SOUNDING BOARD

Clinical Research and the NIH — A Report Card

David G. Nathan, M.D., and Jean D. Wilson, M.D.

In 1995, Harold E. Varmus, who was then the director of the National Institutes of Health (NIH), convened the NIH Director's Panel on Clinical Research. The panel was charged with making recommendations to foster the NIH's support of clinical research, a field that was pervaded by discouragement and believed to be in jeopardy.[1-4] The panel met between July 1995 and November 1997, when it issued a series of recommendations.[2,5] In this article, we review these recommendations, inventory the changes made within the NIH and in clinical-research portfolios within the private sector since 1995, and assess the effects of these changes.

DEFINITIONS AND RECOMMENDATIONS

The panel defined clinical research as studies of living human subjects, including the laboratory-based development of new forms of technology; studies of the mechanisms of human disease and evaluations of therapeutic interventions (which are known collectively as translational research); clinical trials, outcome studies, and health care research; and epidemiologic and behavioral studies.[2] The definition excluded disease-oriented studies of tissue samples obtained from individual patients or groups of patients who were unknown to the investigators. On the basis of this definition of clinical research, the panel recommended the establishment of programs for clinical-research training of medical students, postgraduate training programs (funded by K30 grants) in the methods and ethics of clinical research, research grant support for young clinical investigators (funded by K23 grants), grant support for experienced clinical researchers who act as mentors (funded by K24 grants), the restructuring of the study sections that review applications for clinical-research grants, increased responsibility within the General Clinical Research Center program for ensuring the high quality of clinical research, and educational-debt relief for young clinical investigators, including those who are members of minority groups.[2] The panel invited private foundations and pharmaceutical and health insurance corporations to assume strong, supporting roles in these recommended endeavors.

INVENTORY OF CHANGES AND EVALUATION OF THEIR EFFECTS

SPENDING FOR CLINICAL RESEARCH

Before 1996, when the NIH began to measure its expenditures for clinical research, the only indexes of such spending were derived indirectly, from assessments of the number of grants awarded to physicians in any given year and from the budgets for clinical trials of the individual institutes. Neither index is reliable. Clinical trials represent only about one third of the NIH's expenditures for clinical research. Furthermore, whereas researchers with Ph.D. degrees are the principal investigators for many NIH-funded clinical studies, the panel was particularly concerned about the support of translational (bench-to-bedside) research, which is more likely to be conducted by physicians.

THE CLINICAL-RESEARCH PORTFOLIO

The panel's first task was to develop a working definition of clinical research that would permit NIH staff to make an inventory of expenditures by the NIH for clinical research. The panel studied the abstracts of the proposals for all the competitive grants that were awarded in 1996 and found that approximately 27 percent of the awards and 38 percent of the dollars were devoted to clinical research as the panel had defined it (Table 1).[2] The NIH has subsequently continued to use such a system to track its expenditures for clinical investigation. As shown in Table 1, the commitment has been well maintained. Between 1996 and 2001, the total number of competitive NIH awards increased by approximately 40 percent, and the dollars awarded increased by almost 100 percent. The percentage of these awards and dollars devoted to clinical research, however,

Downloaded from www.nejm.org at UNIV OF NC/ACQ SRVCS on June 7, 2005 .
Copyright © 2003 Massachusetts Medical Society. All rights reserved.

remained constant, at about 25 percent and 34 percent, respectively. The consistent support for clinical research during a five-year period of substantial growth in funding by the NIH suggests that the availability of research funds was a source of optimism among clinical and basic scientists alike. In addition, the consistency of the support suggests that the interests of applicants for funding and the function of the peer-review system were unchanged.

The ratio of applications submitted to the NIH by Ph.D. and M.D. investigators for individual research projects (77 percent of which were investigator-initiated individual grants, or R01s) gradually increased from 1.0 in 1965 to 2.6 in 1979, and it has remained approximately 2.5 since 1990.[2] The average annual increase in the number of competitive applications from physicians before 1990 (2.3 percent) was roughly half the annual increase in the number of applications from Ph.D. investigators (4.0 percent), but the success rates for the two groups were similar (data not shown). The high ratio of Ph.D. applicants to M.D. applicants reflects the strong commitment of the NIH to basic biomedical science, the commitment of holders of the Ph.D. degree to research careers, and the increase in the number of Ph.D. degrees awarded in the biomedical sciences. The panel's efforts had no influence on these ratios.[2]

