The future of clinical investigation[1]

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The author discusses the decline of physician involvement in clinical investigation and describes programs established by the National Institutes of Health to encourage more participation in such research by M.D.-degree holders.

Index terms: Clinical trials • Irvine H. Page lectures • Physicians • Research

Cleve Clin Q 51:567–574, Winter 1984

Irvine Page, throughout his illustrious career, has epitomized the finest qualities of the scientist, physician, educator, and writer. I have known Dr. Page for many years, though not as well as I would have liked. We served together for a time as advisers to Jack Whitehead when Jack was first envisioning a Whitehead Institute for Medical Research. I enjoyed that brief association. I knew, of course, of Dr. Page's contributions to hypertension and his discovery of angiotensin and serotonin, but I learned much more about him from an article in the *Journal of the American Medical Association*, especially where Dr. Page comments on himself.[1]

The research commitment and accomplishments at the Cleveland Clinic to which Dr. Page made such seminal contributions are illustrative of the fact that a healthy and productive clinical research effort is a mosaic of achievements by universities, academies, clinics, foundations, industry, government, and the scientific and health communities. There is little need to be convinced of the importance of clinical research, but sometimes, one cannot help

[1] Delivered at The Cleveland Clinic Foundation, June 24, 1983.

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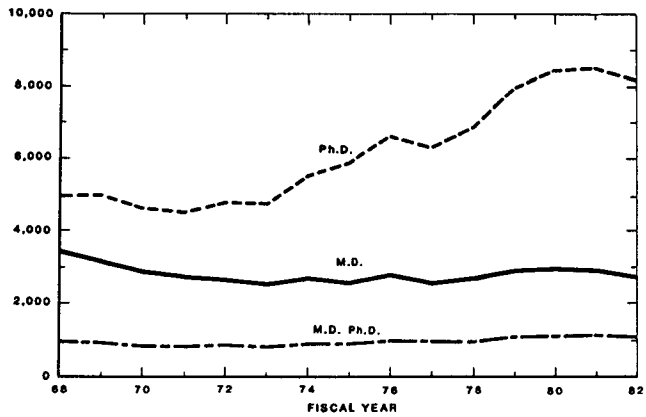

Fig. 1. Number of principal investigators with M.D., Ph.D., or M.D. and Ph.D. degrees that have been awarded RO1 grants.

but be struck by the importance of specific contributions, especially research done by recent winners of the Hazen Award for Clinical Research: Jesse Roth for explaining the basic defect in cell receptors in diabetes of the obese, Henry Kunkle for demonstrating the role of circulating immune complexes in disease, Aaron Lerner for explaining the biology of benign and malignant pigment cells, and Joseph Goldstein and Michael Brown for elucidating the LDL receptor pathway. One could also cite recent Lasker Award Winners in Clinical Research, such as Elizabeth Neufeld for elucidating the metabolic defects of mucopolysaccharidoses and Roscoe Brady for his contributions to the biochemistry and experimental therapy of certain lipid storage diseases. Awards such as these recognize outstanding examples of clinical research. In this type of research, the clinical question is the central force of the investigation. The work requires someone who is both medically knowledgeable and scientifically trained. Clearly, the clinical investigator provides the indispensable link between the laboratory and the human being who is the ultimate focus of all our endeavors.

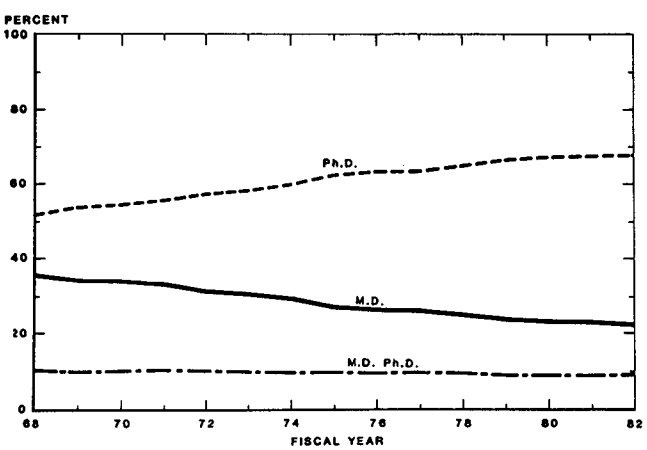

Fig. 2. Principal investigators with M.D., Ph.D., or M.D. and Ph.D. degrees expressed as a percent of all principal investigators with RO1 grants.

