Research and the National Cancer Program

National Cancer Institute support of basic cancer and other biomedical research is described.

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The emphasis placed on the National Cancer Program has caused alarm among some scientists, physicians, and other health-oriented people in the belief that cancer is receiving a disproportionate share of federal health funds. They see the National Cancer Program as a deterrent to advances in control of other diseases and, in the long run, as a force that does not best serve the future health needs of the American people.

Concerns have been voiced as to whether cancer should have been singled out for special research effort. Since the funds available to the entire biomedical research community are, of necessity, limited, the enlarged cancer budget is viewed as responsible for deprivation of research on other diseases and health problems and for diminished fundamental biomedical research, particularly in areas other than cancer. Concerns have also been expressed as to whether the expanded cancer program is utilizing its funds to best advantage for future success in controlling cancer; whether the program is placing premature and undue emphasis on targeted research, which builds from existing knowledge and technology ready for implementation; and whether the National Cancer Institute (NCI) is supporting basic research of a quality inferior to that supported by other institutes of the National Institutes of Health. The net result of these various concerns has been to create a fairly strong impression of general dissatisfaction with the National Cancer Program among some in the scientific and health communities. This is understandable and important.

Some of the issues raised are not properly attributable to the cancer program. Others, which relate to its operations, are based at least in part on incomplete knowledge of the facts, due largely to inadequate communication of information by NCI. The purpose of this article is to present a concise description of what the National Cancer Program is doing in support of basic cancer and other biomedical research. Information on the NCI budget for the last 3 years has been published (*1*).

The Problems of Cancers

The National Cancer Program came into being with the enactment of the National Cancer Act of 1971, following an intensive investigation and evaluation of the impact of cancer on the American people and the state of existing knowledge about cancer (*2*). There was a consensus among those who were studying the situation that an immediate mobilization of certain existing research information and technology could benefit cancer patients and prevent cancer. Furthermore, research advances in recent years in a number of fields, such as cell and tumor biology, molecular biology, virology, and immunology, offered a promise of increased capability for producing much needed basic knowledge about the nature of cancer. It was felt that an expanded program could accelerate progress both in application of current knowledge, in the area we call cancer control, and in research to obtain new knowledge (*3*).

The idea of an expanded cancer program was supported by numerous scientists and science administrators, who genuinely believed that progress in basic knowledge had made a renewed attack on cancer practicable and desirable. One of the major forces that influenced the decision of the federal government to establish the National Cancer Program was public support of the intent to do more about cancer. More than one poll has shown that people fear cancer more than any other disease (*4*). At one point in what seemed to be slow progress in the development of the legislation, a prominent newspaper columnist mentioned it in a column. Within about a week, more than 5 million letters were delivered to the White House and the Congress.

The widely shared fear of cancer is understandable, because it is a grim group of diseases. The cold reality of figures on current and projected cancer incidence, morbidity, and mortality, and on its costs, is sufficient to arouse apprehension. This year, cancer will account for an estimated 665,000 new patients, more than 1 million patients under treatment, and 365,000 deaths. In the 1970's in the United States alone, at present rates, there will be an estimated 6.5 million new patients diagnosed, more than 10 million under medical care for cancer, and 3.5 million cancer deaths. About 53 million Americans now living (one in four persons) eventually will have cancer. Cancer will strike over the years in approximately two of three families (*5*). Its financial burden, often catastrophic for a family, is estimated at $15 to $25 billion annually, or nearly one-fifth of the national costs for all health care (*6*).

Almost half of the persons who die of cancer are under age 65. Cancer, particularly leukemia, is the largest disease killer of children between the ages of 1 and 15 years. Cancer is the leading cause of death among women between the ages of 30 and 54, many of them mothers. Most of the major-site cancers—cancer of the lung, breast, colon and rectum, pancreas, and bladder—are increasing in incidence. Incidence of cancer of the stomach is decreasing steadily in the United States, for reasons that are not completely understood but may be related to diet (*7*).

