba Varticovski, who provided valuable information, discussion, and critical review.

advances in biologic science that have occurred in the past 50 years. Furthermore there is every indication that advances will continue at an increasing rate. For example, the genome project is providing a new language and dimension for the study of physiology and disease and is already responsible for elucidation of the molecular basis of many acquired and inheritable diseases. The next area appears to be the combination of molecular, computational, and structural biology and imaging to understand the integrated function of organs and organisms. Even the mysteries of the brain are becoming accessible for study in cells, organs, and patients. Regrettably there is an increasing gap as a consequence of the seemingly exponential rate of acquisition of new information and the arithmetic rate of its application to medicine. This gap became apparent in the 1970s (Wyngaarden, 1979), and continues to widen. Because it is an obligation of medical science to solve longstanding disease-related problems, bridging this gap is arguably the major challenge confronting biomedical research. In order for medicine to progress there is need for physician-scientists who understand clinical medicine and for basic scientists who can effectively communicate and collaborate with them.

Several years ago Sir James Black was asked, "What is the biggest challenge in biology today?" His response was, "The triumph of physiology over molecular biology." The genome project will give us a book, but learning to read it and understand what all its entries signify is the challenge of a lifetime, possibly several lifetimes. Thus, organismal physiology is the biggest challenge ahead in both basic and clinical research. The problem is who will accomplish this task, and why, given today's incredible opportunities, are we having such a difficult time bridging basic science with medicine?

This review will consider the following:

1. Major factors that produce the gap.
   - Basic science advances exceed the ability of medical schools to incorporate them into student and postgraduate programs.
   - Decline in the number of physician-scientists.
   - Ph.D. students and graduates infrequently interact with physician-scientists and have comparatively little understanding of pathobiology.
2. Bridging the gap requires multiple approaches.
   - Making science and research more available to medical students and residents.
   - Attracting and training physicians in research.
   - Expanding and modifying combined M.D./Ph.D. degree programs.
   - Training Ph.D. scientists in pathobiology.

THE GAP BETWEEN BASIC SCIENCES AND MEDICINE

The concept that federally funded research was in the public's best interest began during World War II when problems such as malaria, bacterial and viral infection, and trauma resulted in mobilization of the nation's scientific community. Vannevar Bush and others promoted the view that the country would benefit from federally funded research to be performed in university laboratories (National Science Foundation, 1960). However, it was the leadership and wisdom of James Shannon that resulted in postwar growth of basic science at the National Institutes of Health and of basic science departments in the nation's medical schools (Farber, 1982). In part influenced by the Flexner report (1910) the Shannon model was based on the concept that diseases will be cured only when science produces fundamental understanding of physiology and pathophysiology.

Federal funding converted U.S. universities and medical centers into research-intensive institutions. Physician-scientists and basic scientists flourished, as did scientific interactions between them. The extraordinary accomplishments of this so-called golden era of medical research have been extensively reviewed (Comroe and Dripps, 1976; Goldstein and Brown, 1997; Healy, 1988; London, 1964). Research laboratories were often built adjacent to clinical facilities to facilitate exchange between basic and clinical investigators. Becoming a physician-scientist was a highly sought goal and it was realistic to plan a career in which one could be a productive investigator, expert clinician, and outstanding teacher. Many Ph.D. scientists held joint appointments and worked collaboratively in clinical and basic science departments. The result was a homogeneous culture predicated on the premise that laboratory and bedside were interdependent as well as indissolubly linked.

By the 1970s, however, there were troubling signs. Despite the steady advances in basic science and clinical research, laboratory technologies were becoming more complex, budgets for research and training were reduced in real dollars, and a new rule (the payback provision) became a further deterrent to clinical research. In 1979, based on study of NIH grant applications for research and training, James Wyngaarden, who later became director of the NIH, was the first to express concern publicly about the declining interest in research on the part of medical students, house officers, M.D. postdoctoral fellows, and young faculty (Wyngaarden, 1979). In an article in the *New England Journal of Medicine* he predicted that because the academic pipeline (i.e., the time required for training prior to acquiring an academic position) was about eight years at that time, the effects he observed would not be fully manifested for another decade, which proved to be the case.

In 1984 Gordon Gill observed that physician-scientists were attracted to the power and comparatively simpler systems of molecular biology and consequently were abandoning patient-oriented research. He presciently commented, "It seems ironic that a separation of functions (i.e., science and medicine) occurred when physicians became scientists and when the work of basic scientists became clinically relevant, but such is the case, and there is no going back . . . the paths will not again merge" (Gill, 1984).

Indeed, over the ensuing 15 years the trend has increased and has now reached crisis levels (ASCI, 1998; Feinstein, 1999; Goldstein, 1986, 1999; Goldstein and Brown, 1997; Healy, 1988; Healy and Keyworth, 1985; Nathan, 1998; Rosenberg, 1999). Between 1992 and 1997 there was a 51 percent reduction in the number of NIH postdoctoral traineeships awarded to physicians—from 2,613 grants to 1,261 (Zemlo and Garrison, 1999). If this trend continues unabated, there will be no physicians in the postdoctoral pool by the year 2006! The irony is that physicians are not entering patient-oriented research at a time that provides the greatest opportunities for research into the cause, mechanism, prevention, and treatment of major diseases.

Many factors are responsible for the steady decline in the number of physician-scientists that contribute substantially to the gap. These factors have been discussed in several important articles (Goldstein and Brown, 1997; Healy, 1988; Healy and Keyworth, 1985; Nathan, 1998) and most recently by Leon Rosenberg in his Shannon lecture (1999). The major factors are agreed to by all who have considered the problem.

- Increased financial indebtedness of medical graduates pressures them into practice and away from the risk and uncertainties of an academic career. According to the AAMC Graduation Questionnaire of 1999, medical school graduates who were indebted had an average debt of $90,000; over 13 percent of them owed $150,000 or more, and those who attended private schools owed an average of $109,000.
- When the prolonged postgraduate training period for specialty boards is added to the time needed for training in scientific skills, 10 years may be required after medical school graduation. Fledgling physician-scientists are well into their thirties before entering the academic world.
- It is considerably more difficult today for a physician to acquire the training needed to enter a career in biomedical research than it was in the 1960s. One reason is the inadequacy of postgraduate training in medical research, as revealed by NIH outcome data (Arias, 1989; National Research Council, 1994; Nathan, 1998; Zemlo and Garrison, 1999). Few medical specialty training programs include obligatory courses in basic sciences; basic scientists infrequently serve as preceptors; and mechanisms

for establishing collaboration and teamwork between basic and clinical scientists are neither identified nor widely fostered. Training in basic science demands additional time, dedication, and temporary detachment from clinical activities. Joseph Goldstein and Michael Brown suggested that M.D.s and M.D./Ph.D.s should gravitate to a career in basic science because of the seductive perception that basic science research is easier to perform successfully than is clinical research (Goldstein and Brown, 1997) and is sustained by technological breakthroughs (e.g., cDNA clones, cell lines, recombinant proteins, and monoclonal antibodies), which are readily available for application to study cellular processes in health and disease.

In reality it is increasingly difficult for an academician to be expert in each of the traditional components of the three-legged academic stool: clinical medicine, teaching, and research. With the exception of a small number of individuals who aspire to achieve this role the vast majority of physician-scientists inevitably choose one path or another but not the hybrid form.

- Increasing competition for research funding has progressively decreased the number and proportion of physician-directed research grants. Throughout a nearly 30-year interval the rates at which M.D. and Ph.D. applicants have been awarded NIH grants have been virtually identical, but physician-scientists have become a progressively smaller minority of those seeking and obtaining NIH project support (Zemlo and Garrison, 1999). The actual number of first time M.D. applicants for NIH research projects decreased by 31 percent from 1994 to 1997, without a compensatory increase in applications from M.D./Ph.D.s. Rosenberg (1999) noted that if this progression were to continue linearly, there would be no first-time M.D. applicants by the year 2003!
- Dramatic changes in the health care system, largely the advent of managed care, have shortened hospitalization periods, increased patient turnover, and de-emphasized the value of research and innovative teaching by accelerating the pace at which physicians work in a clinical setting. These changes have imposed financial constraints on all academic health centers. To accommodate for financial shortcomings clinical faculties are pressured to see more patients and earn more of their income from clinical practice, thereby accelerating a cycle that reduces research and teaching time and thus the investigator's competitiveness for acquiring research funding.
- From an educational standpoint public emphasis over the past 30 years that physicians should be directed more into primary care than into medical specialties, has resulted in changes by academic leaders in curriculum, student selection, and other clinical programs. According to Rosenberg (1999) this "ha[s] not been balanced by the equally important

message that improving health of the public requires more research in which physicians must be key participants."

All these factors have diminished the image of the physician-scientist professor as role model and thereby have contributed substantially to decreasing the number of physician-scientists and to widening the gap between advances in basic science and their application to human disease.

PROPOSALS TO BRIDGE THE GAP

Federal agencies and private foundations are considering numerous proposals to ameliorate the continued decline in number of physician-scientists, such as recruitment, debt reduction and long-range support for competitively selected physician-scientists, and training programs in clinical research, including clinical trials, epidemiology, and outcome analysis (ASCI, 1998; Goldstein, 1999; Nathan, 1998; Rosenberg, 1999; Zemlo and Garrison, 1999). Changes in the attitudes of medical school leadership and curriculum committees to enhance incorporation of advances in science into teaching and to provide research opportunities for medical students are being encouraged.

THE ROLE OF M.D./PH.D. PROGRAMS

Combined M.D./Ph.D. programs (Medical Science Training program, MSTP), begun under the auspices of the National Institute of General Medical Sciences in 1964, now involve 130 medical schools and encompass 500 students per year (Kornfeld, 1999; NIGMS, 1988). In contrast to the initial MSTP programs, which were entirely supported by NIH, the majority of MSTP students throughout the country are currently supported by private funds. Stuart Kornfeld reviewed the experiences at Johns Hopkins; Harvard; University of California, San Francisco; Chicago; Pennsylvania; Stanford; and Washington University schools of medicine (Kornfeld, 1999). In general, the results were similar in each program. The average time to graduation was 7.8 years. The duration of training was further increased because 95 percent of graduates took a clinical residency. Because MSTP students often spend four to five years in residency programs, they commonly require additional postdoctoral research training in preparation for faculty positions and competitive grant proposals. Approximately 75 percent of MSTP graduates in Kornfeld's study acquired academic positions and slightly less than 20 percent were in medical practice or industry. Almost 85 percent of graduates were engaged in research that was classified as basic and less than 10 percent were performing research classified as clinical. Although MSTP programs have proven to be successful in providing outstanding basic science-oriented physician-scientists, the training period is long (making a quick fix to the current crisis in physician-scientists unlikely) and the costs are high. In addition, given that the major objective of medical schools is to train physicians, there are limits to expanding the number of applicants who are accepted into an M.D./Ph.D. program per year. For example, currently at Washington University School of Medicine, 15 percent of all medical students are M.D./Ph.D. candidates. Because most M.D./Ph.D. graduates perform basic research, increasing their numbers, although desirable for other reasons, does not directly address the problem of increasing clinical or translational research. Thus, MSTP programs are important parts of the bridge linking basic science and human disease but cannot be considered as the sole or major component.

THE ROLE OF PH.D. SCIENTISTS IN BIOMEDICAL RESEARCH

In the late nineteenth and early twentieth centuries pathology and physiology were the dominant medical research disciplines. Major important advances were often based on clinical observations and came from chemists, some of whom were also trained as physicians. For example, Pasteur and Ehrlich attended pathology sessions and conferred with clinicians and their patients. Before World War II, medical institutions in Europe did not offer Ph.D. degrees, which accounts for the fact that the early twentieth-century leaders in biochemistry, such as Krebs, Myerhoff, Lipman, the Coris, Ochoa, and many others, were trained as physicians before becoming scientists. Increased congressional funding for biomedical science after World War II resulted in the establishment of medical school basic science departments, which increasingly produced Ph.D. graduates; in contrast to the prewar European tradition they received little or no training in pathobiology. The decline in physician-scientists began simultaneously with increased progress in basic biologic sciences. Ph.D. scientists continue to make critical contributions to the understanding of disease; however, because of the increasing pace of scientific accomplishment and the decline in physician-scientists, the gap is progressively increasing.

Many clinical investigators contributed to basic science by identifying key problems as well as by making original discoveries, and basic scientists have made discoveries that profoundly changed clinical practice. In 1964 Irving London commented on this distinction: “The essence of fundamental investigation lies not in whether it is done in a preclinical or in a clinical department or on a ward. It is rather the quality of the question which is asked and the quality of the experiment which is designed to answer the question that determines whether research is fundamental in character (London, 1964)." In those days what were limiting were more often ideas than funding or even space. Research training for physician-scientists could be accomplished in two to three years and Ph.D. scientists were relatively abundant in clinical departments where they usually held joint appointments in basic science departments. Even medical grand rounds were frequently shared between clinical and basic scientists who discussed patients and their illnesses.

All components of this seemingly idyllic existence have changed. Since the 1970s the gap between basic science and medicine has increased largely because science has become more complicated. Clinical scientists have greater difficulty in applying these advances to disease and basic scientists are needed. Many problems are so complex they exceed the ability of traditional clinical scientists to deal with them; others are less complex but necessitate collaboration between basic and clinical scientists. Unfortunately most basic scientists have little knowledge of pathobiology or clinical medicine; therefore, it is logical that basic scientists should learn enough pathobiology to attack disease-related problems in collaboration with physician-scientists. Ph.D. scientists cannot replace physician-scientists in performing clinical or translational research.

The goal is to have Ph.D. graduates who can function in the interface between basic science and disease and collaborate with physician-investigators who work in the interface between the patient and basic science. Achieving this objective is made more difficult because training in basic science is usually absent from the third and fourth year medical school curriculum and from postgraduate residency programs.

TRAINING PH.D.s IN PATHOBIOLOGY

As in a structural bridge there are many components to bridging the gap between the advances in basic science and disease. Virtually all efforts to bridge the gap have been based on the premise that "biomedical research is tightly linked to physician manpower" (Healy, 1988; Healy and Keyworth, 1985; Rosenberg, 1999; Wyngaarden, 1979). Most notable are M.D./Ph.D. programs and public and foundation efforts that are directed at students at every academic level. One approach that has not received much attention concerns the role of Ph.D. students, fellows, and graduates.

Almost every basic science department in our medical schools has a graduate program. Based on an ongoing poll of 372 graduate students in two leading institutions, 97 percent of the students chose training in a medical school rather than in a university because they sought careers that impact on human health. More often than not their graduate training was highly focused and not different from what could have been obtained at a university. A survey of 98 Ph.D. graduates who spent over six years in great medical centers revealed that the majority of the graduates had little knowledge of basic mechanisms of pathology, how their research related to organ physiology or pathophysiology, or what constitutes research in a clinical setting. In addition, their career directions were virtually the same as those of students who received a Ph.D. from university basic science departments. More than 90 percent of students graduating from medical school basic science programs sought the same goals as did graduates of university-based graduate programs in biology or chemistry, namely, stable positions in basic science departments, research institutes, or industry. Interest in pathobiologic mechanisms had severely waned and knowledge of disease processes, including pathology, diagnostics, and therapeutics, was deficient. It is not uncommon for such graduates, despite their research brilliance and ability, to be unable to describe what, for example, inflammation, necrosis, or fibrosis look like, let alone what they may feel like to a patient. The reason is that few graduate programs teach pathobiology, and many thesis advisers in basic science departments have little knowledge and interest in disease mechanisms or clinical problems.

These students are unaware of the changing scene in academic clinical departments and the increasing opportunities for Ph.D.s graduates to have productive careers in clinical departments. Longstanding academic problems regarding the role of a Ph.D. scientist in a clinical department are slowly changing primarily as a result of the decline in physician-scientists. In many institutions Ph.D. graduates are not attracted to a primary academic appointment in a clinical department because their scientific independence and academic tenure are limited or nonexistent. One of my students succinctly described the situation: "You work *for* and not *with* a physician." As research funding for physician-scientists declines and advances in basic science continue, medical centers are under increasing pressure to restore research efforts and solve the academic problems associated with recruitment of basic scientists into clinical departments. As will be apparent in data to be presented later, a 1989 proposed scenario has proven to be at least partially correct: "According to this scenario basic scientists who have been trained in pathobiology will have an exciting opportunity for productive careers in clinical departments" (Arias, 1989).