FIRST-TIME APPLICANTS AND THEIR RENEWAL RATES

The number of first-time applicants for NIH research grants (largely R01s) has varied since 1990,[5] but from 1996 through 2001 it increased by 23 percent for M.D. researchers, 50 percent for those with both the M.D. and Ph.D. degrees, and 29 percent for Ph.D. researchers (Fig. 1). During this five-year period, increases in the NIH's budget induced both new and established investigators to submit grant requests. The average success rates (including those for revised and resubmitted applications in this period) were 27 percent, 34 percent, and 33 percent, respectively, for these three groups of applicants. The success rate for first-time applicants with Ph.D.s was consistently higher than that for first-time applicants who were physicians, and the success rate for first-time applicants was lower than that for established investigators. Although the number of clinical investigators in each of the three groups of applicants is not known, many NIH-supported clinical investigators hold the Ph.D. degree alone.

The only year for which long-term outcome data

Table 1. Competitive Clinical-Research Awards by the National Institutes of Health, 1996 through 2001.*

Fiscal Year	Total		Clinical Research	
	No. of Awards	Millions of Dollars	No. of Awards (% of total)	Millions of Dollars (% of total)
1996	10,493	2,361	2795 (27)	906 (38)
1997	11,592	2,572	2767 (24)	877 (34)
1998	11,780	2,984	2882 (24)	1,000 (34)
1999	13,971	3,946	3470 (25)	1,257 (32)
2000	15,357	5,278	3862 (25)	1,722 (33)
2001	14,622	4,717	3874 (26)	1,609 (34)

* The awards include grants for research projects, training grants, career awards, and contracts. R01s (investigator-initiated grants) accounted for 46 to 47 percent of these awards.

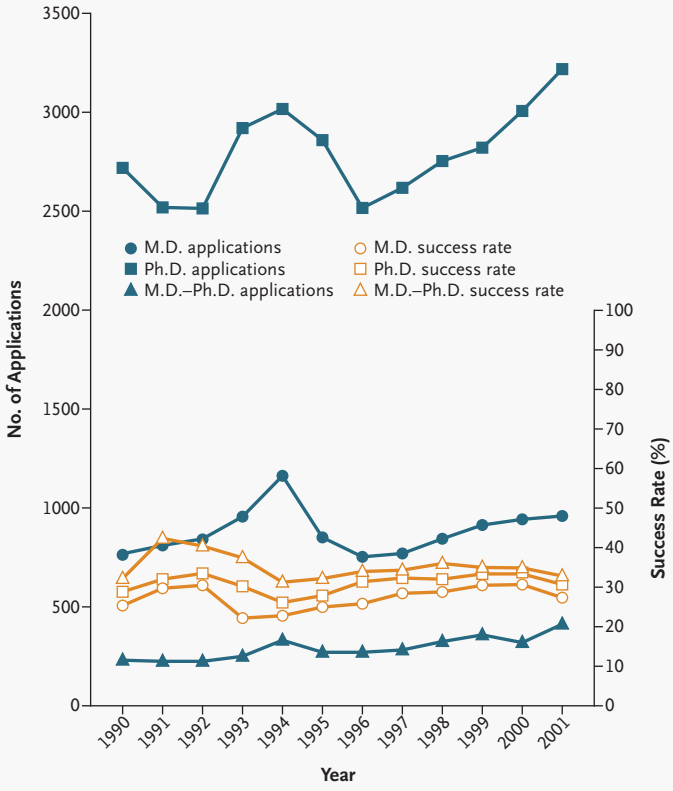

Figure 1. First-Time Applications and Success Rates of Applications for Clinical-Research Grants from the National Institutes of Health.

Investigator-initiated individual grants (R01s) accounted for approximately 77 percent of the applications.