Yet, often forgotten as a major branch of clinical research are the clinical trials. The progress in our ability to manage disease would stagnate if such work were not pursued. An illustration of this is the work of Emil Frei III and Emil J. Freireich, who recently received the 1983 Charles F. Kettering Prize for Cancer Research from the General Motors Cancer Research Foundation. These scientists, who began their careers together at the National Cancer Institute in 1955, developed, over the years, the first curative treatment of childhood leukemia and, in the process, established nearly all the principles of scientific chemotherapy trials for cancers of all kinds.

Clinical trials, as a segment of clinical research, are expensive and time-consuming. Sometimes the gains seem slow. When Frei and Freireich began their clinical studies, less than 1% of patients lived long enough to be considered cured. Today, the cure rate for childhood leukemia is approximately 56%. These studies, given their impact on the treatment of leukemia *and* their impact on chemotherapy for other types of cancers, were major contributions. Clinical trials must continue to move biomedical science from the bench to the bedside; however, during strained economic periods, industry, including the health insurance industry, as well as government agencies that are concerned with the financing of health care, must cooperate to meet the large costs of such trials. Dr. David A. Hamburg, former president of the Institute of Medicine, put it well when he spoke before a group gathered in 1980 to discuss needs and opportunities in clinical investigation in the 1980s:

> We must do everything in our power to see that the great fundamental advances—indeed the inspiring advances in molecular and cellular biology—will be available as soon as possible for health interventions of a demonstrably useful character. But the authentic biological revolution that has been generated by several decades of intensive basic research is not easily

> translated into clinically valid applications. An interpreter is needed, and it is the clinical investigator who serves that function. The flow of information is by no means unidirectional; if basic science has something to say to clinical investigation, so too does clinical investigation offer much to basic science. Clinical research remains the vital bridge between advances in basic science on the one hand and improvements in health care—diagnostic, therapeutic or preventive—on the other.[2]

Dr. Hamburg went on to say, "I was concerned in 1975, and remain concerned today, that the interwoven fabric of basic science and clinical investigation is to some extent unraveling."[2]

I would like to examine his concern, which to some extent, I share. Yet, I do not believe that the current situation regarding physician involvement in research constitutes a crisis. That would be an exaggeration. Available data show that the system is in a period of adjustment.

The two-way flow from basic science to clinical application and from clinical observation to basic science does not simply occur. It requires initiation, preparation, a conducive institutional atmosphere, and sustained support. The stakes are so high and the system so delicate that nurturing of the clinical investigation system needs the attention of the government and the private sector, including industry and the foundations.

We, the National Institutes of Health (NIH) and the scientific community, need to look at a number of factors that appear to be contributing to a declining interest in clinical investigation on the part of young physicians: (*a*) unfavorable social climate (in the society at large and within medical schools), (*b*) lack of early exposure to research, (*c*) funding constraints, (*d*) time demands on academic physicians, (*e*) regulatory burdens, (*f*) and tenure-associated problems.[3] In a cooperative effort, we need to examine what might be done to alleviate some of these strains on the system.