Literature search reveals two brief published letters but no detailed commentaries on the teaching of Ph.D. scientists in biomedical research before the 1970s. The major reason is that before the increasing gap the problem, if it existed, was not of major concern. There were some exceptions. Irving London's 1964 presidential address to the American Society for Clinical Investigation described the excitement of basic research, its importance to medicine, the reciprocal and interactive relationship between basic science and medicine, and anticipated some problems that could result from the increasing complexity of science (London, 1964).

In 1979 Morris Karnovsky observed that graduate students at Harvard, although outstanding in their knowledge of basic science, knew comparatively little about organismal physiology and disease mechanisms (M. Karnovsky, personal communication, course in pathology and pathophysiology at Harvard Medical School, 1980). With support from the Josiah Macy Foundation, Karnovsky created a one-semester course that during the subsequent five years accommodated approximately 50 graduate students from institutions in the greater Boston area. The course involved lectures on histology, the general basis of pathology, and reactions to injury in major diseases. Gross and microscopic specimens were frequently demonstrated. Participants reviewed and discussed original basic and clinical research papers. The course was successful and continued for five years, at which time funding ceased. Further support was not forthcoming from other foundations, industry, or the university. No formal outcome studies were performed, but Karnovsky recalls that attendance was full, enthusiasm was high, and many students wrote that the course changed their career interest to pathophysiology (personal communication). This novel course tapped into the unfulfilled interests of Ph.D. graduate students in a medical center. Although these interests have not diminished with time, I am unaware of other similar academic ventures from the late 1970s until 1984.

In a 1989 article in the *New England Journal of Medicine* I proposed that Ph.D. students, postdoctoral fellows, and faculty receive training in pathobiology as part of the effort to bridge the gap between basic science and its application to medicine (Arias, 1989). A one-semester course in pathobiology for Ph.D. students, fellows, and faculty was described. Colloquially it may be said that the goal of the course was to demystify medicine for Ph.D. students, fellows, and faculty members. There are several unique features to the course.

- Participants see patients, handle pathologic specimens, and are exposed to most of the major diagnostic and therapeutic facility in a modern hospital.
- Clinical and pathology sessions regarding approximately 20 major diseases are followed by Socratic-style analysis of the related basic biologic problem (e.g., growth control, autoimmunity).
- Students are given substantial reading material for analysis, but the course is intended to elicit their enthusiasm, long-term interest in

pathophysiology, and understanding of where basic science and disease intersect.

- The course is available to all graduate students, fellows, and Ph.D. faculty at Tufts and is heavily oversubscribed. It is limited to 15 individuals at a time when a larger group would make the clinical activities impossible. The group invariably consists of seven or eight second- to sixth-year graduate students in different graduate programs, three to five postdoctoral fellows mainly from an NIDDK Training Grant in Molecular and Cellular Pathophysiology, and one to four basic science faculty, visiting faculty from institutions seeking to replicate the course, or biotechnology or pharmaceutical company scientists. Heterogeneity in the group has been important to group dynamics and learning.

Outcome data are available because the course has been given for 15 years and we have followed all participants. The results are encouraging and unambiguously support the desirability of such activities. From 1984 to 1998 there were 214 participants in the course; 151 were graduate students, 42 were postdoctoral fellows, 13 were Ph.D. basic science faculty, and 8 were biotechnology and pharmaceutical industry scientists. By 1998, 88 individuals had completed all postdoctoral training and entered the academic arena. Twenty-seven (30 percent) have tenure-track positions in basic science departments, mainly in medical schools; 38 (40 percent) have responsible pathobiology-oriented positions in leading biotechnology and pharmaceutical companies, and 23 (25 percent) have tenured track positions in medical school clinical departments throughout the country. The departments and the distribution of graduates include medicine (15), parasitology (2), pathology (4), neurology (1), and pediatrics (1). The represented divisions in departments of medicine and the number of graduates are endocrinology (2), cardiology (1), gastroenterology (3), pulmonary (2), hematology-oncology (3), infectious disease (2), and immunology (2). Only 3 graduates who completed postdoctoral training are not currently working in science, 2 of which are recent mothers! Each of the 8 biotechnology scientists who participated in the program directs a major human disease research effort. Six Ph.D. faculty who participated in the program subsequently acquired NIH grants in collaboration with physician-scientists in clinical departments.

The course has been funded progressively by the Josiah Macy Foundation (1984-1988), Lucille P. Markey Charitable Trust (1989-1996), a Boston-based private foundation (1997-1999), various private donors, and a NIDDK Training Grant in molecular and cellular pathophysiology. Aside from stipends provided by the training grant, the annual cost is $ 60,000, which is largely spent for supplemental support for graduate students, supplies, printing, and administrative assistance. Nineteen institutions in the United States, Canada, and Europe have expressed interest in our program and 11 have begun similar activities.

Karnovsky's course at Harvard and our experience at Tufts played a part in influencing the leadership of the Lucille P. Markey Charitable Trust to support additional programs in pathobiology. From 1992 to 1996 the Markey Trust supported eight other programs that specifically seek to bridge basic science and medicine by instructing basic scientists in pathobiology. As described in this volume (Bunn and Casey, 1995; Lucille P. Markey Charitable Trust, 1996), each program has a different orientation and composition. Most involve additional time in graduate school, some provide degrees (M.S. or Ph.D.), all provide student stipends and some include clinical demonstrations. The Tuft's program is unique in that the duration of graduate school training is not increased, gross and microscopic pathology are presented, and selected patients are seen in a clinical setting. Participants also become acquainted with most major diagnostic and therapeutic facility in a modern medical center.

Unfortunately funding by the Markey Trust ended in 1998, and there is little outcome data on graduates of the other eight programs. Of greater concern is that despite the demonstrated need for and interest in demystifying medicine for many Ph.D. scientists, no other major funding source has assumed the mantle for sustaining and encouraging further development of this important component in our academic bridge or for performing outcome studies of existing programs. Whereas outcome evaluation of basic and clinical scientific studies is required for their continuing support, outcome evaluation of educational and training programs invariably lacks support from government agencies and private sources.

Several other graduate programs, such as Edward Kravitz's course at Harvard Medical School on the pathobiology of neurologic disease (E. A. Kravitz, personal communication, 1989), have created disease-oriented courses for their students and fellows. The general format involves lectures, which are often supplemented by presentation of patients and discussion of their illnesses. The goal of these programs has not been to direct Ph.D. scientists into clinical studies but to demonstrate how the fundamental research they are engaged in is relevant to human disease.

It is hoped that with increased awareness of the need to rejuvenate clinical investigation, there will be accompanying efforts to benefit from recent experiences regarding the training of Ph.D. scientists in pathobiology. Our experience does not indicate that Ph.D. scientists can replace physician-scientists in the study of human disease, particularly at the clinical level. However, Ph.D. graduates are important struts in the bridge that links basic science and medicine, and their incorporation into the process seems timely and long overdue.

CONCLUSIONS

Bridging the increasing gap between advances in basic science and their application to medicine requires changes in the training of both basic scientists and clinical investigators. The following conclusions regarding the education and training of physicians are based on a personal assessment of available published data and commentaries by others:

- Premedical students should be advised that quantitative skills in biology, chemistry, and mathematics are increasingly required for careers in research or in medical practice.
- Medical school teaching should be restructured to make research opportunities more readily available for students and residents and provide teaching of scientific advances throughout the curriculum. Greater selectivity in courses should be provided for medical students who are seriously interested in research.
- Reconsider the timing, duration, and number of M.D./Ph.D. programs to make them more efficient and productive.
- Revitalize physician-scientist recruitment and training by addressing the problems that contribute to the gap.

The following conclusion regarding the training of Ph.D. students and scientists is based on our outcome data:

Encourage and support programs to train Ph.D. students and fellows in pathobiology. Ph.D. students in medical school graduate programs seek careers that bridge with human disease, however, most students graduate with little knowledge of human clinical disease or pathology. Changes in medical research and the decline in physician-scientists create exciting opportunities for Ph.D. graduates to work with but not for physician-scientists as tenure track faculty in clinical departments. The bridge between advances in biological science and medicine has many components, including pathobiologically versed Ph.D. scientists who supplement but do not replace physician-scientists or clinical investigators. Pathobiology programs for Ph.D. students and fellows meet student and society's needs, are a good investment, and should be encouraged and supported nationally.

Bridge building in biomedical research has parallels with a structural bridge, which serves as a useful metaphor (Shapiro, 1983). Both require many different kinds of parts, each of which is essential for proper function. Bridge traffic is bidirectional. Once it has been erected, life on either side of the bridge is no longer as it was. The challenges inherent in both bridge building and maintaining its integrity transcend the merely structural. Meeting those challenges requires imagination, dedication, creativity, and a willingness to take risks.

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B

The Endangered Physician-Scientist: Opportunities for Revitalization Emerge[1]

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In 1979 Wyngaarden wrote that physician-investigators (now generally called physician-scientists and defined as M.D.s or M.D./Ph.D.s whose principal professional activity is research) were an endangered species (Wyngaarden, 1979). This conclusion was based on an examination of trends at the NIH concerning postdoctoral research fellows, research-career-development awardees, and research-project-grant-principal investigators. Only now, more than 20 years later, has this prescient albeit unwelcome truth been widely accepted. No single publication or lecture overcame the denial and dismissal of Wyngaarden's message. Rather, it has taken work by several individuals (Ahrens, 1992; Gill, 1984; Goldstein and Brown, 1997; Rosenberg, 1999, 2000; Schechter, 1998; Thompson and Moskowitz, 1997; Williams et al., 1997) and an impressive number of organizations, including the Institute of Medicine (Kelley and Randolph, 1994), the NIH Director's Panel on Clinical Research (Nathan, 1998), the National Research Council's Committee on National Needs for Biomedical and Behavioral Research (NRC, 2000), the American Medical

[1]A number of individuals generously provided us with information for this report: Marc Horowitz, Ruth Kirschstein, Burton Shapiro, and Judith Vaitukaitis of the National Institutes of Health; Andrew Quon of American Association of Medical Colleges; Carl Rhodes of the Howard Hughes Medical Institute; and Hui Wen Chan and Tamara Zemlo of the Federation of American Societies for Experimental Biology.

Association (AMA, 1996), the Association of American Medical Colleges (AAMC, 1999), and the Federation of American Societies for Experimental Biology (Zemlo et al., 2000) to achieve consensus that a serious problem exists.

EVIDENCE FOR ENDANGERMENT

There are threats to the physician-scientist career path throughout its length and breadth.

- During the 1990s there was a progressive, statistically significant decline in the intention of matriculating and graduating medical students to pursue a research career. This decline was noted at the most research-intensive medical schools as well as those with less research activity. A distinctly smaller fraction of female students, who now constitute about 49 percent of all medical students, expressed stronger research intentions than did their male counterparts (Guelich et al., under review).
- During the 1990s progressively fewer M.D.s obtained postdoctoral research training positions from NIH (Rosenberg, 1999). This conclusion was reached by summing all of NIH's training mechanisms for M.D.s (T32, F32, K04, K08).
- In the past several years there has been a decline in the number of first-time M.D. applicants for research project grants, a trend not observed for M.D./Ph.D.s or for Ph.D.s (Rosenberg, 1999).
- M.D.s constitute a progressively smaller fraction of members of chartered NIH review panels, a trend that has been ongoing for 20 years (Zemlo et al., 2000).
- There has been a progressive shift toward older age of M.D. principal investigators supported by NIH. In 1977, 56 percent of NIH principal investigators with the M.D. degree were less than 45 years old. In 1997 this fraction had fallen to 44 percent (Zemlo et al., 2000).
- Since the 1970s the number of Ph.D.s applying for NIH grants has grown much faster than the number of M.D. applicants. Whereas M.D.s and M.D./Ph.D.s made up 43 percent of NIH principal investigators in 1970, they account for less than 30 percent now, despite having a success rate indistinguishable from that for Ph.D. applicants (Rosenberg, 1999; Zemlo et al., 2000).
- The total number of physicians engaged in research has declined over the past 15 years, while the total number in practice has increased dramatically; the percentage of all physicians engaged in research has, therefore, decreased sharply over this period of time (Zemlo et al., 2000).

TWO GENERAL MECHANISMS FOR BECOMING A PHYSICIAN-SCIENTIST

The historical pathway to becoming a physician-scientist is the postdoctoral (or "late bloomer") one. These M.D.s become seriously interested in research during their clinical residency (two to three years) and subspecialty years (two to three years). This interest is then pursued during an additional three to six years devoted exclusively, or nearly so, to laboratory, patient-oriented, or epidemiologic study. In contrast, the second pathway starts at medical school matriculation, when candidates enroll in combined M.D./Ph.D. programs leading to receipt of both degrees in seven to eight years.

These pathways differ in many ways other than when the career choice is made. First, the late-bloomer pool remains far larger than that of the M.D./Ph.D.; M.D.s still account for about 70 percent of physician-scientists serving as principal investigators on NIH research project grants. Second, M.D./Ph.D.s generally complete their formal education with a much smaller debt burden than do those with an M.D. degree only, because M.D./Ph.D students usually receive tuition and stipend support from the NIH or other agencies. Third, the kind of research these two groups do tend to differ. M.D./Ph.D. students frequently perform their thesis work in basic science departments, which are naturally focused on basic research. Their initial research topic is often not influenced by clinical experiences. M.D. postdoctoral candidates, on the other hand, generally select a research topic based on their own experience with sick people. This results in a far higher fraction of late bloomers being engaged in disease-oriented and/or patient-oriented research. Fourth, the number of people seeking the M.D./Ph.D. route is growing, whereas the number of late bloomers is declining, making this subset the truly endangered one.

WHY PHYSICIAN-SCIENTISTS MATTER

How important to the health of the public is this endangerment of physician-scientists? What is the proof that they matter? A definitive answer to these provocative questions could be obtained by permitting physician-scientists to disappear over the next generation and then assessing the impact on health research, health care, and health status. We hope this Swiftian knockout experiment will be rejected in favor of reasoned arguments.

First, physician-scientists continue to make major contributions to health research. If one takes the Nobel Prize in physiology or medicine as the ultimate emblem of scientific distinction, M.D.s have done well, garnering about 50 percent of all such awards during the past 50 years. Let us mention just a few of the discoveries these Nobelists and others have made. Physician-scientists doing basic or disease-oriented research have discovered oncogenes, the low-density lipoprotein receptor, prions, HIV, pulmonary surfactant, and the genes responsible for cystic fibrosis and Huntington's disease. Those doing patient-oriented or epidemiologic investigation have pioneered in the eradication of smallpox; the near eradication of polio; the cure of childhood leukemia, Hodgkin's disease, and testicular cancer; the development of open heart surgery and of organ and bone marrow transplantation; and the elucidation of means to decrease mortality due to heart attacks and strokes. Based on this past performance there is every reason to expect that physician-scientists will make equally important contributions in the new millennium.

Second, whereas medical school education is not aimed at teaching one how to obtain scientific *answers*, it is the ideal place to raise a wide range of *questions* about health and disease that can be answered only through basic or applied research. It is the questions that physician-scientists ask because of their involvement with sick patients that distinguish their approach to research, and that make them critical members of the health research workforce. These questions should be even more robust in the postgenomic era, and more capable of being answered.

Third, the bridge between bedside and bench depends on bidirectional traffic and communication. Physician-scientists are in an ideal position to communicate and collaborate with Ph.D. scientists on one side and with health care providers on the other. They can make the strongest case for the clinical relevance of basic research to legislators, advocates, and health agencies. Without physician-scientists the bridge will weaken, perhaps even collapse. This would have serious implications for the funding of health and medical research because the public supports such investments in the hope of securing longer, healthier lives—they want to see science translated into cures. The public supports medical science not for what it is, but what it is for.