Progress in cancer therapy is responsible for achieving 5-year survival rates of about 65 percent for women with breast cancer, about 45 percent for patients with cancer of the colon, and 60 percent for patients with cancer of the bladder. More and more patients treated for Hodgkin's disease, non-Hodgkin's lymphomas, and acute lymphocytic (childhood) leukemia are surviving for 5 years free of detectable disease, and can be expected to live normal lifetimes. In the last few years, with the broader application of combination therapy—combinations of drugs and combinations of chemotherapy with other therapeutic methods such as surgery or radiotherapy—"good life" survival of patients with various types of cancer has been achieved. New leads have emerged in treatment of ovarian cancer, colon cancer, and

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osteogenic sarcoma, a tumor of bone usually in young people.

Improved survivals can be expected from not only more effective treatment, but also from advances in detection, diagnosis, and prevention. Examples of the application of existing knowledge that can be further investigated and disseminated to reduce cancer in the population are use of the Pap test to detect early cancer of the uterine cervix, use of mammography and xeroradiography to detect localized breast cancer, and reduction of smoking or modification of smoking or tobacco itself to prevent lung cancer. Other advances will result from new control techniques and new methods of application and communication.

In spite of the progress made, vast areas of ignorance about the basic mechanisms of cancer still exist. Fundamental research must be supported in those areas. It is the type of untargeted, unprogrammed, unstructured research whose outcome cannot be directed or anticipated, but it is the research that will assure a continued flow of basic knowledge and will ultimately yield the means for the conquest of cancer.

Basic "versus" Applied Research

How is the National Cancer Program assuring the search for new, basic knowledge? Since the NCI was created in 1937, it has used a variety of mechanisms in conducting a broad array of programs designed to achieve the control of cancer. The National Cancer Act of 1971 and the 1974 amendments are not scientific documents and do not imply that we should change our assumptions concerning the nature of the scientific problems or of the efforts made to solve them. The legislation has as its purpose "to enlarge the authorities of the NCI and the National Institutes of Health [NIH] in order to advance the national effort against cancer." The act specifically requires the director of NCI to "plan and develop an expanded, intensified, and coordinated research program encompassing the programs of the NCI, related programs of the other research institutes, and other Federal and non-Federal programs." He is required also to update the plan and to submit a 5-year projection each year (*8*).

Implicit in the legislation is the intent that the best people and strongest institutions will be united in a common effort to mount the strongest attack possible against cancer. Thus, more than 450 highly qualified scientists in the country participated in developing and updating the plan. It is intended to provide the framework for coordinating, monitoring, updating, and reporting progress of the National Cancer Program. It is an inventory of scientific areas to be investigated. It is a guide to the state of the science: it reflects new scientific knowledge. It is not, cannot, and will not be used to direct research.

Both the legislation and the plan provide for a large element of unplanned, investigator-initiated science of the type that has produced major scientific discoveries in the past. The National Cancer Program will continue to rely on independent, unstructured research for the much needed basic knowledge.

An important consideration in operating the National Cancer Program is the balance that must be maintained between research aimed primarily at extending fundamental knowledge and at improving the technology of clinical care, between grant-supported and contract-supported research, between traditional research project grants and center grants, and between extramural activities conducted in research institutions throughout the country and intramural activities conducted by NCI itself. These balances, which are weighed in light of resource constraints, scientific knowledge, and need, and are worked out according to our best judgment and with the advice of the President's Cancer Panel and the National Cancer Advisory Board, are reflected in the operating level for fiscal year 1974.

Table 1. NCI funding for FY 1974.

Item	Amount (10^6 dollars)	
Intramural funds		86.5*
Extramural funds		
Research grants	219.7	
Research contracts	103.2	
Supply and support contracts	77.2	
Fellowships and training grants	23.6	
Construction grants and contracts	38.1	
Cancer control grants and contracts	32.8	
Subtotal		494.6
Total		581.1

*This includes $16.8 million for the NIH management fund, $20.2 million for NCI research management and program services, and $49.5 million for intramural research programs.

Research Grants

In fiscal year (FY) 1974, NCI obligated a total of $581.1 million on cancer research and control (Table 1). Of this amount, approximately $86.5 million, or 15 percent, was spent intramurally (within NCI or NIH) on research and administration. The balance, approximately $494.6 million, was spent outside NIH. Approximately 50 percent of the total NCI budget was spent through the grant programs (*9*).

With regard to the amounts spent for research projects, a breakdown of the $219.7 million for research grants shows expenditures of $115.6 million for regular, undirected, untargeted, investigator-initiated grants, $92.4 million for center grants, $10 million for organ-site task forces, and $1.7 million for research career program awards.