As shown in *Figure 1*, the absolute number of NIH research grants (RO1s) awarded to M.D.s decreased from approximately 3,400 in 1968 to approximately 2,500 in 1973. There has been some recovery since, but the number was still below 3,000 in 1982. The number of grants given to M.D.-Ph.D.s (and these are, of course, in much smaller numbers) has been holding

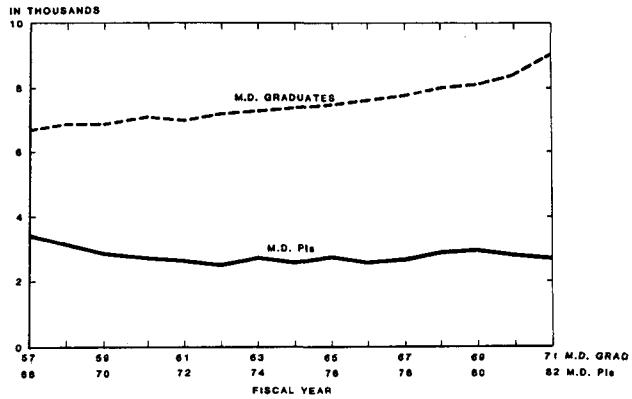

Fig. 3. Number of principal investigators (*PIs*) with M.D. degrees that have obtained RO1 grants compared with the number of individuals with M.D. degrees who graduated 11 years previously. (This is based on the average interval of 11 years between medical school graduation and the acquisition of the first research grant.)

rather steady. The steady rise of participation by Ph.D.s coincided with expansion of the National Cancer Institute and their large thrusts into many areas of basic science generally. *Figure 2* shows that the percentage of M.D.s with NIH research grants has progressively decreased over the years. M.D.-Ph.D.s comprise a small proportion of the grant holders and this group's percentage has remained nearly constant. Currently, Ph.D.s hold approximately 68% of the NIH research grant (RO1) portfolio while M.D.s hold only about 22%. If M.D.-Ph.D.s are added, the percentage of grants held by those with professional degrees would increase to approximately 31%. Although the *proportion* of research grants awarded to M.D. investigators is about one-half that of a decade

Table 1. Approval, award, and success rates for competing RO1 applications

	Approval Rate (%)		Award rate (%)		Success rate (%)	
Fiscal year	M.D.	Ph.D.	M.D.	Ph.D.	M.D.	Ph.D.
1974	72	76	60	56	43	43
1975	72	76	60	60	43	46
1976	68	73	50	46	34	34
1977	71	75	41	37	29	28
1978	74	79	45	45	33	36
1979	76	78	50	52	38	40
1980	76	80	42	42	32	33
1981	80	83	40	38	32	32
1982	83	85	34	34	29	29

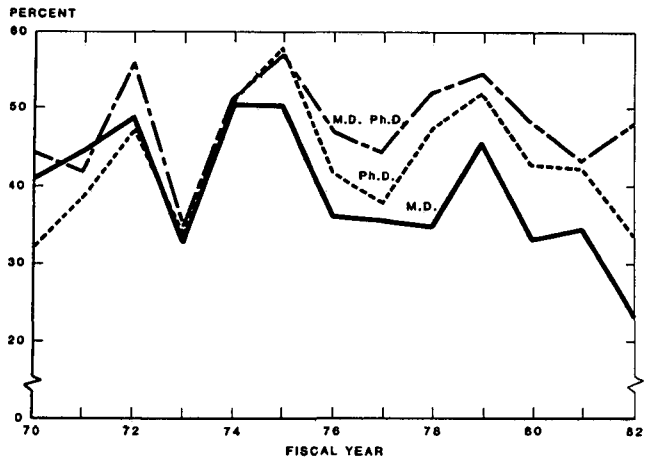

Fig. 4. Success rates of new RO1 applicants as expressed by type of degree(s) held.

ago, the *absolute number* of awards to professional degree holders has held fairly steady. NIH currently funds more than 16,000 RO1-type research grants, compared with 9,000 in 1972. This increase has been caused almost entirely by more applicants with a Ph.D. degree. Meanwhile, many additional M.D.s are participating through other research mechanisms, such as specialized research centers and clinical trials.