REASONS FOR ENDANGERMENT

Why is the physician-scientist career path in decline just when scientific opportunities to diagnose, treat, cure, and prevent disease have never been greater? This paradox has many explanations, which affect all participants in the pathway and all stages of development. College students interested in medicine are too often advised that they can become either a physician or a scientist but not both unless they are superstars who can be accepted by the M.D./Ph.D. programs at medical school, which enroll only about 2 percent of all medical students. Medical school admission committees reinforce this view in that they tend neither to try to recruit students with experience or interest in research nor to indicate that it is plausible and exciting to be a physician *and* a scientist. Thus most matriculating medical students focus exclusively on becoming clinicians.

The opportunity for medical students to try their hand at research varies widely. A few schools require all their students to conduct a research project and to write a doctoral thesis. At such schools as many as 50 percent of medical students take a year out to do research, but these patterns are the exception, not the rule. Most students at most medical schools have no research experience. They graduate with a great deal of information about sick people and a great deal of debt, now averaging nearly $90,000. After graduation, exposure to research depends on the specialty chosen and even more the subspecialty. These are the critical years for the late bloomer. Such individuals require lengthy, rigorous research experience equivalent to a Ph.D. in either laboratory, patient-oriented, or epidemiologic research. Too often the subspecialty fellowships provide scientific training that is too narrow, too abbreviated, and too superficial to provide a foundation for a long research career. Too often the stipends are insufficient to meet individual or family responsibilities and repay enormous medical school loans.

For those intrepid enough to soldier on and achieve faculty status, the challenges continue, and perhaps grow even larger. One must have protected time to establish an independent research program, usually at least 75 percent of effort in the first three to five years. Such protection is required to obtain research grant funds and build a team. Such protection is now very difficult to find in clinical departments, particularly in this era of managed care with its resultant demands to see more patients so that the clinical earnings that most departments depend on will be maintained. Once having risen to the status of an established investigator with advanced faculty status, it remains necessary to obtain and re-obtain external funds from NIH or other sponsors in an environment that is extremely competitive.

The emotional and structural barriers just described are daunting. If we are to revitalize the physician-scientist career path and refill the human pipeline, these barriers must be lowered or better still, removed, so that the decisions made by would-be physician-scientists will be tilted toward the great excitement they can have doing science in the name of health.

EMERGING OPPORTUNITIES

We are encouraged by a series of recent developments aimed at offering incentives and removing disincentives.

• The Clinical Research Enhancement Act, signed into federal law in 2000, finds that "clinical research is critical to the advancement of scientific knowledge and to the development of cures and improved treatment for disease." It provides for "increasing the involvement of the NIH in clinical research." Among its many provisions the Act directs the NIH to establish a broad extramural loan repayment program (LRP) for M.D.s engaged in training in clinical research. This program was initiated in 2002, and will provide a maximum of $35,000 per year of loan repayment plus the taxes on this "income" for up to three years of training. Clinical research is defined broadly so that a large number of M.D.s with identifiable NIH support will be eligible for funding through competitive review. The total number of awards in the first year was 250, growing to at least 500 in later years.

• Two other extramural loan repayment programs were initiated in 2002, as well. One is for individuals engaged in basic or clinical pediatric research. The other is for members of disadvantaged minorities engaged in minority health disparities research. The financial terms of these programs will be identical to that of the Clinical Research Enhancement Act loan repayment programs. The number of individuals to be recruited has not yet been set (M. Horowitz, personal communication, 2001).

• The NIH also supports focused loan repayment programs for trainees in the intramural program working in any of four areas of special need: AIDS; underrepresented minorities doing clinical research; contraceptive and infertility research; and general research. There are currently 152 individuals in these programs. The financial terms of these awards are identical to those described above (M. Horowitz, personal communication, 2001).

• In response to recommendations of the Director's Panel on Clinical Research and the Clinical Research Enhancement Act the NIH has established three new mechanisms aimed at enhancing the career development of physician-scientists doing patient-oriented research. The Mentored Patient-Oriented Research Career Development Award (K23) provides five years of salary and research support to a current total of 279 awardees. It is aimed at young investigators in transition from fellowship to junior faculty. The Mid-Career Investigator in Patient-Oriented Research Award (K24) provides "protected research time to . . . clinical investigators by relieving them of patient care and administrative responsibilities." It is a five-year award currently held by 158 people. The Institutional Curriculum Award (K30) aims "to provide didactic multidisciplinary training in the fundamentals of clinical research." There are currently 55 such programs supported, and new ones are being considered (J. Vaitukaitis, personal communication, 2001).

- The Medical Scientist Training program (MSTP) of the NIH has slowly increased in size. In 1996 the program supported 833 M.D./Ph.D. students at 33 medical schools. In 2001, 927 students were supported at 39 schools (B. Shapiro, personal communication, 2001).
- The NIH has been authorized by the FY2001 appropriation to increase the salary cap on its research grants from $141,000 to $157,000.
- In 2001 the Howard Hughes Medical Institute appointed 5 to 10 new investigators who conducted patient-oriented research. Nominees at the assistant, associate, or full investigator levels were considered from medical schools, hospitals, and schools of public health. Most of those appointed held the M.D. or the M.D./Ph.D. degrees (C. Rhodes, personal communication, 2001).
- A growing list of not-for-profit agencies, now numbering at least 12, provide support for the training and career development of physician-scientists (Chan and Zemlo, 2001)(see Table B.1) in three categories: fellowships; awards to junior faculty; and awards to senior faculty. The newest sponsors on this roster are the Doris Duke Charitable Trust and the Damon Runyon Fund.
- A growing number of academic institutions (e.g., Duke, Harvard, Johns Hopkins, Yale, UCLA, and Washington University) have devel-

TABLE B.1 Nonprofit Organizations Supporting Training and Career Development of Physician-Scientists

	Stage of Support Offered		
Organization	Fellow	Junior Faculty	Senior Faculty
American Cancer Society		X	X
American Federation for Aging Research	X	X	
American Gastroenterologic Association		X	
American Lung Association	X	X	
American Society of Hematology	X	X	
Berlex Foundation		X	
Burroughs Wellcome Fund			X
Damon Runyon Fund	X	X	X
Doris Duke Charitable Trust	X	X	X
Leukemia and Lymphoma Society			X
National Foundation for Infectious Diseases	X		
Rockefeller Brothers Fund		X	

SOURCE: Modified from Chan and Zemlo (2001). The list should be seen as illustrative rather than comprehensive.

oped degree-granting postdoctoral programs in clinical research for M.D.s. Some of these programs offer a Ph.D. in clinical science; others offer master's degrees. These multiyear programs combine didactic and mentored research experience.

• The Association for Patient-Oriented Research was established in 1999 and has already had two annual meetings at which research directly involving patients has been presented by investigators from departments of medicine, surgery, pediatrics, and psychiatry. This association now has more than 300 members from the United States and abroad.

RECOMMENDATIONS

This list of opportunities demonstrates that some of the key players in the health research enterprise recognize the imperative to revitalize the physician-scientist career pathway. These steps are good ones and we hope will catalyze other actions by these and other participants. But much more must be done. For example, doubling the number of students in the MSTP program (as recommended by the Federation of American Societies for Experimental Biology) is justified by the large applicant pool and the positive outcome of those so trained. But this action alone will not solve the problem of M.D.s doing clinical research with patients.

A larger and broader NIH loan repayment program for M.D. postdoctorals in both the intramural and extramural programs of the NIH would further mitigate this key economic disincentive. Such a program should support M.D.s training in basic as well as applied research, because such diversity of training will enhance the contributions made by future physician-scientists. In like fashion, tuition relief for medical students taking a full year out of medical school to do research would be an inducement for more students to get this early kind of exposure.

Nonmonetary efforts are also important for revitalizing the pathway. Medical schools can take steps to make it clear that an interest in research is one of the qualities sought in their applicants and can strive to reduce the gender gap in research intentions between male and female medical students. Successful academic physician-scientists must make it an ongoing priority to talk with students and residents about the excitement and gratification they have experienced doing research. The NIH and the National Research Council should define national goals for the number of physician-scientists needed in the long term and develop a national database to continuously monitor key trends concerning physician-scientists.

It has taken a generation for the endangerment of physician-scientists to be acknowledged. It will take at least another generation to restore the physician-scientist cadre to its rightful size and diversity. Just as medical research is viewed as a national priority that offers hope to sick people, revitalizing the physician-scientists career path should be viewed as a national priority that offers hope for the continued success of medical research.

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C

Workshop on Training Programs in Patient-Oriented Pathobiology for Basic Scientists

October 6, 1999
Omni Parker House, Boston, Massachusetts

Agenda

8:00–9:00	Breakfast
9:00–9:15	Introduction Virginia Weldon, Markey Committee Charlotte Kuh, Marilyn Baker, Office of Scientific and Engineering Personnel
9:15–10:00	History and Development of Programs to Provide Training in Patient-Oriented Pathobiology for Basic Scientists Irwin Arias, Tufts University
10:00–12:00	Markey Funded Training Programs in Patient-Oriented Pathobiology for Basic Scientists Peter Agre, Johns Hopkins University Franklin Bunn, Harvard University Palmer Taylor, University of California, San Diego Alan Schwartz, Jeffrey Saffitz, Washington University Michael Weber, William Petri, University of Virginia Nancy Schwartz, University of Chicago Moderator—Virginia Weldon, Markey Committee

12:00–1:00	Lunch
1:00–2:30	Panel—What is the Future of Programs to Provide Training in Patient-Oriented Pathobiology for Basic Scientists? Jim Wyngaarden, Markey Committee David Korn, Association of American Medical Colleges Barbara Filner, Howard Hughes Medical Institute Walter Schaffer, National Institutes of Health
2:30–2:45	Break
2:45–3:30	Panel (*cont.*)
3:30–3:55	Workshop Summary and Synthesis L. Hollingsworth Smith, Markey Committee
3:55–4:00	Closing Remarks Virginia Weldon
4:00–5:00	*Closed Session*

D

Workshop on Training Programs in Patient-Oriented Pathobiology for Basic Scientists

October 6, 1999
Omni Parker House
Boston, Massachusetts

Workshop Participants

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E

Descriptions of Programs Participating in the Workshop on Training Programs in Patient-Oriented Pathobiology for Basic Scientists

Programs

Ph.D. Program in Molecular Medicine
University of Chicago

The Harvard-Markey Biomedical Scientist Program

Graduate Program in Cellular and Molecular Medicine
Johns Hopkins University School of Medicine

University of California, San Diego
Markey Fellowship System

Markey Molecular Medicine Graduate Program
University of Virginia

Lucille P. Markey Special Emphasis Pathway in Human Pathobiology
Washington University

PH.D. PROGRAM IN MOLECULAR MEDICINE UNIVERSITY OF CHICAGO

Overall Program Description

The Ph.D. Program in Molecular Medicine at the University of Chicago bridges the gap between basic science research and its relevance to human biology and disease processes. It educates students in the practical application of modem biological techniques to problems of human biology, particularly the etiology of disease. Nancy Schwartz is the program director.

The program accepts second-year students from any one of a number of degree-granting departments and committees, and then provides a focus in molecular medicine for these select students with

- a specially designed curriculum;
- faculty-sponsored research projects in clinically relevant areas;
- a forum for interactive seminars, symposia, and the like;
- student research presentations or faculty lectures at quarterly lunches; and
- a clinical mentor.

In 1995-1996 Dr. Louis Philipson served as associate director. Dr. Philipson, who holds a combined M.D./Ph.D. degree, is active in both clinical work and research.

Bridging the Bed-Bench Gap

In consultation with the mentor, students must carefully select a research topic that preserves and strengthens the translational aspects of the thesis research. Human biology and relevance to disease are crucial to the Ph.D. Program in Molecular Medicine.

The program is unusual in that students also select a second mentor with clinical expertise in areas appropriate to the students' research interests to guide their clinical exposure throughout the research years. In some cases the research mentor and clinical mentor may be the same person. Dr. Louis Philipson assists in finding an appropriate mentor and reviews this aspect of the training with each of the students annually. He or other faculty also periodically provide bench-to-bedside lectures on appropriate topics. The students host an annual seminar speaker in the area of translational research and actively participate in symposia cosponsored by the Molecular Medicine program.

Students may receive their Ph.D. through those departments and committees in the Division of Biological Sciences that concentrate on the cellular and molecular aspects of biological research and teaching. In the first year, students take a broad core curriculum drawn from the basic science offerings across the division.

There are four specific components of the Molecular Medicine program: coursework, symposia, seminars, and lectures. A description of each component is presented below.

Coursework

During their first two years students take courses that were specially designed for the Markey Molecular Medicine program and are a major feature of the program. Three courses—infection and immunity, cardiovascular disease, and cancer biology—were developed early in the program. They have evolved such that the first two have been combined into molecular mechanisms of disease, and cancer biology has expanded into a two-part course. These courses concentrate on an understanding of disease processes, such as a focus on atherosclerosis, AIDS, or the wide range of cancer diseases. Students analyze the disease process by studying the basic biology of the disease as well as its clinical manifestation. This is accomplished through a series of lectures and readings, supplemented by current journal articles, discussions of actual case histories, and patient presentations. Approximately 40 students enroll for these courses each year.

Symposia

A second component of the Molecular Medicine program is a series of cosponsored symposia. Recent examples include a symposium on neurofibromatosis and molecular approaches to the analysis of complex genetic traits.

Seminars

The third component consists of a series of seminars that are cosponsored by the program on such titles as

- In Vivo Regulation of Sonic Hedgehog Signaling;
- Kazbanian, an ADAM Family Metalloportease that Regulates Notch Signaling in Drosophila and Mouse Development;
- Molecular Control of Neuronal Migration: Tales from an Ataxic Mouse;
- From One to Four Dimensions: In Vivo Libraries of Large Insert Transgenic Mice for Functional Genomics;
- Translation Factors in Control of Gene Expression, Cell Growth, and Tumorigenesis;

- The Cellular and Molecular Basis of Neurofibromatosis, I; and
- Human Achondrogenesis: Biochemical and Molecular Aspect.

Lectures

Dr. Philipson has prepared a series of lectures. His most recent lecture topics include the following:

- Cystic Fibrosis—A Sticky Problem;
- G Protein Mutations and Endocrinopathies;
- Short Stature and Dwarfism: Collagen/Connective Tissue Gene Defect; and
- A Weighty Disease: Molecular Biology of Obesity.

Characteristics of Students

Prospective students declare their interest in the Ph.D. in Molecular Medicine program when applying to do graduate work at the University of Chicago. Financial aid has been restructured in the Division of Biological Sciences and all first-year students are supported by divisional funds. They are considered for entry to the program in their second year, once their research interests have been established. For the Molecular Medicine program the student's program of study must be relevant to human biology and in a field where we can offer them clinical expertise and exposure.

The number of applicants has varied each year from three to ten, with a maximum of four students having been accepted in any one year. Applicants all have a minimum grade point average of 3.5, excellent letters of reference, and a broad interest in their fields of research, including the clinical applications of their work.

Financial Data

Thirteen graduate students have been supported, beginning with the 1994-1995 academic year, at an average direct cost of $38,000 per year. This amount included an annual stipend, tuition, and health and student fees. Most students were supported for three years. Additional costs comprise nominal amounts for honoraria for outside speakers; receptions and student and faculty lunches; and part-time administrative staff and program recruitment.

Because funding has been used primarily as a training grant, the program has been able to stretch funding for two more years. The long-range goal is to continue this program by identifying funding from additional sources. The University of Chicago has taken over programmatic costs so that all funding can be applied directly to student costs.

THE HARVARD-MARKEY BIOMEDICAL SCIENTIST PROGRAM

Overall Program Description

There is a critical shortage of young scientists whose expertise in cell and molecular biology is matched by a sound understanding of the pathophysiology of human diseases. In order to address this need the Harvard Medical School, in 1991, undertook a new initiative, the Harvard-Markey Biomedical Scientist program, supported by a five-year grant from the Lucille P. Markey Charitable Trust. The program director is Franklin Bunn. This program offered a new pathway of graduate education designed to give Ph.D. students a broader knowledge of human biology and disease and to enable them to formulate and carry out original and rigorous research that is relevant to clinical medicine. It took advantage of the scientific and clinical resources of Harvard Medical School to provide comprehensive, integrated multidisciplinary training.