At the level of $115.6 million, NCI funded 60 percent of approved competing grants. It is noteworthy that the funds for regular research grants increased from $69.3 million in 1972 to $115.6 million in 1974.

Of the $92.4 million spent for comprehensive and specialized cancer center grants, $72 million was for regular, competitive research projects that could equally well be listed with the regular research grants. About $20.4 million was for planning and core support grants, which are also investigator-initiated.

The $219.7 million spent on research grants during 1974 was more than the entire NCI budget for any year prior to 1971, and more than twice the amount spent on research through the contract mechanism ($103.2 million). About 2200 research grants were awarded in 1974 to 367 institutions. Of these, 1670, amounting to $95.0 million, were recommended by NIH study sections. The remaining grants were recommended by NCI peer-review committees, none of whose voting members were on the NCI staff.

Research Contracts

More than half of the basic research supported by contracts has been in the Virus Cancer Program. Use of the contract mechanism began in the 1950's to stimulate research in cancer chemotherapy, and expanded in the 1960's to support an intensified program of viral oncology investigations. At that time, contracts could be awarded to academic or commercial investigators within about 3 months, as compared with 9 months or more for grants. Also, in the early 1960's, a decision was made by NIH to exclude commercial organizations from competition for grants. Support for the research of some of these organizations was continued through the use of contracts, and contracts became a major mechanism of support by NCI.

During these years, NCI has operated under the philosophy that fundamental research within a developmental or "planned" program can be supported by

the contract mechanism, provided that the same problem is not being investigated by a research grant. Much excellent basic research in virology has been supported by contracts. However, objections were raised about the review and conduct of such research. NCI began to review the management and scientific aspects of the Virus Cancer Program. In March 1973, the National Cancer Advisory Board, at my suggestion, appointed a committee headed by Norton Zinder of Rockefeller University to review the virus program. In the committee's report of March 1974, the major criticism was not of the science, but of the management of the program. As a result of the reviews and recommendations, NCI, with the guidance of the National Cancer Advisory Board, is continuing to introduce organizational and procedural changes to assure peer review for unquestionable quality.

In 1974, NCI entered into about 964 contracts involving $213.7 million. Of these contracts, $103.2 million was for research and $77.2 million was for research support and services. The balance was for cancer control projects ($27 million) and construction ($6.3 million).

The contract funds for research support activities provide resources for grantees, as well as contractors, at no additional direct cost to these investigators or institutions. The amount of $180.4 million for research contracts and research support contracts represented a decrease from 50 percent of research grant and contract funds in 1972 to 45 percent in 1974.

Of the total contract funds of $213.7 million, 58 percent went to universities and nonprofit research institutes, 31 percent to commercial institutions, and the balance to other federal agencies (interagency agreements), state and local governments, and foreign institutions.

Funding for Basic Research

In FY 1974, NCI obligated $305.6 million for basic research (Table 2). This figure includes the amounts obligated for basic research within the various parts of the total NCI program. In comparison with the amounts obligated in FY 1971, before the increases under the National Cancer Act of 1971, the 1974 figure for basic research amounted to 2.4 times that in 1971. In FY 1971, $128.6 million was obligated for basic research; this was 55 percent of a total budget of $232.9 million.

In FY 1974 the total NCI budget of $581.1 million included $33.8 million obligated for cancer control (grants, contracts, and intramural). The cancer control program has a mandate and authorization for appropriation of funds separate from that of the research part of the National Cancer Program. Through this program, the director of NCI has responsibility for assisting and promoting the widespread application of current and newly proved knowledge for the benefit of cancer patients and all who are at risk of developing cancer. This is a program of education, demonstration, and communication. Its support of research is limited to rehabilitation research and research related to improved application of existing procedures and techniques deemed ready for general use.

If the cancer control amount ($33.8 million) is subtracted from the total budget, the remaining $547.3 million comprises the research funds. Thus, 55.8 percent of the total NCI research budget was obligated for basic research in 1974. The balance includes funds for such nonbasic research activities as clinical research, activities pertaining to patient care, and some support activities such as those pertaining to virus production and bioassay of compounds for carcinogenicity.

Table 2. NCI funding for basic research, FY 1974.