Downloaded from www.nejm.org at UNIV OF NC/ACQ SRVCS on June 7, 2005 .
Copyright © 2003 Massachusetts Medical Society. All rights reserved.

are available with regard to first-time recipients of research grants from the NIH is 1996 (Table 2). Of a total of 1139 successful first-time applicants, 293 were physicians or physicians with Ph.D.s and 820 had the Ph.D. alone. Of the projects proposed, 255 (23 percent) were defined as clinical investigations, and 884 were considered to be nonclinical according to the panel's criteria. Strikingly, only 49 (19 percent) of the investigators who had been awarded grants for clinical research applied for renewal of their original grants (through type 2 applications), whereas 184 subsequently applied for new grants (type 1 applications) on different research topics. Of the investigators originally awarded grants for clinical research who reapplied, 112 investigators received 123 type 2 or new type 1 awards (a few applicants received both new type 1 and type 2 awards), for an overall success rate of 44 percent for investigators and 53 percent for awards. In the nonclinical category, the overall success rates for individuals and for awards were 55 percent and 63 percent.

Although this sample is necessarily small — because it is too soon to assemble reliable data for years after 1996 — the results suggest a substantial decrease in the number of researchers in all categories who applied for grants after receiving a first-time grant from the NIH and, in particular, a large decrease in the number of clinical investigators (81 percent). The data suggest that the discrepancy in funding clinical research and nonclinical research in the NIH's grants competition is not solely a result of unequal treatment of applications for clinical-research grants. Perhaps clinical-research projects are completed more rapidly than basic research projects; there may be other reasons for investigators' failure to reapply. Nevertheless, the ratio of awards for clinical research to those for basic research will not increase if clinical investigators fail to apply and reapply and if the success rates for applications and reapplications remain consistently below the rates for applications by basic scientists.

Table 2. Success of Subsequent Type 1 (New) and Type 2 (Renewal) Grant Applications Submitted by Researchers Who Received First-Time Awards in 1996.*

Applications and Awards	Clinical Research	Nonclinical Research	Total
First-time type 1 grants — no.	255	884	1139
Renewal (type 2) grants			
Applications — no. (%)	49 (19)	360 (41)	409 (36)
Awards — no.	26	228	254
New type 1 grants — no.			
Applications	184	605	789
Awards	97	376	473
Total subsequent (type 1 and 2) awards — no.	123	604	727

* R01s (investigator-initiated individual grants) accounted for approximately 77 percent of applications for clinical-research grants. The number of awards exceeds the total number of applicants because some applicants who were awarded grants in 1996 applied for both type 1 and type 2 grants.

NEW CLINICAL-RESEARCH GRANTS

Most members of the panel held that the ratio of expenditures for basic research to expenditures for clinical investigations that characterized the NIH's extramural portfolio — approximately 2:1 — was appropriate for federal support of biomedical research. Advances in clinical research depend on expanded knowledge of basic science, but many basic science projects do not find a practical application. Therefore, the panel believed that the best way to increase commitments to clinical research in the NIH portfolio was to increase the total budget of the NIH. Fortunately, Congress agreed.

Yet the panel also concluded that one type of clinical investigation did not receive sufficient support from the NIH — namely, research at the interface between basic science and clinical application, or translational research. The panel based this conclusion on the members' experience of the conduct of study sections. The understandable bias in favor of basic research on the part of study sections made up largely of basic scientists made it difficult for clinical applications to be funded. Interviews with young investigators in many academic medical centers, conducted by Dr. Lawrence Schulman of the NIH staff in 1996, confirmed the pressing need to rectify this problem,[6] and to that end, the panel recommended the establishment of NIH grant programs for young clinical investigators and for their mentors, regardless of whether the overall NIH budget was increased.

Accordingly, two types of grants, K23 grants for young investigators and K24 grants for clinical investigators who act as mentors, were introduced (Table 3). In 1999 through 2001, the NIH received over 1400 applications for K23 or K24 support, most of them requests from physicians, whose success rates approached 50 percent. The dollars committed to the K23, K24, and K30 programs were a small fraction of the total extramural NIH budget, but they have had a large effect on clinical research. The

Downloaded from www.nejm.org at UNIV OF NC/ACQ SRVCS on June 7, 2005 .
Copyright © 2003 Massachusetts Medical Society. All rights reserved.

NIH's commitment through 2003 — a nontrivial $460 million (Table 4) — has provided support and improved morale in this field.