The curriculum described below enabled these Ph.D. students to work in class sections and tutorials with second-year Harvard medical students. It was hoped that this close interaction would enable the graduates of the program to be more effective teachers of future medical students and better collaborators with physician investigators. Finally, this training would benefit Ph.D. scientists who choose a career in the biotechnology or pharmaceutical industry since they will have gained a clear understanding of the medical relevance of the projects that they are asked to undertake.

Bridging the Bed-Bench Gap

Ph.D. graduate students apply to the program during the fall term of their first year. They are selected on the basis of motivation, perceived ability to fulfill the workload, and perceived value of the program to the students' career goals. The curriculum for Markey scholars is illustrated in Table E.1.

The Harvard-Markey curriculum begins in the spring semester with a course in anatomy, which features small group discussions stressing biologically relevant relationships between structure and function with de-emphasis of minutiae and memorization. Liberal use is made of demonstration materials, including anatomical images derived from computerized tomography and nuclear magnetic resonance.

During the summer, students enroll in a biochemistry course designed

TABLE E.1 Curriculum for Markey Scholars

Year in Program	Month											
	9	10	11	12	1	2	3	4	5	6	7	8
1st year	Graduate coursework Lab rotations						Anatomy Physiology			Biochemistry lab Rotation		
2nd year	HST pathology				HST human systems					Lab rotations or thesis research		
	Immunology			Integrated site visits								
3rd year	Graduate coursework						Qualifying examinations					
	Thesis research											
4th-6th years	Thesis research											

to supplement material covered in the Division of Medical Sciences core biochemistry and cell biology course. Emphasis is placed on intermediary metabolism and on biochemical pathways that are relevant to specific human diseases. Lectures are interspersed with group discussions and patient-based case-solving problems.

The students also take a physiology course that stresses mechanisms underlying the organization and regulation of specific organ systems and interactions between them. Lectures are supplemented with group discussions and problem sets.

At the beginning of the second year the students enter a pathology course in conjunction with medical students in the Harvard-MIT Program in Health Sciences and Technology. This course has been a particularly valuable experience for the Harvard-Markey students, enabling them to interact with a subset of medical students with strong backgrounds in and aptitude for science.

Harvard-Markey students not concentrating in immunology also take a course comprising lectures, discussions, and case problems designed to cover the principles of immune defense, again with an emphasis on human biology and pathology. These courses are sufficiently small so that active student participation is not only encouraged but also readily realized.

At the beginning of the fall term each Harvard-Markey student joins one of the four Harvard Medical School societies and thereby is included in their curricular and extracurricular activities. Each society organizes a program of student advisement, the core of which is a relationship between student and advisor to foster goals of self-assessment and professional development. The societies also plan extracurricular and social functions that bring faculty and students together. In early November they and the second-year medical students embark on human systems, which is organized according to organ systems: pulmonary, cardiovascular, hematology, gastroenterology, endocrinology, nephrology, and musculoskeletal. Before the course begins Dr. Bunn gives a two-hour session on clinical terminology and the principles of clinical history taking and physical examination. The bulk of the human systems course is taught in small interactive classes and in tutorials, both of which are organized by the society. The Harvard-Markey students are distributed among the tutorials so that each of them is in daily, close contact with a group of six or seven medical students. The collective experience of these groups has shown that the students have gained considerably from such close contact with the medical students. During the human systems course the students' experiences are enriched by attending a site visit about once every two to three weeks at one of the nearby teaching hospitals. Here they have the opportunity to interact with an investigator involved in research at the interface between basic science and clinical medicine. At some of these sessions the students talk to patients and observe clinical facilities and procedures.

In addition to the curriculum described above the students meet regularly with the director and administrator of the program to discuss courses in progress as well as to review those that have been recently completed. A dinner is held bimonthly at which an invited speaker, generally from the faculty at Harvard or MIT, provides an informal presentation or discussion of a topic of special interest to the biomedical community.

Characteristics of Students

The program is first introduced to our Ph.D. graduate students by a brochure sent to all those accepted by the Division of Medical Sciences at the medical school. Soon after they arrive in September an orientation meeting is held to explain the goals of the program as well as the curriculum and the commitment required of them. Most students apply to the program during the fall term of their first year, however six students have entered the program during their second year. A committee consisting of Dr. Bunn, the director of the Division of Medical Sciences, and the Harvard-Markey program administrator interview all applicants. Students are selected on the basis of motivation, perceived ability to fulfill the workload, and perceived value of the program to the student's career goals. During the program's existence approximately 75 percent of applicants have been accepted.

To date, 57 students have been accepted into the program. Eighteen students have graduated and entered into a wide range of positions.

About half of the graduates have entered into postdoctoral positions. Several students have assumed research positions in pharmaceutical companies. Other graduates have entered into nontraditional positions, including consulting and investment banking, and one student has accepted a faculty position in a medical school.

One student who had completed all coursework elected to assume an executive position in a biotechnology venture capital firm. Currently 38 graduate students are actively engaged in the program.

Financial Data

With the cessation of Markey support the overriding problem was the need to obtain continued funding. In 1996, 30 biotechnology and pharmaceutical companies were approached with proposals for funding our program, but continuing support was not forthcoming. The Howard Hughes Medical Institute was contacted on two occasions to obtain support for the program. Again this contact was unsuccessful. In 1997 the program submitted a training grant application to the Institute of General Medical Sciences of the National Institutes of Health. The proposal was carefully reviewed and deemed meritorious, but was not funded, primarily because it did not fit the NIH's customary criteria for graduate training programs. Their support is reserved for programs that carry students from matriculation into graduate school through the award of the Ph.D. degree. Without external funding Harvard was not able to offer the program to this year's incoming graduate students.

During five years of the program yearly operating expenses were approximately $740,000 (see Table E.2). The largest cost categories provided funding for tuition and stipends.

TABLE E.2 Annual Operating Expenses

Administration	
Salaries	$102,000
Student travel (one scientific meeting per student)	7,500
Office expenses	51,000
Harvard Medical School tuition (12 students)	$302,000
Division of Medical Sciences stipend (12 students)	$203,000
Course expenses	
Human systems	$26,620
Pathology	27,040
Biochemistry	10,150
Anatomy	5,440
Physiology	5,900
TOTAL	$740,650

GRADUATE PROGRAM IN CELLULAR AND MOLECULAR MEDICINE JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE

Overall Program Description

The Graduate Program in Cellular and Molecular Medicine is the newest interdepartmental graduate program at the Johns Hopkins University School of Medicine. The program was developed in response to the 1991-1992 School of Medicine strategic planning retreat, which focused on preparing the institution for the twenty-first century. During the previous two decades the number of faculty in basic science departments increased only slightly. In contrast the number of faculty doing basic research in clinical departments increased dramatically, although most of these have not had access to graduate students, since the existing graduate programs were restricted to basic science departments (e.g., the Biochemistry, Cell, and Molecular Biology program) or were restricted to specialized research teachings (e.g., human genetics, immunology). Most importantly no program existed at Johns Hopkins to train graduate students to perform basic cellular and molecular research on clinical problems, an area of anticipated need with the emergence of molecular medicine.

An advisory committee was named to evaluate the possible solutions and an application was submitted to the Lucille P. Markey Charitable Trust for a graduate program in cellular and molecular medicine. This application was funded in 1993 and provided a nonrenewable source of support to initiate the Graduate Program in Cellular and Molecular Medicine (CMM). All Johns Hopkins School of Medicine department directors were notified that CMM would consider faculty nominations, and more than 300 faculty were proposed. From this group 50 core CMM faculty were selected after reviewing multiple criteria: scientific prominence and independence; previous record as a mentor; achievement of substantial NIH funding; and direct clinical significance of their research. Although selection was based on overall merit, faculty from clinical departments were given slight preference, since one mission of the CMM was to provide students for outstanding laboratories in clinical departments that have traditionally not received Ph.D. students. The number of core CMM faculty has risen to 61. These individuals represent 11 clinical departments (42 faculty) with the majority coming from medicine, oncology, pathology, comparative medicine, urology, neurology, and pediatrics. Members of eight basic science departments also participate in CMM (19 faculty). Approximately 40 other associate CMM faculty are invited to attend CMM activities but do not have independent access to CMM graduate students.

A separate CMM Admissions Committee was established to identify and recruit the most qualified students. The first incoming class of six students began in September 1994, and this number has risen in subsequent years to approximately 10. Each year this group usually includes one student from the Hopkins Medical Scientist Training program (MSTP). Although the Markey funds were not restricted, the majority of students are U.S. citizens or permanent residents (26). Several of the international students have faculty positions awaiting them when they return to their countries of origin. The program anticipates achieving a steady state of approximately 50 students.

CMM students have joined laboratories throughout the medical campus, and this has served to enhance interactions among Hopkins faculty. Current CMM students are pursuing thesis projects in multiple clinical departments: medicine (10 students); oncology (7); psychiatry, pathology, urology, neurology, and comparative medicine (1 each). A smaller subset is pursuing thesis projects in basic science departments: biological chemistry (3 students); neuroscience (3); cell biology, microbiology, molecular biology (1 each). The hallmark of CMM students is their cellular and molecular approach to human disease, and all thesis projects are directly relevant to specific human diseases. Current CMM students are pursuing thesis projects directly related to specific clinical problems, including colon and prostate cancer, hematopoiesis and leukemogenesis, brain edema, sudden cardiac death, coronary thrombosis, AIDS, diarrheal diseases, trypanosomal infections, and skin wound healing.

Bridging the Bed-Bench Gap

Program Directors

The CMM program directorship employs a rotating system involving members of the participating departments. The plan is to have most administrative activities overseen by the director, who will serve three years. To ensure smooth transitions the director is assisted by a codirector, who will subsequently serve the next three years as director. The past director will assist the new director for one to two years, when the CMM Organizational Committee and CMM Advisory Board will elect a new codirector.

Thomas Pollard, M.D., served as the first director (1993-1996). Peter Agre, M.D., served as codirector for three years before becoming the second CMM director in September 1996. Dr. Agre is professor of biological chemistry and medicine, and has been a Hopkins faculty member since 1982. Stephen B. Baylin, M.D., has served as codirector since 1996. Dr. Baylin is Ludwig Professor for Cancer Research and has been a Hopkins faculty member since 1974. John T. Isaacs, Ph.D., has served as codirector of CMM since July 1998, and he assumed the directorship in July 1999. A Hopkins faculty member since 1980, Dr. Isaacs is professor of oncology, professor of urology, and codirector of the Division of Experimental Therapeutics in the Johns Hopkins Oncology Center.

Advisory Board

This group of distinguished senior faculty members has been drawn from multiple basic science and clinical departments. The Advisory Board initially oversaw the formulation of CMM, but as the program developed the Organizational Committee took over most details. The Advisory Board meets formally annually to review the director's annual report and to make suggestions. Although the Organizational Committee elects new directors, the Advisory Board must approve them. Members of the Advisory Board are available for numerous ad hoc needs of the CMM program and students.

Organizational Committee

This committee is the functional body that undertakes the various recruiting and teaching activities of the CMM. The Organizational Committee includes representatives of most participating departments as well as chairs of subcommittees. Subsets of members may meet monthly, and the entire Organizational Committee meets quarterly to review the program and make administrative decisions. Frequent discussions include composition of the subcommittees, potential changes in curriculum, changes in funding policies, admission of new members to the CMM faculty, and review of student academic problems. The Organizational Committee nominates and elects new CMM directors.

CMM Faculty

The directors, members of the Advisory Board, and members of the Organizational Committee also serve as laboratory mentors for CMM students. Members of the core CMM faculty were nominated by their departmental chairmen and were reviewed by CMM directors and Organizational Committee members. Every effort is made to employ uniform criteria for membership in CMM. Scientific prominence is evaluated by leadership in various societies and programs, chairing of national and international scientific committees, and organization of meetings and conferences. Scientific independence is assessed by senior authorships on studies in highly regarded publications. Core CMM faculty must have sufficient laboratory space to accommodate CMM students. It is generally required that all faculty will be principal investigators with independent RO1 grants from the NIH. A few exceptions have been made for individuals who have not yet achieved NIH funding but are considered particularly important to the overall program. Faculty members who experience a lapse in RO1 funding will not be allowed to serve as individual laboratory mentors for students but may serve as co-mentors with another active core CMM faculty member who assumes joint responsibility for the student. The suitability of nominated faculty members is in part determined by their record for training postdoctorals or students. The clinical significance of the faculty member's laboratory is considered especially important, with some laboratories studying fundamental problems relevant to many clinical problems and other laboratories focused on a very specific clinical problem.

It is expected that all core CMM faculty members will serve on CMM committees (oral examination committees, admissions committee, or other committees) when asked. Likewise all core CMM faculty are expected to participate in teaching. This may either be as lecturer in the core courses, as faculty preceptor during small group discussions, or as organizer for elective courses.

Faculty will be contacted every two years to provide an assessment of participation in CMM activities. Active participation will require documented teaching and participation in recruiting or other activities. Individuals failing to establish sufficient CMM participation may be relegated to associate CMM faculty after review by members of the Organizational Committee. Such individuals are welcome at CMM activities but may not serve as independent laboratory mentors. Reinstatement may be considered when new CMM faculty are under consideration by the Organizational Committee. The size of the CMM core faculty has been restricted to keep the program at a manageable size (about 60). It is anticipated that additional faculty may be added in future years when annual nominations from departmental chairs will be sought.

First-Year Curriculum

The CMM curriculum was designed by the original Advisory Board, which strongly felt that CMM students should take the most rigorous basic courses offered at Hopkins as well as new courses specifically designed for CMM students. Note that Hopkins graduate program courses are open to all students from all graduate programs at the Johns Hopkins University School of Medicine and students from the School of Hygiene and Public Health.

First-Year Core Courses. The first-year students take six formal lecture courses in the basic sciences. Faculty from throughout the basic science departments and clinical departments teaches these courses. CMM core faculty participate in the organization and teaching of several of these courses. Core courses include biophysical chemistry, molecular biology, biochemistry and cell biology, fundamentals of genetics, topics in human genetics, and principles of immunology.

The above courses are rigorous and demanding. The program directors regularly review the outcome of all major examinations for each course to identify any CMM students experiencing difficulty in any course. CMM students are expected to achieve the grade of B or higher. Students with lower performances will be required to retake the core course. The Organizational Committee will evaluate any student receiving a lower grade in two courses for possible dismissal at the end of the first year. So far CMM students have performed well and very few have needed to repeat courses.

First-Year Discussion Group. Once each week after the morning lectures, first-year students participate in a discussion group organized by a CMM faculty with expertise pertinent to the lectures. The faculty member will select a short review and research paper. All students are expected to read the paper, but one student is assigned to lead the discussion. The faculty member will be in attendance to answer questions and provide supplemental information. The sessions are designed to supplement the lectures by providing insight into the lecture topic for the week and they last about one hour.

First-Year Tutorial. To enhance the formal presentations the Pollard scholars tutorial was initiated as a study group to help first-year students understand the course materials by teaching one another. These sessions are held once per week during lunch and take about one hour. Upperclass CMM students who have achieved outstanding performances in the core courses and who exhibit strong interest and talent in teaching lead this popular activity.

First-Year Seminar Series. To bridge the gap between basic science courses and clinical diseases and to inform students of research opportunities, first-year students attend a weekly one-hour seminar. Two faculty members are invited to speak for 30 minutes; each is introduced by a first-year CMM student, who is assigned to meet with the faculty member in advance.

Oral Examination. As required by the Graduate Board of the Johns Hopkins University, CMM graduate students must pass an oral examination of the student's competence in areas covered in the first-year curriculum and in other areas of general scientific relevance. After completion of the first year courses CMM students identify a committee of five faculty members from outside the thesis laboratory. Not more than two committee members may be from the student's thesis department. After approval by the faculty education coordinator the examination is scheduled to occur during the autumn or winter of the second year. Students generally take a two- to three-week pause in their laboratory work to review for this examination.