Item	Amount (10^6 dollars)
Regular research grants	115.3*
Cancer centers	41.7
Organ sites	1.0
General research support grants	0.8
Fellowships and training grants	15.4
Construction	19.0
Contracts	64.4†
Intramural research	25.0
Rehabilitation research	5.0
NCI-NIH management costs	18.0
Total	305.6

*Includes $20.7 million for clinical cooperative groups. †Includes $38.6 million for research support contracts, the reagents and services of which are provided to qualified research institutions and investigators at no cost to their research grants and contracts.

Quality of Fundamental Research

Regardless of whether research is supported by grant or contract, or by intramural or extramural funds, or whether research is for basic science or development of clinical technology, the available funds must be allocated for research of the highest quality. Indeed, one of the baseline criteria for the scientific program of the National Cancer Program, in addition to balance in scope of research and in funding, is the emphasis on research excellence.

In considering the support of high quality research, questions have been raised about whether the NCI, in its rapid expansion, has supported projects with priority ratings lower than those of other institutes, has narrowed the focus of research so sharply as to reduce the possibility of serendipitous discoveries, and has, in effect, siphoned off funds that might otherwise have been appropriated to the other institutes.

The NCI is funding about 60 percent of approved, competing grants, and this figure is only slightly higher than the percentage funded by the other institutes. The NCI cutoff point in the merit scores for competing applications is not much different from those of other institutes. It could be argued that, since NCI has more dollars available for disbursement, its cutoff point, although similar to that of other institutes, could allow funding of a larger number of mediocre projects. This is not the case, however, since the majority of NCI basic research grant applications are reviewed by the NIH study sections with the applications of the other institutes.

Not only is NCI supporting more regular research grants than ever before, but it is also supporting investigator-initiated, competitive research projects under center grants. The center grant mechanism provides intensive peer review of the applications from scientists at comprehensive cancer centers and specialized cancer centers in some of the leading academic institutions in the country. We believe that the fundamental research conducted under center grants is as good as that conducted under regular research grants.

To help assure that no good research that is reasonably related to cancer goes unfunded, NCI adheres to a firm dual assignment policy for grant awards. Thus, cancer-relevant projects may be referred to NCI as well as to other NIH institutes. The interpretation of cancer relevance is broad and may include fundamental life processes. The priority of these projects is determined by NIH study sections and they may be funded by NCI if not funded by the institute receiving the primary assignment. In 1974, 31 such research grant applications of other NIH institutes were funded in a total of $1.6 million.

This year, the NCI is introducing a modification of the grant mechanism, cancer research emphasis grants (CREG), to ensure the widest possible participation of the scientific community in determining what research will be done. The need for specific research will be established with broad input and advice from outside consultants and advisory committees. CREG will be used to support research projects for which (i) the applicant responds, within a designated period of time, to an individual public announcement, by the NCI, for research within specific program areas, such as cell kinetics or viral oncology; (ii) the research approach is proposed

by the investigator; and (iii) the application is reviewed by the applicant's peers for scientific merit. As soon as the CREG system can be implemented, the contract mechanism will no longer be used to support best effort, basic research projects in which NCI does not need or want to provide frequent direction and control.

One of the best ways of assuring high quality basic research is adequate support for biomedical research of all the NIH institutes. While NCI has increased its support of basic research, the appropriations of other NIH institutes that support basic biomedical research have been reduced. This is evident from Table 3, showing the budgets of four other institutes over the last few years. These reductions cannot in fairness be attributed to the existence of the National Cancer Program, although this would be difficult to prove beyond a doubt. On the other hand, it is just as difficult to prove that the other institutes would have received more funds if the National Cancer Program did not exist. In fact, I am told by people in the Office of Management and Budget that the latter would not have happened in 1972 to 1974.

The chairman of the President's Cancer Panel has repeatedly stated that at the time when the increased effort in cancer was being discussed, the medical and health witnesses were explicit in the position that it should not be at the expense of other biomedical research (*10*). He has championed before the Congress and the President the cause for increased appropriations for the other NIH institutes to a level that would, at a minimum, permit them to operate without cutback of important programs. He also has stated that in the face of the costs of medical care in this country, we cannot afford to economize on the basic research and training on which we depend for the discoveries that will facilitate prevention and control of diseases.