Private foundations have also instituted programs to provide grant support for young clinical researchers and their mentors. For example, since 1998, the Doris Duke Charitable Foundation has made 71 Clinical Scientist Awards to young physician-scientists and 17 Distinguished Clinical Scientist Awards to established, midcareer scientists engaged in translational research; its investment in these two programs, thus far, is $79 million. Since 1998, the Burroughs Wellcome Fund has made 52 clinical-research awards, for a total commitment of $39 million. The Howard Hughes Medical Institute has also established a program in clinical research, with 12 investigators each receiving an estimated $1.2 million per year. From 1997 to 2001, total private-sector funding of clinical research, as defined by the NIH panel, exceeded $200 million (Table 5). These developments reflect an increased awareness in the private and public sectors of the need to support clinical research.[7]

Table 3. Competitive K23 and K24 Grant Applications, 1999 through 2001.*

Applicant's Degree and Fiscal Year†	K23		K24	
	Applications	Success Rate	Applications	Success Rate
	no.	%	*no.*	%
M.D.				
1999	182	42.3	167	45.5
2000	314	49.4	153	46.4
2001	315	48.3	111	45.9
Ph.D.				
1999	12	33.3	13	23.1
2000	53	32.1	15	33.3
2001	66	37.9	13	46.2
Other				
1999	9	55.6	5	40.0
2000	27	74.1	4	25.0
2001	18	38.9	4	25.0
Total	996		485	

* K23 grants are for beginning clinical investigators, and K24 grants are for clinical researchers who act as mentors.
† The category M.D. includes the combination of an M.D. and a Ph.D., and "other" includes nurses and veterinarians. Applicants with M.D.s were more successful than those with Ph.D.s in the competition for K23 and K24 grants.

REORGANIZATION OF STUDY SECTIONS

The NIH panel also addressed the makeup of the study sections that review translational investigations. In the course of the panel's deliberations, Ellie Ehrenfeld, Ph.D., director of the NIH Center for Scientific Review, undertook an evaluation of the study sections and instituted major changes in their organization and composition. In particular, it was decided that clinical-research applications would be reviewed by the study sections that review a large proportion of clinical applications. Theodore A. Kotchen, M.D., was appointed as adviser for review of clinical research, and changes in the organization of the review process were instituted. As a result, six study sections now deal almost exclusively with patient-oriented research, including the sections for clinical oncology and the cardiovascular sciences. In approximately 25 additional study sections, more than 75 percent of grant applications involve research with human subjects, including studies of psychology, epidemiology, nursing, and behavior that puts persons at risk for disease. Moreover, the entire system of study sections is undergoing reor-

Table 4. NIH Clinical Research Career Awards (K23, K24, and K30), 1999 through 2001, with Estimates for 2002 and 2003.*

Fiscal Year	K23		K24		K30		Total	
	No. of Awards	Millions of Dollars	No. of Awards	Millions of Dollars	No. of Awards	Millions of Dollars	No. of Awards	Millions of Dollars
1999	139	17.1	81	8.3	38	7.0	258	32.4
2000	325	41.5	158	16.5	55	11.6	538	69.6
2001	492	64.4	215	23.4	57	11.5	764	99.4
2002	594	79.3	259	28.4	66	12.2	919	119.9
2003	689	92.7	303	33.7	66	12.2	1058	138.5

* K23 grants are for beginning clinical investigators, K24 grants for clinical researchers who act as mentors, and K30 grants for training programs in clinical research.

Downloaded from www.nejm.org at UNIV OF NC/ACQ SRVCS on June 7, 2005 .
Copyright © 2003 Massachusetts Medical Society. All rights reserved.

Table 5. Collective Investment of 11 Private Foundations in the Training and Career Development of Physician-Scientists in Clinical Research, 1997 through 2001.*

Award Recipients	No. of Annual New Awards	Total No. of Recipients, 1997–2001	Annual Support	Total Support, 1997–2001
			millions of dollars	
Medical students				
Before 1997	100		3.4	
New since 1997	43		1.5	
Subtotal	143	530	4.9	18.9
Fellows and residents				
Before 1997	153		20.1	
New since 1997	5		3.0	
Subtotal	158	574	23.1	64.1
New investigators				
Before 1997	61		9.5	
New since 1997	92		20.2	
Subtotal	153	361	29.7	82.6
Midcareer investigators				
Before 1997	10		4.0	
New since 1997	20	125	16.8	93.5
Subtotal	30	125	20.8	93.5
Total	484	1590	78.5	259.1