Second-Year Curriculum

Second-year students take two courses specifically designed for CMM students by CMM faculty. These courses introduce students to organ systems and pathobiology. The basic anatomy and physiology of organ systems is taught in a series of 12 two-hour afternoon interactive sessions. (This course will be taught to first year CMM students in the future.) Topics include embryology, central nervous system, autonomic nervous system, endocrine systems, blood, reproductive organs, lymphoid organs, skin, respiratory system, urinary tract, cardiovascular system, and gastrointestinal tract.

Understanding human disease is an essential part of the CMM curriculum. An in-depth review of fundamental pathobiologic mechanisms and specific human diseases is team taught to our students by two faculty members. Each week one clinician and one basic researcher will provide a series of papers to the students and lead a discussion pertinent to a fundamental process and the associated diseases. Topics covered include Alzheimer's, breast cancer, colorectal cancer, acute infectious diseases, chronic infectious diseases, cystic fibrosis, storage diseases, autoimmune diseases, atherosclerosis, heart disease, renal transport disorders, gastrointestinal diseases, hematopoiesis and leukemia, coagulation, and motor neuron diseases. At the end of the course students identify a research problem, write a short proposal (similar to the individual National Research Service Awards fellowship applications), and make an oral presentation to the faculty.

Subsequent Years

CMM students in the third year and beyond are required to take four electives. These may be elective graduate school courses or selected medical school courses. Participation in the seminar series and journal clubs is expected of all CMM students. Even though attendance is not monitored, it is suggested that the students attend at least one faculty seminar and at least one journal club session per week.

Laboratory Research

CMM students have a variety of laboratories in which to perform research. New CMM students are encouraged to undertake an extra laboratory experience in faculty laboratories during the summer preceding their first year. During the regular academic year CMM students will perform three rotations of 10 weeks duration. Selection of the rotation laboratories involves several steps.

Retreat. A half-day retreat is held early in the academic year during which selected faculty present short research talks to describe the research activities in their own laboratories and answer questions the new CMM students may have regarding CMM research opportunities. A keynote talk is presented by a longtime Hopkins faculty member whose career pathway seems especially appealing to CMM students. Following a buffet supper a panel discussion is presented by CMM faculty members and upperclass CMM students who share their experiences and provide suggestions for choosing laboratories. Students also meet with faculty members who present their laboratory programs during the first-year seminar series.

Rotation Assignments. During September of the first year all CMM students are given a list of five CMM faculty with whom to meet to discuss potential laboratory rotations in that faculty member's laboratory. The rotation coordinator compiles this list after consulting with the director and other CMM faculty. Students are encouraged to contact other CMM faculty members to discuss potential rotations and meet with the first-year advisors or another faculty advisor selected by the student. In early October the students rank their choices, and are matched to laboratories. So far all have gone to a laboratory of their first or second choice. Program needs or special situations may also be considered in this decision.

Because first-year CMM lectures occur in the mornings, the students spend afternoons in faculty laboratories, where they are given research projects under the direct supervision of the host faculty member. Student research efforts may spread into the evenings and weekends, however faculty are aware that the students' coursework is their higher priority during the first year. The goal of lab rotations is to provide the student with the opportunity to learn new techniques and sample the atmosphere and approaches taken in multiple labs before selecting one laboratory for a thesis project.

At the end of each 10-week rotation a mini-symposium is held at which each first-year CMM student will present a 10-minute talk with slides or transparencies during which the project is described, findings are presented, and conclusions are stated. All CMM faculty are welcomed and all rotation faculty members are required to attend. Faculty are requested to provide short written comments about each student's talk. Each rotation faculty member is requested to provide a short evaluation of the student, and each student is requested to provide a short evaluation of the lab experience. The rotation coordinator subsequently discusses these comments and evaluations in private with each student. If deemed necessary, the program director discusses the evaluations of faculty labs with the rotation faculty.

Thesis Projects. By the end of the third rotation most CMM students have a clear idea about the choice of laboratory in which to undertake a thesis project. When students exhibit some lingering doubt, a fourth rotation is recommended for the summer after the first year. Each year one or two CMM students request a fourth rotation, and often this laboratory is chosen for the thesis project. The thesis commitment is made after discussion by the student and the rotation coordinator and after consultation with the program director. To date, only one student has subsequently requested reassignment to another thesis laboratory, and this occurred because the faculty thesis advisor developed a terminal illness.

The second-year CMM students spend most of their time undertaking research projects that will lead to the thesis project. It is generally expected that the students will need close guidance during this time. By the end of the second academic year the students, after consulting with their thesis advisor, should have undertaken sufficient experimentation to have an idea of potential thesis projects. After consulting with the thesis advisor the student will then draft a short thesis proposal (generally up to five pages) outlining the experimental question, the preliminary data, and the approaches to be taken.

Together the student and thesis advisor will identify a group of three to four faculty members from other laboratories to serve on the thesis committee. The thesis proposal is then distributed to Thesis Committee members, who will read it. The student then schedules the first thesis committee meeting at which the student formally proposes the thesis project. The thesis committee will provide the student with specific advice regarding aspects of the project and suggestions for approaches. Thereafter students are expected to hold at least one thesis committee meeting per year, and these meetings are documented by the education coordinator.

Usually by the fifth year the student and thesis advisor will schedule the final thesis committee meeting. With approval of the thesis committee the student then writes the thesis and submits it to the thesis advisor and one member of the thesis committee for a detailed reading. Once the document is approved the student will schedule a seminar at which the student will formally present the thesis to members of the Hopkins faculty and will answer questions. The thesis, transcript, and letters are then submitted to the School of Medicine registrar for approval by the M.A./Ph.D. Committee.

Distinguished Lectureships. As part of the celebration of our first year a series of distinguished scientists have been invited to spend a day with the CMM students and faculty and give a lecture that is open to the entire Hopkins medical campus. This tradition has been continued in subsequent years with the participation of one or two prominent biomedical scientists whose work is particularly relevant to the CMM program. This program is organized by advanced CMM students who select the speaker, invite the individual, and make all of the arrangements.

Young Investigators' Day. Each spring the graduate and medical students from throughout the School of Medicine are invited to submit an abstract and essay describing the research they undertook while students. This event is referred to as "Young Investigators' Day."' Competition for the awards is extremely strong, with more than 50 students submitting their work in competition for seven named prizes. CMM has had a close affiliation with this activity.

Responsible Conduct in Research. In compliance with federal guidelines the Johns Hopkins University School of Medicine sponsors several activities to ensure that our trainees receive proper instruction in the ethical approach to science. The Hopkins Graduate Student Association and the dean of graduate student affairs have instituted an honor code to emphasize scientific and academic integrity. All Hopkins graduate students are required to read and sign the document during the first day of orientation. Students noticing behavior inconsistent with the honor code are expected to notify the program director, the CMM Grievance Committee, or the associate dean for graduate student affairs.

The School of Medicine has established policies on conflicts of commitment, conflicts of interest, procedures for dealing with professional misconduct, grievance procedures, and rules and guidelines for responsible conduct. As established by recommendation of the School of Medicine Advisory Board and the Faculty Medical School Council, all Hopkins students, fellows, and faculty are required to follow the policies in the booklet *Honor in Science* published by Sigma Xi. These policies are illustrated in a series of lectures held in the School of Medicine. Attendance at one lecture per year is expected of all CMM students.

First- and second-year CMM students will receive additional instruction in responsible conduct of research as part of two presentations in the topics in cellular and molecular medicine. Attendance is required and will be monitored by the CMM educational coordinator. Third-year CMM students will attend the all-day workshop in biomedical ethics sponsored by the Department of Medicine and taught by several CMM faculty. This intense course comprises formal presentations and group discussions about specific problems in bias, fraud, and misconduct. Advanced CMM students will attend special activities held in the departments where their thesis projects are located.

Characteristics of Students

A major CMM objective has been to recruit outstanding Ph.D. candidates to Johns Hopkins. Three sorts of individuals have joined CMM: U.S. nationals enrolling as straight Ph.D. students (21 individuals), U.S. nationals enrolling as M.D./Ph.D. students (5 individuals), and international students (16 individuals). To advertise our program a full page is included in *Peterson's Guide*, and there is an entry on the Hopkins website at <www.med.jhu.edu/gradweb/cmm>. We have also mailed our CMM poster to multiple undergraduate institutions. Importantly, CMM faculty lecture extensively at universities throughout the United States to provide visible evidence of the program to highly motivated undergraduate students, who are often in attendance.

Requests for application forms are received throughout the year. Since 1996, students who apply to graduate programs at the Johns Hopkins University School of Medicine submit a single universal application form. Applications are mailed directly to the CMM office.

While individuals are free to apply to more than one program, applicants generally have a strong preference for one Hopkins program. Although the Hopkins graduate programs work together to facilitate student visits, each program evaluates students without conferring with the other programs. Each applicant is thereby assured that decisions are independently reached by each program, and no internal deals are made by any Hopkins programs.

During the first five years CMM has averaged 90 applications (see Table E.3). During the first two years other Hopkins graduate programs included a CMM program brochure in mailings to potential applicants; consequently the number of applications received was slightly higher (89 and 107). Subsequently CMM managed its own publicity, and while the number of applications declined somewhat, the number has increased every year (74, 82, and 102).

TABLE E.3 Summary of CMM Admissions During the First Five Years

Summary of Admissions	1994	1995	1996	1997	1998
Number of applicants	89	107	74	82	102
Offers made	14	17	15	19	25
Accepted our offer	6	8	9	10	10
Completed training	0	0	0	0	0
Still in training	5	5	9	9	10
Left program	1 (Graduated in 1999)	3 (Graduated in 1999)	0	1 (Health reasons)	0

The CMM Admissions Committee operates completely independently of other Hopkins graduate programs, and each application is read by at least two Admissions Committee members, who assign a preliminary score of 1 to 5 (1.0 = best). The students are evaluated on the following criteria:

- Academic performance in the sciences;
- Academic performance overall;
- Graduate Record Examination scores;
- Letters of recommendation;
- Accomplishment and experience in research;
- Evidence of dedication to a research career; and
- Reputation of undergraduate institution.

Those students ranked in the top third are invited to Hopkins for an interview (typically about 30 applicants). During the interview weekends students are interviewed by CMM students and at least five faculty. While interviewers rate the student on the same criteria as the initial readers, the ability of the applicant to communicate effectively, and the individual's creativity and commitment to science are scrutinized closely.

The Admissions Committee holds a follow-up meeting at which the scores from the preliminary evaluations are compared with the interview scores and notes, and an average is calculated for each student. The Admissions Committee also consults the present CMM students for feedback about the suitability of applicants. Applicants with a CMM ranking of 2.0 or better usually receive an offer. Those with 2.1 to 2.5 are waitlisted, and a subset may eventually receive offers. To date, about 40 percent of offers result in matriculation.

The 1998 applicants who accepted a CMM offer and those who declined have been compared. To assess our weaknesses students who have declined the offer were contacted to learn of their alternative choices. Applicants who declined the offer did so after accepting offers by graduate programs in outstanding universities. This information also offers evidence of the independence of CMM from other Johns Hopkins graduate programs, since only five students who received CMM offers declined in favor of more established Johns Hopkins programs (biochemistry, cell and molecular biology, and human genetics).

Financial Data

The Markey funds have been expended. Nevertheless, the John Hopkins University School of Medicine is seeking funding to continue the Program in Cellular and Molecular Medicine with new funding. CMM staff has applied to the NIH for funding for a new program, and anticipates funding in the near future.

UNIVERSITY OF CALIFORNIA, SAN DIEGO MARKEY FELLOWSHIP SYSTEM

Overall Program Description

The Markey Fellowship System was an interdisciplinary program involving both the academic campus and the School of Medicine at the University of California, San Diego, the Salk Institute, the Scripps Research Institute, and the La Jolla Cancer Research Foundation (now the Burnham Institute). George Palade was the program director. The program relied heavily on the use of tutorials and small group conferences to establish close and effective interactions of the Markey fellows with program faculty. This approach was the best way to train students in a critical assessment of relevant scientific literature. These activities were added systematically to the requirements of the different graduate programs in which the students were enrolled.

The program also included symposia dealing with major health problems still in need of effective solutions. One-day symposia with the following titles were conducted:

- The Interface of Science and Medicine: Human Immunodeficiency Virus;
- The Cardiovascular System: Biology, Pathology, and Therapeutic Strategies;
- Cancer: Progress Toward a Molecular Understanding and Rational Therapy; and
- A Multidisciplinary Approach to Alzheimer's Disease;

Most speakers were from the UCSD faculty, but in one case the speaker was an outstanding investigator from another university.

The program also included an annual retreat at a nearby ranch at which the Markey fellows presented their research accomplishments. These presentations were remarkable in substance and format, and their professional quality impressed the faculty and other fellows.

Bridging the Bed-Bench Gap

The Markey fellows were exposed to a discussion of current health problems by experienced clinical and basic science investigators. The fellows had no contact with real patients because University of California, San Diego, hospitals discourage contact of nonprofessionals, such as graduate students, with patients for a variety of reasons. However, the fellows heard from experts about the status of current efforts to understand and control the major diseases that were the topics of the symposia. The "seeds" put in the fellows' minds by the topics of the symposia may germinate into active research involvement by the time they are ready to start their own research careers. Interestingly, many Markey fellows took the tutorials and small group conferences dealing with HIV infections and Alzheimer's disease.

A listing of tutorials and small group conferences offered by program faculty in the last year of the program is listed below to illustrate the variety of topics and the broad participation of faculty from UCSD School of Medicine and campus and affiliated institutions.

- Protein Structure Determination by NMR
- Macromolecular Structure and Chemistry
- Development of the Immune System;
- The Molecular Mechanisms of Neural Development;
- Autoimmunity and Tolerance;
- The Biology/Epidemiology of AIDS;
- Molecular Modeling Techniques in Chemistry;
- Evolution and Adaptation of the Visual System;
- Manipulating the Mouse Genome;
- Receptor Tyrosine Kinases and Their Role in Neurodevelopment;
- Developmental Neurobiology;
- Comparative Neurophysiology of Integrative Mechanisms;
- Protein Sorting Pathways in Eukaryotic Systems;
- Signal Transduction: Coupling Mechanisms, Mediators, and Selectivity; and
- Drosophila Neurogenesis.

The core of the Markey Fellowship System was its faculty, and over 150 different faculty participated (see Table E.4). These faculty were located in UCSD graduate programs, School of Medicine graduate programs and at the Salk Institute, Scripps Research Institute, and La Jolla Cancer Research Foundation. Students interacted with faculty from more than one institution.

The Markey Fellowship System conducted annual retreats during which approximately 20 students presented synopses of their research.

Characteristics of Students

The leading candidates of each graduate program were nominated for Markey Fellowships. The nominations were discussed, assessed, and

TABLE E.4 Location of Markey Fellowship System Faculty

Location	Number of Faculty
UCSD Graduate Departments	
Biology	44
Biochemistry	13
School of Medicine Graduate Programs	
Biomedical sciences	31
Neurosciences	23
Molecular pathology	7
Affiliated Institutions	
The Salk Institute	21
The Scripts Research Institute	12
La Jolla Cancer Research Foundation	4

compared by an executive committee (steering committee) for the Markey Fellowship System, which included representatives of each program, as well as representatives of the collaborating institutions: the Salk Institute, Scripps Research Institute, and La Jolla Cancer Research Foundation. This committee made the final decisions for appointing Markey fellows.

The number of fellows in the Markey Fellowship System averaged nearly 18 per year, with 89 fellows enrolled during the five years that new fellows were admitted (see Table E.5). The most popular programs of the Markey Fellowship System were biology and biomedical sciences; pathology had the fewest fellows. In the Biomedical Sciences program one or two fellows come from the Medical School's Medical Scientist Training program.