The numbers of M.D.s actually succeeding in getting NIH grants (RO1s) were compared to the entire field of M.D.s who could have chosen biomedical research for a career (*Fig. 3*). M.D.s serving as principal investigators on NIH investigator-initiated grants from 1968–1982 is indicated by the solid line. Against this line is plotted

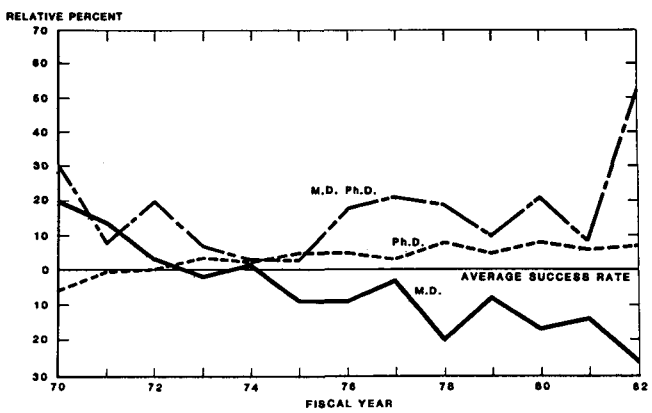

Fig. 5. Success rates of new RO1 applicants with M.D., Ph.D., or M.D. and Ph.D. degrees compared with the average success rates of all new RO1 applicants during the same year.

the number of M.D. graduates for each year starting in 1957. The 11-year offset reflects the fact that on average the M.D. in research does not receive his or her first independent research grant until 11 years after graduation. The ratio between M.D. principal investigators and the number of M.D. graduates has not widened much during the years shown. These rough data need to be viewed cautiously, however. Since medical school enrollment increased dramatically after 1968, this gap may soon widen.

The decline in the percentage of M.D. investigators with RO1 grants reflects the submission of fewer grant applications by M.D.s than Ph.D.s. In 1970, M.D.s comprised approximately 30% of the applicants; by 1980, only 24%. Another important factor is the intense competition. For all competing research grant applications, approval and award rates did not differ greatly for M.D. and Ph.D. applicants between 1974 and 1982 (*Table 1*). The approval rates for applications submitted by Ph.D. investigators have been only three or four percentage points ahead of rates for M.D. investigators. Of the grants approved by study sections, the award rates (that is, the chance of getting funded once approved) for M.D. and Ph.D. principal investigators were virtually the same. Nevertheless, when one examines the success rate of *new* applicants alone, one finds that there has been a divergence since about 1974, with new M.D. applicants competing less well than new Ph.D. applicants and with both groups competing less successfully than the M.D.-Ph.D. applicant (*Fig. 4*). This trend is even more dramatic when expressed in comparison with the average success rate of all research grant applications of that year (which has been given a score of "0") (*Fig. 5*). Increasingly, the greatest success is obtained by the M.D.-Ph.D. applicant, followed by the Ph.D. applicant at slightly above the average rate, and the M.D. applicant increasingly below the average rate.

One factor that may be playing a role in the record for M.D. applicants is that applications for clinical research tend to fare less well than basic science applications in the NIH grant review system. Clinical research applications (those involving human subjects or human tissues) are more often disapproved and more often assigned poorer priority scores than are applications in which no human subjects are involved. As *Table 2* shows, approval rates for studies which do not involve human subjects are substantially higher

than those for studies with human subjects, regardless of whether the principal investigator is an M.D. or a Ph.D.

In order to discover why applications to NIH for grants to conduct clinical research may either be disapproved or receive poor priority in the review process, the Division of Research Grants examined 256 applications rated by 13 different study sections (*Table 3*).[4] "Clinical research" was narrowly defined as research involving human subjects that included a doctor-patient relationship. It is interesting and important to note that the qualifications of the investigator and resources at the institutions played a minor role in a poor-rating outcome. Flaws in research design and conception of the hypothesis led to poor scores from reviewers. The most frequent deficiencies, faulty hypotheses and inappropriate experimental design, were the same flaws that were cited in the basic research proposals that were disapproved.