* The 11 foundations are the American Cancer Society, the American Diabetes Association, the American Heart Association, the Arthritis Foundation, the Burroughs Wellcome Fund, the Damon Runyon Cancer Research Foundation, the Doris Duke Charitable Foundation, the Howard Hughes Medical Institute, the Juvenile Diabetes Research Foundation, the Leukemia and Lymphoma Society, and the Robert Wood Johnson Foundation. The data were provided by Dr. Nancy Sung of the Burroughs Wellcome Fund.

ganization (with completion expected in two to three years), with the goal of assuring that at least 25 percent of clinical applications will be reviewed in all study sections that review clinical applications and that all such study sections will include clinical investigators. The Center for Scientific Review has developed specific guidelines for peer review of applications for clinical-research grants and plans to track the outcome of these reviews.

TRAINING IN CLINICAL RESEARCH

A substantial part of the NIH panel's attention was focused on training. Reasoning that an interest in careers in clinical research should begin in medical school,[8] the panel recommended the establishment of a program to provide medical students with experience in clinical research on the NIH campus, and a proposal was swiftly implemented with the support of Pfizer. Since 1996, 85 medical students have spent at least one year in clinical research at the NIH, and it is hoped that many will devote their careers to clinical research. The Doris Duke Charitable Foundation also made a commitment to the training of clinical investigators, including support at 10 institutions for training programs in which a total of 65 medical students were enrolled in 2002. It is anticipated that many of these students will eventually join research training programs and that many will choose careers in clinical research.

The panel also recommended that the NIH award grants for didactic training programs in clinical research (K30 grants) at academic medical centers. Fifty-seven such grants have been awarded, and the NIH has begun to assess the effect of these programs on the training of research fellows. Surely, the knowledge base of clinical researchers of the future is in the process of expansion.

EDUCATIONAL-LOAN RELIEF

The panel addressed the burden that educational debt imposes on physicians who aspire to academic careers. In particular, the increase in the average educational debt makes it difficult for young physicians to spend the required amount of time as trainees or junior faculty members. The panel did not offer a firm recommendation in this difficult area, other than to state that clinical researchers who are members of minority groups are badly needed in academic medicine. Fortunately, other members of the academic medical community have addressed this issue, and with the support of members of Congress such as Senator Edward M. Kennedy (D-Mass.) and Representative Nita M. Lowey (D-N.Y.), a bill to provide a competitive loan-relief program for eligible clinical researchers, pediatricians, and minority-group members was passed (the Public Health Improvement Act of 2000).[9,10]

In 2002, $30 million was committed to the NIH's educational-loan–relief program, with the stipulation that clinical researchers had to hold a K23 (young-investigator) award; of 766 applications reviewed, 55 percent of those from members of minority groups and 80 percent of other applications were approved. There may be several reasons for the lower-than-expected number of applications. The most likely reason is that the requirements for eligibility for this program were too stringent; in 2003 they were relaxed for non–minority-group applicants. The new eligibility requirements include a half-time commitment to research for two years,

Downloaded from www.nejm.org at UNIV OF NC/ACQ SRVCS on June 7, 2005 .
Copyright © 2003 Massachusetts Medical Society. All rights reserved.

research support from a private, nonprofit sponsor or a government sponsor, a doctoral degree, educational debt equal to or greater than 20 percent of the applicant's base salary, and U.S. citizenship or permanent-resident status. The NIH should advertise this program widely in order to encourage applications.

GENERAL CLINICAL-RESEARCH CENTERS

The panel considered the role of the General Clinical Research Centers in the approximately 70 academic health centers in which they are located. The staff members of the centers understand protocol design and the issues of safety and integrity in clinical research, and they undergo periodic, in-depth, peer review to ensure the productivity and integrity of research at the centers. If the numbers of support personnel within these staffs could be enlarged, the centers would be well placed to take responsibility for the quality and integrity of clinical research in the host institutions. This increase in staffing might prevent some of the serious accidents that may occur in clinical research, which on occasion have brought an unfortunate notoriety to the field. The General Clinical Research Centers have already instituted research-advocacy positions as a step toward strengthening oversight of the clinical research conducted at these sites. But academic health centers must make every effort to support the infrastructure of clinical research as well as they support that of basic research,[11-13] and they need to make certain that their relations with the pharmaceutical industry are free of conflicts of interest.[14-16]