TABLE E.5 Markey Fellows at the University of California, San Diego, 1992-1996

	Programs					
Academic Year	Biochemistry	Biology	Biomedical Sciences	Neuroscience	Pathology	Total
1992-1993	3	5	6	4	2	20
1993-1994	1	6	5	2	1	15
1994-1995	3	5	7	3	1	19
1995-1996	2	5	6	4	1	18
1996-1997	2	4	5	4	2	17
Total	11	25	29	17	7	89

Financial Data

Each Markey fellow received a stipend of $16,000 per annum and a travel allowance of $1,000. Small amounts of money were used for the administration of the Markey system.

MARKEY MOLECULAR MEDICINE GRADUATE PROGRAM UNIVERSITY OF VIRGINIA

Overall Program Description

The Molecular Medicine Graduate Program at the University of Virginia School of Medicine is designed to provide rigorous disciplinary training in basic sciences as well as exposure to the problems and opportunities of research on human disease. The central mechanism for achieving these goals is dual mentorship: Each student has a research mentor in a basic science department and a clinical mentor in a clinical department. Ideally the student's research will serve as a collaborative venture between the basic scientist and the clinician. Thus, this program supports the research activities of both the basic and the clinical departments.

The participating basic science departments and programs are microbiology, biochemistry and molecular genetics, pharmacology, neuroscience, biophysics, molecular physiology and biological physics, and cell biology. The participating clinical departments are pathology, neurology, urology, medicine, pediatrics, and surgery.

Students spend their first year in coursework and laboratory rotations. Each beginning student is given a three-person advisory committee for guidance until the student chooses a laboratory and has a thesis committee set up. The first-year courses include cell and tissue structure, gene structure and expression, and biochemistry structure and function. Available electives include advanced genetics, molecular oncology, molecular pathogenesis, immunology, physiology, molecular pharmacology, and protein chemistry. At the beginning of the second year, students choose research and clinical mentors and begin their research. During the second year the students take a course on topics on the molecular basis of human disease, which is organized by the program.

The Executive Committee was established to set policy for the program, to advise students, and to handle admissions, and evaluate student progress. The Executive Committee consists of individuals who represent the various constituencies and departments the program serves and represents both basic science and clinical departments.

This is the fifth year of full operation of the program. Superior students are increasingly attracted to the program as people learn about it (almost all applicants now contact the program through the Web). The program received 61 applications last year for a maximum of 3 positions. Ties to the M.D./Ph.D. program have been strengthened along with ties to a newly designated research track for medical students in the didactic aspects of the training.

Bridging the Bed-Bench Gap

The program jointly sponsors an evening seminar and lasagna dinner called "molecular disease rounds" approximately twice a semester. At this event a clinical investigator introduces a disease state, and a basic scientist gives a lecture about the molecular basis of the disease. Where possible, pairs of individuals who are working collaboratively are chosen. This course follows the dual-mentor paradigm initiated by us for graduate mentoring. Topics for the molecular disease rounds include

- Molecular Pathology: New Approaches To Understanding Human Pathogenesis;
- How Mitochondrial DNA Defects Cause Alzheimer's and Parkinson's Disease;
- Influenza Surface Proteins: Crystal Structures and Targeted Drug Design;
- The Human Immune Response to Melanoma;
- The Molecular Dissection of Pancreatic Carcinoma;
- Light Input to the Vertebrate Circadian System;
- The Reproductive System: A Question of Timing; and
- The Science and Clinical Uses of Sperm Check, An Immunodiagnostic for Detecting and Measuring Sperm.

We also have started a new course titled "Topics in Molecular Basis of Human Disease." This course is required for our molecular medicine students, but is also open to other graduate students as well as MSTP and research-track M.D. students. The course addresses the biologic and molecular mechanisms related to selected disease processes as they affect specific cell types, tissues, and organ systems. The format consists of weekly two-hour meetings, and each topic is covered in two sequential sessions with a combination of informal didactic presentations by the faculty and journal article discussions (three to five papers total) by the students. Didactic-style presentation(s) are aimed at providing sufficient background on the relevant pathobiology, histopathology, and clinical manifestations for the students to read and discuss the literature assignments. A strong focus of the course will be the discussion of the basic pathobiologic processes and the contemporary biomedical translation of experimental science to the understanding and treatment of human diseases.

Enrollment is limited to 21 students, with preference given to full-time graduate students in the Molecular Medicine program, first-year students in the Medical Scientist Training program, and medical students participating in graduate research programs. The class meets on Thursday afternoons and the format is similar to the molecular disease rounds. At one session both a physician and a basic scientist introduce a disease topic and papers are assigned that investigate the molecular basis of the disease. At the session the following week students present, discuss, and analyze the assigned papers. The course has been extraordinarily well received. The only difficulty we have had is integrating the course into the medical school schedule.

The most recent offerings in "Topics of the Molecular Basis of Human Disease" were

- Diabetes;
- Growth Hormone Action in the Cell and in the Organism;
- Retinal Degenerations;
- Molecular Genetics of Colorectal Neoplasia;
- Mitochondrial Dysfunction, Neurodegenerative Diseases and Therapeutic Strategies; and
- Pathobiology and Therapeutic Approaches to Melanomas.

Characteristics of Students

The Markey Molecular Medical program gets as many as 60 applicants per year. At least half of the applicants are qualified to enter the program, however fiscal restraints have limited the number of offers to 6 per year, with an average of 4 students admitted each year. A total of 20 students have been admitted to the program. One, admitted as an advanced student, has already graduated from the program and is currently employed by Genentech, doing translational research. One student left the program to continue studies with his science mentor, who moved to another university. Two students have decided to graduate with a master's degree. Currently there are 16 students enrolled in the program.

Financial Data

The major barrier to further development of the program has been funding. The resources have not been committed to admit a cohort of students large enough for this group to achieve an institutional identity. Currently the university is supporting the program at a steady-state level, and there are funds to support second-year and some third-year students.

Markey funds have been shepherded to fund first-year students, as there are no institutional funds for that. The Markey Molecular Graduate program has attempted to secure additional funding from extramural sources. These attempts, however, have been unsuccessful.

The small class size also makes it impractical to develop specific course offerings. An additional barrier has been the fact that the program occurs in a matrix of departmental graduate programs, which also creates identity problems for advanced students, who typically feel more at home with their departmental colleagues.

LUCILLE P. MARKEY SPECIAL EMPHASIS PATHWAY IN HUMAN PATHOBIOLOGY WASHINGTON UNIVERSITY

Overall Program Description

The Lucille P. Markey Special Emphasis Pathway in Human Pathobiology at Washington University School of Medicine was established in 1992 through a grant from the Markey Charitable Trust. The pathway is dedicated to training bright, young Ph.D. students and postdoctoral fellows in various aspects of human disease. The overall purpose of this innovative educational experience is to produce a cadre of excellent young investigators who will carry out basic research in areas related to human disease and serve as role models for future generations of students. The long-term objective is to develop research faculty at the Ph.D. level who are familiar with human diseases and who regard research in human disease as an exciting opportunity.

The driving force behind the development of the Markey pathway at Washington University was (and continues to be) the widening gap between clinical and basic research, and the pressing need to develop training programs that bridge this gap for Ph.D. researchers in the life sciences. U.S. health statistics have documented the magnitude and explosive growth of biomedical science in the past two decades. The basic sciences, including molecular biology, have expanded and evolved rapidly. Advances in basic science have created extraordinary opportunities for understanding the fundamental biological basis of clinical medicine and using this information in innovative ways to help patients. At the same time, however, the changing landscape of the U.S. health care system and serious financial pressures facing academic medical centers have had a significant negative impact on the investigative activities of clinical faculty.

Traditional approaches to addressing these issues have been successful to a large degree, but new initiatives are needed. M.D./Ph.D. training programs provide one mechanism by which physician-investigators acquire the basic science skills and education to approach complex biomedical problems. One untapped area in which a major long-term impact on biomedical education can be achieved is the introduction of the biology of human disease to the pool of competent young Ph.D. investigators. Although the rationale for this approach may appear obvious, successful implementation of this strategy has required careful thought and planning, the enthusiastic and dedicated commitment of an energetic faculty, and the institutional will to provide an environment that nurtures innovation, excellence, and an interdisciplinary approach in scientific training and research.

All graduate research training in the life sciences at Washington University is administered through the Division of Biology and Biomedical Sciences. All predoctoral programs and degree-granting units in the biological sciences at Washington University are both interdisciplinary and interdepartmental. The division was established as an independent administrative unit with its own endowment in recognition of the increasingly interrelated nature of all aspects of research in the biomedical and biological sciences, and to facilitate cooperation among faculty in the interdisciplinary training of future biological scientists. At the present time the Division of Biology and Biomedical Sciences is responsible for administering several university programs, including the Ph.D. portion of the M.D./Ph.D. training program, the M.D./M.A. program, the Young Scientist program, as well as the Markey Special Emphasis Pathway in Human Pathobiology.

The Markey pathway emphasizes training a subset of graduate students and postdoctoral fellows to provide them with a basic understanding of human disease without distracting them unduly from the main objective of becoming first-rate basic scientists. The clinical specialties provide limitless opportunities for important, challenging research in the understanding and treatment of human disease, and the main goal of this program is to make these opportunities and challenges known to Ph.D. students and fellows and to entice a number of them into these areas.

Alan L. Schwartz, Ph.D., M.D., Spoehrer Professor and head of the Department of Pediatrics at Washington University, was the principal investigator of the original proposal to the Markey Trust and served as director of the pathway from its inception until 1998. In July 1998 Jeffrey E. Saffitz, M.D., Ph.D., Lacy Professor of Pathology, accepted the post of program director and assumed responsibilities for the day-to-day administration of the program. Dr. Saffitz has been involved with the Markey pathway since its inception. He served on the original Steering Committee and directed the Clinical Mentor program prior to assuming his current position as program director.

Timothy J. Ley, M.D., and George J. Broze, Jr., M.D., both professors of medicine at Washington University, were original members of the Steering Committee and served as coursemasters for the first seven years. In 1998 Dr. Broze stepped down as coursemaster, and was replaced by Daniel C. Link, M.D., assistant professor of medicine. Drs. Ley and Link now serve as co-coursemasters and work together as a team to organize the course, select faculty members who lead the three sections presented each year, and assume overall responsibility for seeing that the course runs smoothly.

As new faculty members join Washington University and participate in Markey pathway programs either as faculty members in the course, clinical mentors, or research mentors of students in the pathway, selected individuals are invited to fulfill leadership roles. Recent additions include Jean Schaffer, M.D., assistant professor of medicine, and Samuel Speck, Ph.D., professor of pathology, who are now members of the Steering Committee and serve on the Postdoctoral Fellow Admissions Committee.

Bridging the Bed-Bench Gap

Although much of the nation's basic biological and biomedical research takes place at academic medical centers, pre- and postdoctoral Ph.D. trainees (including those who train in the laboratories of physician-scientists) have traditionally had little or no access to the clinical enterprise at these centers. Until the development of the Markey Special Emphasis Pathway in Human Pathobiology there had not been a training model at Washington University designed to engage Ph.D.-level scientific trainees in the clinical realm.

The three principal components of the Markey pathway through which Washington University bridges the bed-bench gap are a course in human pathobiology; a clinical mentorship program; and enrichment activities, including an annual retreat and guest lecturers. The following is a brief description of each of these components.

The Markey Pathway Course on the Pathobiology of Human Disease States

A fundamental premise upon which our philosophy is based is that all pathophysiology is an integrative function. Each cell type, organ system, physiological state, and pathological stress involves complex interactions that can be dissected and studied in isolation but which must also be evaluated as a whole. A single disease state provides a paradigm in which students can experience several of the principal areas in human pathobiology.

The Markey Pathway Course on Human Pathobiology is organized into three sections, each of which focuses on a major disease state. The course is offered each fall semester. Because the pathway encompasses two years, each student will have been exposed to course curricula on six different diseases. Diseases covered include sickle cell anemia, AIDS, acute leukemia, multiple endocrine neoplasia, osteoporosis, and rheumatoid arthritis. The selection of disease topics and the organization of each component of the course are the responsibilities of Drs. Timothy Ley and Daniel Link, coursemasters, together with the program director and Steering Committee. The course is presented at an intermediate or advanced graduate level appropriate for second- and third-year graduate students. As noted above, Markey pathway trainees include postdoctoral fellows. The mixture of pre- and postdoctoral trainees enriches the milieu for both students and faculty, and also ensures that the level of teaching and discussion is on a high plane.

Enrollment in the course is limited to Markey pathway trainees to maintain a forum for active interchange between the teaching faculty and students and to encourage student participation in the course. The Markey pathway students evaluate every section presented and comments are relayed to the coursemasters, the faculty section leader, and the program director.

Course faculty are selected each year to include both clinical and basic science faculty, with special attention paid to teaching skills and enthusiasm, as well as their ability to integrate into a cohesive educational effort. The majority of the course faculty are young and active investigators in the clinical sciences. In general the course material for each disease state is presented in 10 sessions of 1.5 hours duration (total of 15 hours). Each week there are two sessions, typically including a 60-minute lecture (or other type of presentation, including patient interviews) and a 30-minute discussion of papers from the historical and current medical literature. Students lead the literature discussion and the faculty participate as moderators. The focus of these discussions is to address major disease states of comparable complexity and importance that affect society. An obvious benefit of a disease-oriented course is the attraction of students to future research opportunities in that disease state.

One example of a disease state covered in course material is chronic myelocytic leukemia (1998 course topic). Chronic myelocytic leukemia (CML) is an acquired clonal disorder of hematopoiesis that is manifest by an accumulation of mature and immature granulocytes in the blood. A cardinal feature of CML is the presence of the Philadelphia (Ph) chromosome in leukemic cells. Of note, the Ph chromosome was the first chromosomal abnormality associated with a specific human cancer. Subsequently it was determined that the Ph chromosome is a result of a translocation between chromosomes 9 and 22 t (9; 22). Nearly 20 years ago it was discovered that this translocation fuses the BCR gene with the ABL gene, resulting in the production of a novel chimeric protein termed bcr-abl. Since then extensive studies have been directed at characterizing the molecular mechanisms by which bcr-abl induces leukemia.

CML provides an exemplary model to study the impact of basic research on clinical medicine. Throughout this course the students were asked to consider two questions: (1) How has the study of bcr-abl contributed to our understanding of the pathogenesis of CML and impacted its clinical management? and (2) What are the important clinical problems in CML and how can basic research help to resolve them?

During the course the students developed a thorough understanding of the clinical presentation and management of patients with CML. Patient interviews were performed on two separate occasions and served to highlight therapeutic dilemmas. More importantly these interviews provided the students with valuable insights into the emotional and social aspects of this disease. Interspersed with the clinic-oriented lectures was a detailed presentation of the molecular biology of bcr-abl with an emphasis on its impact on clinical management.

As is readily apparent from this model there is enormous potential to integrate vast areas of human pathophysiology. The key is integration and achievement of a moderate degree of depth (i.e., avoiding superficiality while not attempting to provide an entire medical education). The curricular format based on a single disease requires that faculty relate their particular discussions to the central theme, chronic myelocytic leukemia in this case.

During some courses Washington University invites outstanding lecturers to complement the Washington University faculty. For example, Orah Platt, M.D., Harvard Medical School, has spoken twice on sickle cell disease; J. Joseph Marr, M.D., Searle, has spoken on malaria; and Richard Lawn, Ph.D., Stanford University, has spoken on coronary artery disease. James Griffin, M.D. also from Harvard Medical School, spoke on cell biology of CML. Washington University has also invited keynote visiting professors to present seminars to the entire medical center community toward the end of each theme. For example, in the case of cystic fibrosis, Michael Welch, M.D., Ph.D., professor of medicine and cell physiology, investigator of the Howard Hughes Medical Institute, University of Iowa, presented a lecture titled "The Pathway of Discovery in Cystic Fibrosis."