Table 3. Appropriations of NCI and other NIH institutes; NIGMS, National Institute of General Medical Sciences; NIAID, National Institute of Allergy and Infectious Diseases; NIAMDD, National Institute of Arthritis, Metabolism, and Digestive Diseases; NINCDS, National Institute of Neurological and Communicative Disorders and Stroke.

Institute	Amount (10^6 dollars)			
	FY 1972	FY 1973	FY 1974*	FY 1975
NCI	378	492	588	691.6
NIGMS	166	149	191	187.4
NIAID	104	101	117	119.5
NIAMDD	145	139	171	173.1
NINCDS	111.5	105	139	142.5

*Includes released impounded funds.

Training for Research

Another way of assuring high quality research is to ensure the availability of adequate numbers of well-trained investigators. It is widely believed that the use of federal funds to assist the training of young scientists is of utmost importance to cancer as well as other areas of biomedical research. NCI spent more in 1974 on training and fellowship programs than ever before in its history. The total of $23.6 million obligated for this purpose surpassed the $20 million spent in 1972, which was the previous peak year for supporting training.

The decision to end NIH research training programs announced 2 years ago was not made because of the increased cancer effort, but for various reasons including the assertion that such programs were no longer needed to bring scientists into biomedical research and could therefore be eliminated. Here again, the chairman of the President's Cancer Panel has fought for the training programs of all NIH, in recognition of the interdependence of the total training effort and the potential for benefit to all biomedical research.

The NCI currently is in the process of phasing out four training programs. The clinical cancer training program, an institutional program of grants to medical and dental schools to upgrade cancer teaching, and the graduate training program, an institutional research training grant program of pre- and postdoctoral traineeships, will be phased out by the end of FY 1978. Fellowships awarded directly to individuals, rather than to institutions, for research training either in the United States or abroad are also being phased out. Included in the phaseout are the "Weinberger" fellowships, which were initiated in July 1973 in response to the hue and cry that followed the abrupt termination of NIH research training programs early in 1973. The "Weinberger" fellowships, of which NCI awarded more than 350 in FY 1974, had a payback provision and specified that support could be offered only in areas having an acknowledged shortage of appropriately trained manpower.

To replace legislative authority for the programs being phased out, the National Research Act was enacted in July 1974 (*11*). National research service awards may be made, subject to certain public service requirements, both to individuals for research training and to institutions, which will select individuals for research training. Awards may be made for pre- and postdoctoral training. With the consent of an applicant, applications for "Weinberger" fellowships can be considered for national research service awards. After 1 July 1975, awards can be made only in subject areas that have a shortage of manpower, as indicated by a mandated study of biomedical and behavioral research personnel being conducted by the National Academy of Sciences. Regulations and guidelines for national research service awards are being developed by the NIH.

The National Cancer Act Amendments of 1974, which amended the 1971 act, gave NCI authority for clinical training (*12*). Shortly before this time, a new program designed to replace the clinical cancer training program, called the clinical cancer education program, had been developed and is being implemented. In addition to clinical cancer education grants, guidelines for other clinical training programs are being developed, in the hope that they can be funded in FY 1976.

Conclusion

The fight against cancer was set on its course in 1937 with the creation of the NCI. It was strengthened by the 1971 and 1974 acts. These acts promised the American people that high quality research will be conducted by the best minds available, and that the research will cover the broadest possible sweep of knowledge, from basic research on cellular and molecular behavior to research in cancer prevention, diagnosis, treatment, and rehabilitation. These acts also promised that, at the same time, everything possible will be done to bring the best care available with current technology to cancer patients and the best knowledge for prevention of cancer to all people at risk of developing the disease.

Among the expanded research efforts of the National Cancer Program are activities in environmental carcinogenesis and nutrition in relation to cancer. The basis for emphasis on environmental carcinogenesis is the premise that in cancer, as in other diseases, prevention offers the best hope for ultimate control. The total cost of research on identifiable environmental carcinogenesis in 1974 was $100.2 million, or 17 percent of the total NCI budget. Environmental factors can either be direct causes of cancer or may act to increase the susceptibility to environmental carcinogens by affecting the normal metabolic or immunologic responses of individuals. Thus, NCI funds for research in the environmental origins of cancer are not contained exclusively under the rubric of "environmental carcinogenesis," but are supplemented by part of the research funds allocated to immunology, nutrition,

oncogenic viruses, comparative biology of normal and cancerous cells, and genetic determinants of cancer.