CONCLUSIONS

The Director's Panel on Clinical Research provided a description of clinical investigation that has made it possible to define the actual clinical-research portfolio of the NIH's extramural program. The consequence has been a reinforcement of the importance and value of clinical research in academic medicine. Other interested groups have joined this effort, as shown by the establishment of the educational-loan–relief program and steps taken by private foundations and at least one pharmaceutical company to support clinical investigation and training. The net result of these efforts has been to diminish the aura of discouragement and crisis surrounding clinical investigation. But continued, careful attention to the support of clinical research by academic health centers, private foundations, the pharmaceutical industry, and the NIH remains crucial. In addition, investigators as well as academic health centers must pay particular heed to research ethics and to potential conflicts of interest, so that the reputation of clinical research is not sullied.

Drs. Nathan and Wilson were members of the NIH Director's Panel on Clinical Research. The full roster of panel members is available at http://www.nih.gov/news/crp/97report/1report.htm.

We are indebted to Marc S. Horowitz, J.D., of the Office of Loan Repayment, Ms. Kenya McRae of the National Center of Minority Health and Health Disparities, Belinda Seto, Ph.D., Della Hann, Ph.D., and Robert F. Moore of the Director's Office, NIH, and Ellie Ehrenfeld, Ph.D., and Theodore Kotchen, M.D., of the Center for Scientific Review, NIH, for their generous assistance; to Elaine Gallin, Ph.D., of the Doris Duke Charitable Foundation, and Nancy Sung, Ph.D., of the Burroughs Wellcome Fund, for their help and their excellent support of clinical research; and to Toby Church for the provision of vital administrative assistance.

From the Department of Pediatric Oncology, Dana–Farber Cancer Institute, Boston (D.G.N.); and the Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas (J.D.W.).

1. Campbell EG, Weissman JS, Moy E, Blumenthal D. Status of clinical research in academic health centers: views from the research leadership. JAMA 2001;286:800-6.
2. Nathan DG. Clinical research: perceptions, reality, and proposed solutions. JAMA 1998;280:1427-31.
3. Crowley WF Jr, Thier SO. The continuing dilemma in clinical investigation and the future of American health care: a system-wide problem requiring collaborative solutions. Acad Med 1996;71:1154-63.
4. Schechter AN. The crisis in clinical research: endangering the half-century National Institutes of Health Consensus. JAMA 1998; 280:1440-2.
5. Nathan DG, Varmus HE. The National Institutes of Health and clinical research: a progress report. Nat Med 2000;6:1201-4.
6. Shulman LE. Clinical research 1996: stirrings from the academic health centers. Acad Med 1996;71:362-3, 398.
7. Sung NS, Crowley WF Jr, Genel M, et al. Central challenges facing the national clinical research enterprise. JAMA 2003;289:1278-87.
8. Mark AL, Kelch RP. Clinician scientist training program: a proposal for training medical students in clinical research. J Investig Med 2001;49:486-90.
9. Nathan DG. Educational-debt relief for clinical investigators — a vote of confidence. N Engl J Med 2002;346:372-4.
10. Ley TJ, Rosenberg LE. Removing career obstacles for young physician-scientists — loan-repayment programs. N Engl J Med 2002;346:368-72.
11. Oinonen MJ, Crowley WF Jr, Moskowitz J, Vlasses PH. How do academic health centers value and encourage clinical research? Acad Med 2001;76:700-6.
12. Gallin JI, Smits HL. Managing the interface between medical schools, hospitals, and clinical research. JAMA 1997;277:651-4.
13. Nathan DG. Careers in translational clinical research — historical perspectives, future challenges. JAMA 2002;287:2424-7.
14. Hirsch LJ. Conflicts of interest in drug development: the practices of Merck & Co., Inc. Sci Eng Ethics 2002;8:429-42.
15. Schulman KA, Seils DM, Timbie JW, et al. A national survey of provisions in clinical-trial agreements between medical schools and industry sponsors. N Engl J Med 2002;347:1335-41.
16. Nathan DG, Weatherall DJ. Academic freedom in clinical research. N Engl J Med 2002;347:1368-71.

Copyright © 2003 Massachusetts Medical Society.

Downloaded from www.nejm.org at UNIV OF NC/ACQ SRVCS on June 7, 2005 .
Copyright © 2003 Massachusetts Medical Society. All rights reserved.