The Markey Pathway Clinical Mentor Program

Another central element of this approach to bridging the bed-bench gap and developing basic scientists who aspire to focus on investigative aspects of human disease is the Clinical Mentor program. The overall goal of this pathway component is to enhance awareness of the underlying biology and pathobiology of human disease. Thus, Washington University has established a mechanism for sustained interactions of trainees and clinical scholars in an area of mutual investigative interest. The clinical mentor component re-establishes the traditional student-mentor relationship, a foundation of scientific training but one that has been relegated to a minor position in many of today's graduate education programs. This provides for a close interpersonal relationship between student and mentor.

Under the guidance of Dr. Jeffrey Saffitz, professor of pathology and medicine and clinical mentorship director for the pathway, trainees together with their research advisors will select members of the faculty with clinical involvement to serve as clinical mentors for the students. This liaison in essence establishes a basic science and clinical science mentor pair for each student. The clinical science mentor will be a top-notch investigator. The principal goal here is to provide a forum for and continuity with the exciting issues in clinical medicine. In practice this is accomplished by having the student join the clinical mentor for about two hours per month to participate in any of the various clinical activities of the mentor. Often students attend combined specialty conferences with their mentors. The medical center has a well-organized, ongoing series of interdisciplinary clinical specialty conferences, which are interdepartmental and interdivisional. These conferences generally meet weekly or biweekly and provide an interactive forum for discussion of current concepts and emerging ideas in clinical medicine. Examples of these conferences are

- Medical genetics conference (includes faculty from obstetrics, pediatrics, medicine, pathology, and surgery);
- Autopsy conference (includes faculty from pathology, radiology, medicine, pediatrics, and surgery);
- Allergy-clinical immunology conference (includes faculty from medicine, pediatrics, and pathology);
- Metabolism-endocrinology-nutrition conference (includes faculty from medicine, pediatrics, pathology, and surgery);
- Hematology-oncology conference (includes faculty from medicine, pediatrics, pathology, and surgery); and
- Transplantation biology conference (includes faculty from medicine, pathology, surgery, and pediatrics).

These conferences expose the student to the concepts and the faculty in the targeted areas. In addition, students and mentors are encouraged to participate together in inpatient attending or consultation rounds, outpatient activities, various clinical procedures, or other activities that the clinical mentor would normally perform as part of clinical responsibilities. It is important not to micromanage the type of interactions between students and mentors. The best results usually come from providing some basic ground rules for the program and then allowing two highly motivated and energetic people to develop their own mutually fulfilling relationship. The goal is not to detract from investigative scholarship, which is the major focus for graduate students after their first three semesters, but to supplement it. The clinical orientation of the mentor interaction provides a longitudinal program during the thesis years. The trainee's time commitment is typically small (a few hours per month) but the potential impact can be great and long lasting.

The clinical mentor component of the human pathobiology pathway has been a major success since it was begun seven years ago. For most of the pathway students this program has provided the first (and for many probably the only) opportunity to participate in the clinical activities of an academic medical center and to do so as the personal guest of an outstanding physician-scientist. Responses of the students to annual surveys about the program have been uniformly strongly positive. Many have commented that their experiences significantly broadened their scientific horizons and deepened their commitment to careers in which basic research is directly linked to important clinical problems. Many medical mentors and students mentioned that their relationships lasted longer than the required three semesters and frequently was for many more hours per month than the proscribed minimum.

Both the program director (Dr. Saffitz) and the program administrator (Ms. Deborah Sinak) evaluate the mentor program on an ongoing basis. In addition to the annual survey, which gives participants an opportunity to comment in detail on their individual experiences, Dr. Saffitz and Ms. Sinak communicate informally with both students and faculty mentors throughout the course of the 18 months of this portion of the program to monitor progress. When students and wisely chosen mentors are brought together under the aegis of this program, they tend to develop extremely effective working relationships to the great benefit of both parties.

The Markey Pathway Human Pathobiology Annual Retreat

One of the important components of the pathway in human disease is providing the students with a sense of identity and of being part of a group accomplishing something meaningful. For this reason several special activities have been organized, including an annual two-day retreat to provide students with an opportunity to present their own research and exchange ideas. Each year in late spring all pathway students, mentors, course faculty, steering committee, and selected medical school scholars are invited to participate in a retreat. There is always a keynote speaker, generally from outside the university. For example, in May 1997 Professor Kari Raivio, M.D., Ph.D., rector of the University of Helsinki, Finland, and a world-renowned human developmental biologist and physician, scientist, and educator, served as the keynote speaker and discussed educational pathways for human biologists in Europe.

The retreat provides an environment of intimacy for personal and scientific interactions between trainees and faculty. It includes a session devoted to student presentations and roundtable discussions of selected scientific topics, including a critique of the course in pathobiology and the clinical mentor program. The retreat offers a chance to exchange information and ideas in a rural setting (at selected sites a few hours' drive from St. Louis), where recreation and social events are also featured. After dinner on the first evening a lecture is presented, which provides a way for introduction of the keynote speaker.

Roundtable discussions are planned to acquaint students and junior faculty with elements of professional life. Senior faculty and guests present information on various topics, such as how to select a postdoctoral position; how to acquire funding for research; the nature of positions in academia, government, and industry; and the changing climate of biomedical investigation.

Characteristics of Students

The Markey pathway program is now in its eighth year. It is obviously too early to formally define the long-term success of our program. The academic growth of the trainees, the ability of the trainees to successfully secure peer-reviewed grant support, their election to esteemed scientific societies, and selection to peer-review panels are criteria that will be used to judge the success of the program. Long-term success of Markey trainees will ultimately be judged on the basis of successful application of sophisticated tools of biological inquiry to studies of human disease.

Recruiting and Admissions Process

Recruiting for Markey pathway students has employed the usual brochures and listings in *Peterson's Guide*. There is also a Web link from the division's Web page (<http//dbbs.wustl.edu>). The mainstay of the recruiting effort has been the contacts with a number of smaller colleges known for the quality and rigor of their programs. Washington University offers a program of summer research internships to students from these colleges. The Markey pathway is announced to all students who apply for graduate research training in the Division of Biology and Biomedical Sciences, as well as publicized nationally through mailings to undergraduate schools, for example. The result of these intensive efforts was that the division received greatly increased numbers of applications from these high-quality sources, and the overall quality of the applicant pool has been trending steadily upward for the last several years.

Over the past eight years the Markey pathway in human pathobiology has provided a powerful recruiting incentive that has enhanced the quality of the overall pool of applicants to the Division of Biology and Biomedical Sciences. Another advantage of the pathway has been the potential to attract undergraduate students who have leanings toward both human disease and basic science. This can most effectively be done with the pre-professional advisors (i.e., general pre-medical advisors) at most colleges. In order to maintain the integrated strength of the Division in graduate education, Pathway students are generally selected during their first year of graduate studies and are formally enrolled during years 2 and 3 of their 5 to 5.5 years of graduate education. Following their two years in the pathway students continue to attend seminars and usually maintain close relationships with their clinical mentors.

As stated above, graduate students are selected for the Markey pathway in the second half of their first year. Students apply to the pathway by April 1 of each year. Applications along with academic credentials (including graduate record exams and grades in undergraduate and graduate school), course evaluations, lab rotation evaluations while at Washington University, letters of recommendation from mentors for the predoctoral applicants and project and goal statements for the postdoctoral applicants are reviewed and ranked by the Admissions Committee. Pre- and postdoctoral admissions committees (subcommittees of the Steering Committee) endeavor to recruit the brightest, most motivated applicants, while achieving a good mix of graduate students and postdoctoral fellows, and a reasonable balance among various interests (e.g., neurobiology, immunology, genetics) such that substantial cross-fertilization will occur during the courses and other activities of the program.

Financial Data

The Markey pathway at Washington University has operated much like the other components of the Division of Biology and Biomedical Sciences. Finances are required to support trainee tuition and stipends, administrative costs of the division, programmatic costs of the pathway (faculty leadership), and ancillary costs directly associated with the pathway (e.g., annual retreat, invited speakers). The total costs per annum supported by the Markey Trust were approximately $600,000. Since termination of the Markey support it has been necessary to shift some of the costs for tuition and stipends to the trainee's laboratory, thus allowing the pathway to continue with total costs per annum of approximately $173,000. This cost shifting consisted primarily of eliminating tuition reimbursement for graduate students and stipends for postdoctoral students. In addition, because all current funding is intramural, overhead costs are not applicable. Additional economies were achieved by reducing expenditures for the Markey retreat and visiting scholars, and eliminating funding for invited speakers.

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Summary of Site Visits to Markey-Funded Programs That Provided Training in Basic Research to Physicians

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO MOLECULAR MEDICINE PROGRAM

The University of California, San Francisco, Molecular Medicine program was developed to address the problem of declining numbers of M.D. investigators just as biomedical science stood on the threshold of a new era. Currently most physician-scientists start their training in research only after four years of medical school and a minimum of four years of clinical training. Their initial research experience occurs when they are in their late twenties or early thirties. There is typically no requirement for formal coursework in the biological sciences or for contact with the preclinical faculty. These factors make it nearly impossible for promising physician-scientists to assimilate a new language and a new way of thinking that integrates the biomedical sciences. Training has generally been limited to clinical departments and is critically inbred. Most physician-scientist faculty train their students in exactly the same ways they were trained. This system favors short-term over open-ended investigations and its isolation deters the assimilation of new ideas and technologies.

The Molecular Medicine program (MMP) overcomes these problems in training physician-scientists by integrating their training with the Program in Biomedical Sciences (PIBS), an umbrella organization of biological science disciplines. Fellowship positions are available at different stages of clinical training: in conjunction with residency training or post-clinical fellowship. At the time of acceptance into the program MMP fellows are guaranteed access to three years of training positions in laboratories of molecular medicine or other appropriate faculty either in the Program in Biomedical Sciences or the Biomedical Sciences program. Although funding for three years of research is guaranteed, the fellows can accept alternative sources of funding, which may provide greater financial support and national prestige. Participating faculty are members of interdisciplinary programs, including Biochemistry and Molecular Biology, Immunology, Microbiology, Cell Biology, Developmental Biology, Genetics, and Neuroscience.

The MMP is designed primarily for individuals who have completed medical school and are entering internship. Candidates are expected to have a strong science background and a demonstrated commitment to laboratory investigation. Candidates are screened by both clinical and research faculty, and the candidates must meet the academic rigor expected of the basic scientists in the Program in Biomedical Sciences. Fellows take rigorous coursework in biochemistry, cell biology, and molecular genetics. This assures that fellows have a theoretical background comparable to those with graduate degrees in biochemistry. To date, 35 individuals have participated in the MMP, which began accepting fellows in 1992.

MEETING WITH DAN GANEM, ORIGINAL PROGRAM DIRECTOR

The site visit team met with Don Ganem, the originator of the MMP, who described its history and evolution. The program was designed to attract M.D. candidates who were finishing a UCSF residency or the clinical portion of a fellowship. Candidates were not expected to have an extensive research background, as the idea was to identify and develop talented trainees for careers as physician-scientists who might not otherwise have had this opportunity.

Originally the mission was to develop a new program in the Markey Program in Biological Sciences (PIBS), called the Program in Biomedical Sciences (BMS) that would focus on disease-related research. However, there were very few physician-scientist faculty in this program and furthermore, their research was not always valued by the more traditional Ph.D. scientists. The clinical departments did not relate well to the PIBS and had not been encouraged to cooperate. The clinical faculty either did not have the pedagogical skills or did not appreciate the structure of graduate education. This lack of cooperation was perhaps due to the fact that the clinical faculty was not involved in the initial planning of the program to develop the BMS.

Early in the BMS's development the fellows were required to take PIBS basic science courses. These courses were selective and very labor intensive for both faculty and students, which resulted in very high quality, but put clinical faculty and students at a disadvantage. The PIBS faculty viewed disease-related science as an enrichment activity and did not initially appreciate the depth of curricula necessary for training clinically oriented scientists.

Because of the faculty tensions, the lack of depth in disease-related research, and the disadvantage of clinical students in the PIBS and BMS, Dr. Ganem proposed that Markey funding be used to develop a parallel Molecular Medicine program (MMP) that allowed off-campus instruction and modified entry criteria for clinical faculty. This new development reduced resistance from clinical faculty. Existing course work in cell biology and genetics was used, but the new program also introduced course work in tissues and organs.

By 1996 when Marc Shuman became director of the program, it became apparent that changes were required in the admissions procedure. Previously fellows were recruited primarily from UCSF. In an attempt to attract more and better-qualified candidates the program administrators decided to focus on a national recruiting effort of M.D./Ph.D. fellows. Before 1996, 21 fellows were admitted and only one was an M.D./Ph.D. Between 1996 and the current time 14 fellows were admitted—all with M.D./Ph.D. degrees. Currently about two-thirds of the fellows are supported by research grants. About three-fourths of the fellows in the initial cohorts work in academic medical centers. Part of the focus on recruiting M.D./Ph.D. fellows was a consequence of the realization that the structure of teaching hospitals has changed. With the emergence of managed care the focus is on getting patients out of the hospital as quickly as possible. Attending physicians cannot spend their time on teaching the science of the patient's illness, efficiency in medicine, or outcomes research.

Recruiting for fellows who would enter into the program in 2001 was begun. The applicant pool was about 65 candidates, of whom two-thirds were M.D./Ph.D.s. Four candidates had been accepted for the 2001 class.

MEETING WITH PROGRAM FACULTY AND MENTORS

Faculty attending this portion of the site visit were Art Weiss, Shaun Coughlin, Mark Goldsmith, Don Ganem, and Marc Shuman. The faculty emphasized the changing nature of academic medical centers. Because of managed care, hospitals are required to release patients sooner than before. Attending physicians do not have the opportunity to observe and study disease processes. Outcomes research has practically vanished from the teaching hospital. Those residents on the primary care track receive a good amount of support, while medical track residents often seem to flounder.

The faculty stressed the importance of the organizational culture of the institution. For example, the faculty believes that the PIBS would not succeed at institutions like Harvard because of their exclusively departmental focus.

Mentorship, a clear pathway for the physician-scientist, and an understanding of the value of disease-related research are the most important contributions of the MMP. The faculty also stated that disease-oriented research is the domain of the M.D./Ph.D., while patient-oriented research may be more effectively done by an M.D. with some scientific training.

MEETING WITH MMP FELLOWS

Fellows attending this portion of the visit were Dan Lerner, Joshua Reddy, Robin Shaw, Michelle Herrington, Andrai Goga, Chris Haqq, Al Fisher, Tony Gerber, and Mary Beth Humphrey. These fellows overwhelmingly stated that the main attraction of UCSF and the MMP was the guaranteed funding for research. Not only was funding secure but the stipend was about 25 percent greater than NIH stipends. The fellows also take advantage of short-tracking (exchanging one year of residency for one year of research) their training. The fellows found that Markey has enabled them to collect pilot data, which helped them obtain initial grants. They reported that they felt supported by the clinical faculty while doing their research and that the MMP status gave them access to labs that they might otherwise not have had.

The fellows also reported a few disadvantages of the MMP. There is a lack of protected time while an intern or resident, which hinders them from starting their research; sometimes the lab director's interest and the fellow's interest are not compatible; and there is no formalized mentorship. Marc Shuman does most of the mentoring, and while he does a very good job (the fellows spoke very highly of him), the program is getting too large for him to effectively continue in this capacity.

FINANCIAL DATA

Because many fellows obtain funding through multiple sources, Markey funds have been shepherded. Consequently Markey funding will end in three years; UCSF administration is committed to continuing the MMP. Fellows for the 2001 academic year are actively being recruited, and they will require funding beyond that provided by the Markey award.

SUMMARY

The Molecular Medicine program is a highly organized training program that takes advantage of the resources available at UCSF. The leaders of the PIBS recognized that they had a medical mission, and the MMP emerged as a way to fulfill that mission. The organizational culture at UCSF that led to the development of the PIBS was an essential element in the development of the MMP.

The site visit team came to three major conclusions about the program.

1. To replicate this program, a critical mass of physician-scientists who are externally motivated (not just interested in their particular field) is needed. There would have to be a minimum of six faculty and their labs along with support from the chair or dean.
2. The residents need stronger mentorship to keep them in touch with science. Marc Shuman, who currently serves as program director and mentor to all the fellows, will soon become overwhelmed. The fellows are concerned about mentoring, especially while they are residents.
3. The MMP fellows know in general what they want to do when they arrive at UCSF. They know the subspecialty and the direction of research, even to the point of knowing the lab they want to work in. These are highly motivated students who will probably do well wherever they decide to train.