The facile explanation of the greater difficulty inherent in working with human subjects may not be the entire reason why there are lower approval rates for physician investigators. Science has become complex, methods have become intricate, and the training period has become so long that the physician, even after two or three years of fellowship training, remains less well prepared than the Ph.D. scientist who has been training for a research career since the baccalaureate. In my view, the trends of the past decade reflect the progressive professionalization of biomedical research, in particular, clinical research. I hope that there will always be room for the creative amateur in clinical investigation, but recent history indicates that such a person is less likely to secure external support for his or her work. Success for an M.D. investigator is increasingly dependent on substantial training in working with the information, concepts, and methodologies of complex modern science. To be a first-rate scientist and a well-qualified physician is a demanding calling. Moreover, clinical research requires experiences not encountered in most medical schools and on most house staffs. The quality of a research grant is a reflection of the competence and sophistication of the investigator applicant. As Damon Runyon said, "The race is not always to the swift or the battle to the strong, but that's the way to bet."

The integral relationship between training and the later conduct of research seems almost self-evident, but I would like to cite several pieces of data that support this contention. One study by the Association of American Medical Colleges has shown that for both M.D.s and Ph.D.s, postdoctoral training has the greatest influence on approval rate of first research grant applications; other significant factors are: the institution conferring the degree and the place of employment.[5] A recent review of NIH grant files indicates the worth of the National Research Service Award Program training for the M.D. and the Ph.D. applicant (*Table 4*). This analysis showed that M.D.s with NIH-supported training had an average success rate of 36.5% *versus* 25% for M.D.s without such training. A similarly large difference based on training was found in the average success rates for Ph.D.s

Because of the established primacy of postdoctoral training in enhancing the participation of physician investigators in independent research, it is important to look at the status of NIH training levels to assess accurately the future picture for clinical research. The numbers of M.D. trainees and fellows decreased from approxi-

Table 2. Competing RO1 applications, 1976–1981

	Number reviewed	Percent recommended	Award rate (%)	Success rate (%)
Research not involving human subjects				
M.D.s	10,552	73	42	31
Ph.D.s	40,815	74	40	30
Research involving human subjects				
M.D.s	12,166	64	39	25
Ph.D.s	12,078	61	38	23

Table 3. Shortcomings of poorly rated or disapproved NIH grant applications

Research problems
- –Hypothesis (47%)
- –Significance (30%)

Experimental design
- –Study group or controls (40%)
- –Technical methodology (66%)
- –Data collection procedures (41%)
- –Data management and analysis (31%)

Investigator (17%)

Resources (4%)

Table 4. Average success rates of NIH competing research grant applications, 1967–1978*

Doctoral degree	Success rates (%)	
	With training support	Without training support
M.D. or equivalent	36.5†	25.0†
Ph.D. or equivalent	37.9†	27.1†
Professional and academic (e.g., M.D. and Ph.D.)	40.4	29.4
Other professional doctorates	41.7	27.6

* Based on a 5% random sample of the NIH Grant Applicant Summary File, which includes R, P, M, and S grants. The success rate is the ratio of funded competing research grant applications to all such applications multiplied by 100.
† Significantly different (<0.01 level)

mately 4,600 to approximately 1,900 between 1971 and 1981. This seemingly drastic decline was somewhat artificial because cessation of Federal support for *clinical* training in the early 1970s certainly contributed to the drop-off. Data from 1975 correspond to the inception and development of the National Research Service Award Program (*Fig. 6*). M.D. participation continued to decline until 1976 and then apparently leveled off. At the same time, Ph.D. participation greatly increased.

The modification in authority in 1974, under the National Research Service Awards Act, limits training exclusively to *research* or academic development. Under the same Act, a committee of the National Academy of Sciences, has recommended that 2,800 clinical research training slots be offered by NIH annually—2,400 as traineeships and 400 as direct fellowships. This figure of 2,800 clinical training positions was not reached until 1980, but at that time, 900 of these clinical traineeships were held by Ph.D. trainees

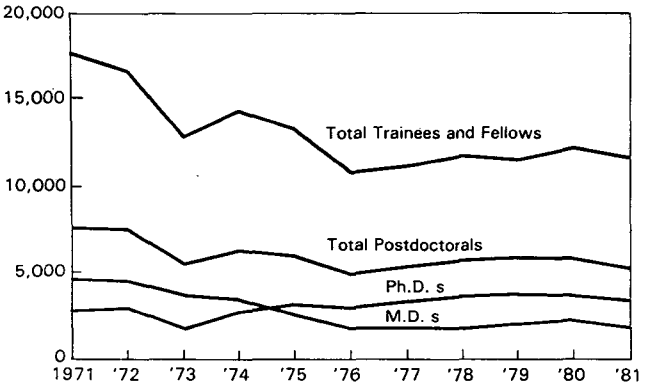

Fig. 6. Trainees and fellows with NIH research training awards.