An NCI diet, nutrition, and cancer program has been established to sponsor research and collect information on the role of diet and nutrition in the etiology of cancer and in the treatment, long-term management, and rehabilitation of the cancer patient. Some of the areas involved to date in NCI-supported nutrition research are carcinogenesis, epidemiology, and chemotherapy.

Other opportunities to increase knowledge of cancer have expanded as a result of accelerated exploration in areas such as cell biology, molecular biology, virology, and immunology. For example, results of basic cellular research are providing clinical research investigators clues to more effective treatment of cancer patients with improved chemotherapy regimens and the emerging modality of immunotherapy.

At the level of fundamental research, which has been receiving substantial NCI support, it is often impossible to distinguish advances in knowledge that will eventually be used in cancer from those that will help other areas. Information from basic biomedical research supported by NCI increases the total accrued knowledge and may well assist research on other diseases. Similarly, important fallout for cancer derives from research in other areas, for the fundamental processes of life and growth are inexorably linked with cancer.

Health-oriented research requires the continued advice and collaborative endeavors of scientists of all the basic laboratory and clinical disciplines. The National Cancer Program will affect all of us, scientifically and personally. NCI welcomes comments and counsel from the scientific community. It will continue the productive biomedical research efforts whose goal is not only new ideas and new knowledge but a better quality of life.

Summary

Fundamental research is supported to obtain the knowledge lacking about the basic mechanisms about cancer. The NCI supports basic research through grants, contracts, and in-house activities. In FY 1974, the increasing amounts obligated for basic research within the various parts of the total NCI program accounted for more than half of the total budget. The high quality of research is assured through use of peer review of applications and support of research training. The NCI has consistently backed the cause of adequate budgets for biomedical research for all the NIH institutes.

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NEWS AND COMMENT

Genetic Screening: NAS Recommends Proceeding with Caution

Genetic screening is a good thing—but only in carefully controlled circumstances, according to a committee of the National Academy of Sciences (NAS). After a 2½-year analysis of the state of the art and the politics of the situation, the committee concluded that it is not yet time to recommend community, mass screening programs. The committee's feelings on this point, according to chairman Barton Childs of the Johns Hopkins University School of Medicine, were not accurately stated in a NAS press release that said genetic screening programs should be made available nationwide "as a matter of public health policy."

At a 23 June press conference on the committee's report*, Childs stressed the fact that genetic screening of asymptomatic individuals should still be considered an experimental procedure in need of considerable evaluation of its potential benefits versus its inherent risks. Nevertheless, the committee strongly endorsed the continuation and expansion of genetic screening in the proper setting. What it opposes is the kind of mass screening program in which groups of citizens are virtually recruited off the streets to have their genes checked.

Genetic screening used to be a rather uncommon medical procedure that touched the lives of relatively few families. Even a decade ago, there were not many genetic disorders that could be detected in individuals who had no symptoms of disease. Moreover, most of the disorders that could be picked up were identifiable only by techniques that were difficult to carry out and were considered highly experimental.

Then, in the 1960's, it became possible to screen newborn babies for phenylketonuria (PKU), an inborn error of metabolism that leads to severe mental retardation if not treated early. PKU had a lot to recommend it as a candidate for mass screening. The methods for detecting it were simple, requiring only a small sample of blood taken from the infant at birth. It was not very expensive. It presumably harmed no one. And, best of all, if a PKU baby were detected, he could be spared mental retardation by being fed the correct foods. If foods containing phenylalanine, such as bread, were kept out of the diet, brain development would not be significantly impaired. (The difficulties of keeping a young child on a low-phenylalanine diet cannot be overestimated.)

PKU screening seemed like a very reasonable thing to do, and eager geneticists went to their legislators seeking state help in setting up mass screening programs. The legislators in most states readily complied; since 1963, the NAS says, 43 states have passed laws requiring or recommending PKU screening in newborns.

Looking at the PKU programs with hindsight, the NAS committee is among many groups that have come to the realization that everything was not as right as it first seemed. For one thing, it turns out

**Genetic Screening—Programs, Principles and Research* is a report of the Committee for the Study of Inborn Errors of Metabolism. A limited number of copies are available without charge from the National Academy of Sciences, 2101 Constitution Avenue, NW, Washington, D.C. 20418.