COLLEGE OF PHYSICIANS AND SURGEONS OF COLUMBIA UNIVERSITY CAREER TRACKS PROGRAM IN POSTGRADUATE MEDICAL EDUCATION

Myron Weisfeldt, the program director, described the purpose and mission of the Career Tracks program at the College of Physicians and Surgeons at Columbia University (Columbia-P&S). Before coming to Columbia P&S Dr. Weisfeldt directed the Johns Hopkins National Research Service Awards training program. It was very successful in producing a number of academic physicians in national and university leadership positions. He decided to implement a similar model of training physicians in research at Columbia-P&S. With the support from both the medical school administration and basic science faculty the Career Tracks program was developed. The goals of the program are to facilitate the clinical and research training and career development of talented medical school graduates who enter residency-training programs at Columbia-P&S with an M.D./Ph.D. degree or other evidence of a strong research background.

The typical training pattern for physician-scientists is believed to be too clinically intense (up to six years following the M.D.) before any training in research is introduced. In the Career Tracks program research training begins following the second or third year of house staff training. The program provides two years of training in biomedical research, with subspecialty training following the Career Tracks program. Because Dr. Weisfeldt felt strongly that exposure to basic research must take place early in the training period, Markey funds were not available to persons with more advanced clinical training, or to those who wanted to return to the research lab after subspecialty training.

There are four tracks in the Career Tracks program at Columbia-P&S: (1) basic research, which is the Markey-funded track; (2) clinical research; (3) traditional internal medicine; and (4) general medicine. These tracks are offered following the first two years of residency. At the conclusion of their clinical training period residents interested in either research track will have the opportunity to identify a research mentor and laboratory in which to conduct research. Research in the chosen basic or clinical laboratories begins after the second or third years of residency, and the period of support is usually two to three years. Thus, residents selected for the research tracks after two years of residency training will be eligible for certification in internal medicine after a combined total of five years of training. If the research is performed in connection with a subspecialty training program, the resident will become eligible for combined certification in internal medicine and the subspecialty after six or seven years, depending on the subspecialty area. During the research-training period residents will continue to follow their own patients in the general medicine outpatient clinic to maintain their clinical skills. Each year the Columbia-P&S house staff comprises about 40 persons. From this cohort approximately eight persons indicate some interest in the basic research career track and three or four are admitted to the program.

A key component of the program is career planning and guidance. House staff who are interested in the basic science track notify program directors by the end of their first or beginning of their second year. Individual meetings with the program directors are arranged to discuss specific plans, including career plans, laboratory possibilities, and timetables. In the months that follow the interested house staff meet with laboratory heads to make a final decision as to lab choice. House staff then submit a letter of intent, which includes overall career plans, a CV, general research interests, and their chosen laboratory. A committee consisting of program directors and Dr. Weisfeldt make program acceptance decisions.

Progress is monitored throughout the year by program directors, laboratory heads, and the fellows. Fellows are asked to present their research findings at several informal meetings. All the fellows are invited to present findings at periodic formal dinners. Fellows are encouraged to apply for research grants during their first year to fund future years of fellowship research.

MEETING WITH PROGRAM MENTORS

The site visit team met with the laboratory mentors of the program: David Hirsh, acting dean and chair, biochemistry and molecular biophysics; Andrew Marks, director, Molecular Cardiology program; Lloyd Greene, professor of pathology; Henry Ginsberg, director, Irving Center for Clinical Research; Rudolph Leibel, chief, Division of Molecular Genetics; Ira Tabas, professor of medicine; and Stephen Canfield, assistant professor of medicine and former fellow.

Career Tracks fellows work very closely with a faculty mentor. The mentor may be either basic science faculty or from a clinical department. During the initial six months to one year the mentor may meet with the fellow on a daily basis. Labs have typically six postdocs and a few graduate students and technicians, all of whom are resources for the fellow. Fellows work on a wide range of projects in order to develop skills before deciding on their particular research project. In some cases fellows take on very ambitious projects, requiring substantial funding for equipment and supplies, such as computers and mice.

The mentors agreed that training someone in basic research is like an apprenticeship and that the mentor/fellow relationship is very important. The mentors stressed that because it is a training program and that because the mentor is not paying for the training, the fellows are not expected to produce results, as some externally funded grants require. Finally, the mentors stated that because the Career Tracks program guarantees up to two years of funding, there is less anxiety about transition into the next phase of the fellows' career.

MEETING WITH MARKEY FELLOWS

Fellows who attended this meeting were Anthony Ferrante, Yi-Hao Yu, Yi-ming Yang, and Stephen Canfield. The first three are current fellows, and Dr. Canfield was a fellow in 1996-1997. The fellows overwhelmingly felt that the program allowed them to pursue their research interests rather than searching for a lab that had an open funding slot. All the fellows attending the meeting plan to develop a career in academic medicine and research.

The fellows all took different pathways to the basic research career track. Three fellows had gone through an M.D./Ph.D. program, although one of them took off a year to serve as chief resident. One fellow had an undergraduate degree in physics and used that background to dovetail his experience with his mentor's interest in development of quantitative assays. This fellow's work was highly successful and culminated in the development of a microarray facility at Columbia-P&S.

The fellows pointed out that the Markey award let them investigate new and more interesting areas of research and blend their interests with the resources at Columbia-P&S. This blending resulted from frequent interaction between fellows and the program directors, who counseled the fellows on potential mentors and directed the fellows to the mentors who would best complement their interests and abilities.

FINANCIAL DATA

The original award was for $2 million. Markey funding for fellows will continue through 2003. To date there has been a total of 25 years of support for 15 fellows. The original cost per fellow was budgeted at $47,520, including fringe, travel, and indirect costs. Because many of the fellows have been able to obtain supplemental funding, the program has actually spent less per fellow on average. University and program administration are fully committed to the continuation of the program.

SUMMARY

Although the Career Tracks program at Columbia-P&S is not the only Markey program that offers research fellowships during the clinical house staff experience—UCSF's Molecular Medicine program occurs at the same point in training—Columbia-P&S is unique in its emphasis on career counseling. Much time is spent on finding the right match of fellows and lab directors so that the fellows feel confident in being able to further their career in their chosen areas of research. A few of the fellows were placed in non-Columbia labs because these labs were deemed the most appropriate match for the fellow. Despite the excellent career counseling provided by the program's codirectors, the level of mentorship was varied among lab directors. Some fellows reported daily personal contact with their mentors, while others reported sporadic contact, such as "when he needs me, which is not that often." More emphasis on mentoring is an area where the program could be strengthened.

The site visit team was impressed with the high quality of the structure and organization of Career Tracks program at Columbia-P&S. It was clear that career counseling and placement of fellows in labs received priority and the results have paid off. The level of sophistication of several of the research projects has led to the acquisition of new equipment that is currently used by several departments. At least one new patent application has resulted from the research of Markey fellows. Columbia-P&S hired at least two fellows at the conclusion of their fellowships. A few returned to clinical practice, which may be an indication of the burdensome financial obligations facing young physician-scientists.

CHILDREN'S HOSPITAL BOSTON/HARVARD UNIVERSITY THE MARKEY CHILD HEALTH RESEARCH CENTER

Philip Pizzo, the program director, stated that the most crucial period in the development of the physician-scientist is the research fellowship years. Those four years represent the "make or break" in the continuum. Rapid, indeed, logarithmic growth must occur during this phase if the physician-scientist is to put roots down firmly in biomedical science and discover its application to relevant clinical problems.

This growth can occur only when aspiring physician-scientists have the firm mentorship of more senior physician-scientists who have been through the process, and will either guide the young persons in their own laboratories or arrange a superb laboratory experience in the laboratory of a close and cooperative colleague. It is this vital nexus between the mentor and the aspiring physician-scientist that underlies this program. The task of training program directors is to make the long road of training financially feasible for young persons who are devoted to family as well as to their profession. Above all, the scientific environment during those crucial early years must be exceptional, requiring the cooperation of Ph.D.-holding scientists and senior physician-scientists to create an ambiance that will lead to success.

The pediatrician-scientist is perhaps more at risk than those in other specialties. The number of students entering pediatric training has dropped from 30 percent to 20 percent. Additionally, because women, who make up about 80 percent of the pediatric workforce, have additional challenges that hinder them from pursuing a research career the pediatric scientist enterprise must receive special consideration.

The mission of the Markey Child Health Research Center is to encourage, train, and develop the careers of young pediatrician investigators through research development. The Markey award helped support young pediatric investigators during a critical and vulnerable period in their career development. Markey fellowships were awarded for one or two years, with the goal being to obtain outside funding for research. If a fellow was able to obtain adequate funding after the first year, Markey funds were stopped.

A total of 17 fellows have rotated through the center. Most of these fellows have M.D. degrees; only 3 have M.D./Ph.D. degrees. Eleven of the fellows were funded for only one year, five fellows received two years of funding, and one fellow received three years of funding. Most fellows were able to obtain grants or other fellowships, such as K-08 awards, awards from Burroughs Wellcome, Howard Hughes Medical Institute, or R-01 awards from the NIH.

MEETING WITH PROGRAM FACULTY AND CLINICAL MENTORS

The site visit team met with the program's lab directors and mentors: David Nathan, the originator of the Markey Child Health Research Center; Steve Harrison, codirector of the program; Allen Walker; Joseph Majzow; Lou Kunkel; and Merton Benfield. These mentors emphasized that time for training and research is critical and that the Markey award gave these young faculty members that protected time. Generally, for M.D.s the greater the amount of protected time for research, the higher the probability of that M.D. receiving an NIH R-01 grant. If the young scientists are cast off too early, their careers never fully develop. Longer training in one place is better than multiple, shorter periods of training. Longer time in training enhances the ability to complete research projects and to publish based on this bottom-line research productivity. This is the typical model of graduate education in U.S. institutions. In comparison, graduate students in Great Britain tend to publish whatever findings they may have at the end of their three to four years in the lab. This is why, the mentors believe, there is a need for four or more years of protected research time. A critical mass is important to generate good research. Departments or labs that are too small may have a greater difficulty in achieving success.

The mentors agreed that one of the strengths of Markey was its approach of identifying programs and institutions with a proven track record and providing them with substantial funding, generally without restrictions. The mentors believed that by allowing the institution to determine who received a grant the mentors were able to choose individuals who they knew would do well. The selection process allowed the mentors to use intangible criteria to identify fellows based on prediction of success. Markey's flexibility in funding the program instead of individuals was very important. The Markey approach could only succeed with private foundations; in fact, the Doris Duke Foundation is probably going to follow this same principle. The K-08 award process is more risky because it funds individuals rather than awarding funds to the program and letting the program staff identify candidates. The mentors believed that this approach might fund those who are less likely to be successful. One solution, the mentors believed, was increasing national funding for training programs in biomedical research for young physicians.

The mentors agreed that the Markey fellows probably would have done well without the Markey funding but that many of them would probably have had to leave Harvard because of the high cost of living in the Harvard and Boston area. Additionally, the Markey funds allowed other resources to be directed to the so-called second-tier scholars who provide support in the labs.

MEETING WITH MARKEY FELLOWS

Fellows attending the site visit were Maureen Jonas, Jordan Kreidberg, Athos Bousvarios, Christina Luedke, Ellis Neufield, Garey Silverman, Dan Nigrin, and Robert Husson. Most of the fellows reported that Markey funds allowed them to concentrate their time and effort on obtaining external funding. For example, Maureen Jonas was a full-time clinical physician in hepatitis. She had been out of training for quite a while and may have been less competitive in a grant proposal. Markey provided time to develop a large, multicentered trial for which she received an NIH grant. Dan Nigrin conducts research in bioinformatics, which does not fit into regular NIH funding categories; the Markey funds gave him time to craft a successful NIH grant proposal. Robert Husson had been developing new techniques for a new knockout mouse; therefore he did not have much to show for his time in fellowship. The Markey funds provided a bridge year so that he could publish and then obtain a K-08 grant.

The fellows had a limited awareness of the Markey Trust and its mission. They never met as a group and had little awareness of other Markey fellows in their program. They did express the desire to have more of a Markey cohort for exchange of ideas and fellowship.

FINANCIAL DATA

The site visit team met with Bill New, who is the financial administrator for Children's Hospital, Boston. The total research budget for Children's Hospital is $100 million, including indirect costs. Because much of the research funding does not include overhead, 30-40 percent of actual funding is lost. He reported that the $2 million Markey program resulted in a $750,000 loss to Children's Hospital. The hospital is freestanding and receives no support for graduate medical education. The hospital lost $61 million last year.

Perhaps most importantly, the Markey funds have been exhausted. Children's Hospital set aside a portion of a $25 million endowment so that the program could continue. Because of other budget priorities, that set-aside is now being used to recruit new senior faculty.

SUMMARY

The Markey Child Health Research Center is a powerful resource for young investigators who need assistance in obtaining external research funding. The site visit team was impressed with the caliber of the Markey fellows and their research at Children's Hospital, Boston. The team found five emerging themes during its visit.

1. The funding of institutional programs is much more valuable than funding individuals.
2. The interdisciplinary culture of the institution is very important. Much credit is given to Dr. Stephen Harrison and his vision for his lab.
3. Time spent on research is critical. Four or more years in the same place are needed for successful research career development.
4. The K-08 award process is not very reliable or a good predictor of success. Consistent programmatic funding allows for better planning.
5. Children's teaching hospitals face special fiscal constraints, as they do not fully participate in Medicare funding for physician training.

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Biographies of Members of the Lucille P. Markey Charitable Trust Programs in Biomedical Sciences Committee

Enriqueta Bond, Ph.D., is the president of the Burroughs Wellcome Fund and a former executive director of the Institute of Medicine. She is also a member of the IOM. Her research interests include genetics, molecular biology, and science policy. She has served on the IOM's Board on Health Sciences Policy and on the Committee to Study Incentives for Resource Sharing in the Biomedical Sciences. Dr. Bond holds a Ph.D. in biology.

William T. Butler, M.D., is the chancellor of Baylor College of Medicine, where he is also a professor of internal medicine and of microbiology and immunology. He served as the College's president and chief executive officer from 1979 to 1996. Before joining the Baylor faculty in 1966 Dr. Butler served as the chief clinical associate in the Laboratory of Clinical Medicine at the National Institute of Allergy and Infectious Diseases at the NIH. He is on the boards of Browning-Ferris Industries, C. R. Bard, Inc., and Lyondell Petrochemical, where he is chairman of the board. Dr. Butler has done extensive research on the effects of corticosteroids and other drugs on the immune system and on the mechanism of rejection of organ transplants. He has written numerous publications in the fields of immunology, infectious disease, and medical administration. He holds an M.D. from Western Reserve University and a B.A. from Oberlin College. Dr. Butler is a member of the Institute of Medicine.

Elaine K. Gallin, Ph.D., is the program director for medical research at the Doris Duke Charitable Foundation. Dr. Gallin's research involves the characterization of ion transport mechanisms in macrophages, leukocyte-endothelial cell interactions, and the effects of ionizing radiation of leukocyte function and vascular integrity. She received her B.S. from Cornell University, her M.S. from Hunter College, and her Ph.D. from City University of New York. She has held positions at the Uniformed Services University, Georgetown University Medical School, was a congressional fellow on the Public Policy Committee, and is a member of the Physiology Study Section at the NIH.

Mary-Lou Pardue, Ph.D., is the Boris Magasanik Professor of Biology at the Massachusetts Institute of Technology and a member of the National Academy of Sciences. As a geneticist and cell biologist she has studied eukaryotic chromosomes with emphasis on sequences involved in the structure and function of chromosomes as organelles. She served as president of both the Genetics Society of America and the American Society for Cell Biology and was chair of the Institute of Medicine Committee on Understanding of the Biology of Sex and Gender Differences. She received a Ph.D. from Yale University in 1970.

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