(twice the number of only three years previously) and only 1,900 by M.D. trainees. The Academy committee has recommended that at least 85% of the traineeships in this category (approximately 2,400) be filled by M.D.s. So, by every type of measurement, a number of qualified physicians, as perceived to be desirable by the Academy Committee, are not being attracted into research training. Fortunately, some of this gap is being closed by Ph.D. scientists interested in clinical research. Nevertheless, this shortfall of physician investigators alters the balance between M.D. and Ph.D. investigators deemed essential for coordinated progress in basic science and clinical research.

Many reasons have been cited for the declining interest of physicians in clinical research. Most medical school curricula provide little or no laboratory experience that is representative of modern-day medical science. The rise of specialty fields and the lengthening of postdoctoral training programs have extended the clinical training necessary for board certification. The requirements of many certification boards are rather inflexible and do not encourage the potentially creative physician to enter research training.

Other considerations may act as deterrents for some potential traineeship applicants. Perhaps dominating the issues is that of the financial disincentives both between the third-year residency salary and the first-year traineeship, which now exhibits an average gap of $6,000, and the substantially larger differences between the income possibilities in research and in procedure-oriented practices of medicine. Especially when the debt load incurred by the graduating student is $20,000 or more, the cumulative financial disincentives are a major factor in dissuading potential investigators from entering the field.

Fortunately, this growing problem has received considerable attention in Congress. In the report of the House Committee on Appropriations regarding the proposed 1983 budget for the NIH, one paragraph read:

> The Committee shares the concerns that have been expressed by official and public witnesses about the difficulty of recruiting and retaining physicians for research careers, especially as all clinical research, involving human patients, must be done by—or at least under the guidance and super-

> vision of—a qualified physician. It is apparent and understandable, that young physicians considering careers in health research are often dissuaded from applying for research training or research fellowships by their perception of the instability of the Federal commitment to research and by their awareness that a research career represents a substantial financial sacrifice when compared with almost any form of medical practice.[7]

The Committee went on to request a report of our plans for dealing with this shortage of physicians in research.

Even without congressional prodding, NIH has devoted considerable attention to the problem and has taken some major steps toward its solution. At the undergraduate medical student level, the Medical Scientist Training Program (MSTP) has been given top priority in our training portfolio. In 1983, 650 students in the program studied for a combined M.D.-Ph.D. degree. MSTP is regarded as one of the most successful at NIH in terms of building up the importance of clinical research. This six-year program, sponsored by the National Institute of General Medical Sciences, gives awards to 24 schools for students who simultaneously earn the M.D. and Ph.D. degrees. A follow-up evaluation of the program showed that 70% of the graduates hold positions in academic medicine and are researching, as well as engaging in the training of other physicians. The program will be strengthened to support approximately 700 students per year, resulting in more than 100 graduates per year of the type of scientist currently competing most successfully for RO1 research support.

A number of programs that provide early exposure to research careers are administered at NIH. Recently, more than 1,100 medical students availed themselves of off-quarter training opportunities supported by NIH. With the new exemption of the first year of National Research Service Award support from payback obligations, NIH last year reinstituted the post-sophomore fellowship or its equivalent to provide a full year of research training within the medical school experience under an NIH fellowship or traineeship. NIH also offers summer research fellowships.

The physician who has completed four years of medical school and one to three years of clinical training is, by and large, only modestly prepared with research skills. Even when successful participation in one or more research projects has taken place, the experience does not substitute for a planned program to develop research expertise. A series of NIH awards, called Career Development Awards, provide research potential. Two mechanisms have been particularly successful in the attraction of physicians: the Clinical Investigator Award and the Special Emphasis Research Career Award. Both provide for three to five years of supervised research development in areas of immediate interest to the funding institute. Both provide up to $30,000 per year in salary plus commensurate fringe benefits and some modest amount of research support. These programs have been successful and thus have demonstrated a potential for expansion.

The latest addition to the Career Development Award Series was announced in July 1983. The Physician-Scientist Award is designed to provide five years of phased supervised research training. The first two to three years are under the guidance of a sponsor who is a basic scientist. The award carries a salary comparable to that earned by a member of the institution's house staff with equivalent experience, up to 10% of the basic science sponsor's salary, and $10,000 for research costs. The second phase, undertaken at a more independent level, provides up to $20,000 to cover research costs. The program is sponsored by seven NIH institutes and complements the MSTP by providing graduate school-level experience for the professional degree holder who begins at a post-medical school stage.

Yet, the wisdom of undertaking research training could easily be questioned by a young physician if the opportunity to engage in supported research in the future is highly uncertain. One major factor affecting a young physician's decision is his or her perception of the long-term stability of Federal support of research. NIH has continually emphasized the need to stabilize the offering of grants for investigator-initiated project research in order to provide a reasonable degree of assurance about future opportunities. The policy of funding a minimum of 5,000 new and competing awards has helped. Currently, 50% of new awards and 10% of all awards are made to first-time applicants, not by allocation, but on the basis of open competition.

Another NIH program, so well established that it is often overlooked, is a major contributor to the strength of clinical research in this country.

This is the General Clinical Research Centers Program of the Division of Research Resources, established in 1959 through action of the Senate Appropriations Committee, which expressed the belief that national clinical research resources were inadequate. Today, more than 3,000 projects are conducted in the centers each year by an even greater number of investigators, most of whom are supported through various types of NIH awards. In 1982, there were 74 centers with 595 research beds and 119,361 outpatient visits.

It is important to maintain an appropriate level of clinical trials in this country in the face of rising costs with new and creative management. A program inaugurated by the National Cancer Institute, the Community Clinical Oncology Program, is an example of innovation accomplished through the cooperative effort of the NIH and the scientific and medical community. The program in 59 locations around the country, including four Ohio cities, involves community physicians affiliating with major medical centers to participate in cancer clinical trials. By substantially increasing the number of patients in treatment studies, the program will reduce the time needed to complete clinical trials and hasten transfer of new technologies to the local level. The program is possible only because of the growth of the field of medical oncology in this country, a field which increased due to the National Cancer Act from approximately 100 individuals in 1970 to approximately 3,000 board-certified specialists today, and because the specialists encouraged their own continued involvement in clinical investigation.

While NIH programs and policies will undoubtedly have a major impact on the future of clinical investigation in this country, maintenance and growth of this field is the obligation of academic medicine, the medical profession, government, industry, and other parts of the private sector. Some medical schools, such as Case Western Reserve University, Duke University, and the University of Pennsylvania, have developed curricula with the aspiring clinical investigator in mind. Private sector entities, such as the American Cancer Society and the American Heart Association, have established special awards for physician scientists. All of these efforts continue to mitigate the circumstances which seem to be hindering the growth of clinical investigation.

In addition, the current generation of clinical investigators has a special responsibility to portray the satisfaction that can come from clinical research as a career. Students should be aware that in clinical research there is an opportunity to be a capable and caring clinician and also to share in the excitement that comes from discovery. Beyond the personal gratification that comes from creative work, clinical research offers the chance to contribute both to the health of individual patients and of groups of people. We must stress that the rewards are great for those exceptional students who will take on the challenge of research.

I believe that our own words and actions as clinical investigators are critical to the future of our profession. John Gardner remarked that the influx of excellent new people into a given field in large part depends on the morale of the people already in that field.[8] A major component of collective morale is the optimism and encouragement portrayed to newcomers and those on the brink of decision. I hope I have made a contribution to optimism by citing the continuing commitment of NIH to the training, development, and research support of the clinical investigator.

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