Biomedical Research (II): Will the "Wars" Ever Get Started?

One of the features of the national wars on cancer and heart disease that is supposed to set them apart from other efforts to conquer disease is that these are being very carefully planned. The implication seems to be that cancer and heart disease have not been wiped out before now because there has been no national plan of attack.

From the beginning, there has been considerable disagreement within the scientific community about whether there should even be a declared war on cancer and heart disease and, therefore, about whether the elaborate plans these wars entail are worthwhile. Nevertheless, the Congress and the President believe in plans and made them law. According to the National Cancer Act of 1971 and the National Heart, Blood Vessel, Lung, and Blood Act of 1972, the directors of the National Cancer Institute (NCI) and the National Heart and Lung Institute (NHLI) had to come up with 5-year plans describing what they intend to do. So, they each got together with literally hundreds of scientists in their respective fields and planned.

Their plans, now made, were recently, and belatedly, laid before the public with a conspicuous lack of endorsement by the Administration which seems to be having second thoughts about coming up with the money to pay for the wars it so vociferously declared.

Money is not the only problem. Freedom from red tape and, in the case of the cancer institute, direct access to the President himself were originally put forward as an additional guarantee that nothing would impede this nation's attack on cancer and heart disease. The problems involved in just getting the plans themselves released make it plain that the NCI and the NHLI are just as bound by red tape as everyone else. In short, for all of last year's rhetoric about all-out efforts, one has the feeling that the wars on cancer and heart disease have yet to get started.

Of the two, the cancer crusade seems to be in the worse shape.

Anticipating the law, the cancer people began their plan in 1970. Now, 3 years later, it remains only partially complete. The summary reports of the director and the National Cancer Advisory Board are in, as are the scientific volumes. But the "operational" plan, which will tell how the cancer program will run, has yet to be finished. The heart plan was put together in less than a year.

The Cancer Plan

The National Cancer Program Plan as it now exists was created at a cost of more than $1 million by NCI administrators and some 250 cancer specialists who met in small groups at Airlie House, a Virginia retreat, between October 1971 and March 1972. (Before that, former NCI director Carl Baker and Louis Carrese, a systems management specialist who is still in charge of the plan, laid out its basic structure.) Among them, the 250 consultants thought of every conceivable way of approaching cancer research and wrote each down. The scientific sections of the plan may well be as comprehensive a catalogue on the subject as has ever been assembled. And, it describes every possibility in great detail.

The plan is written around seven "objectives," which are to be reached by "approaches," which in turn will be achieved through "approach elements" (see box). It is all quite overwhelming to the average reader but, reportedly, is satisfying to administrators both at NCI and in HEW who are said to admire the way it has been constructed. It is obvious that the scientific sections of the plan were not written with Congress in mind. However, the first two volumes were. The reports of the director and the advisory board are intended to spell out the priorities of the program, and the program's problems, in language anyone can understand.

The report of the director, Frank J. Rauscher, Jr., mentions prominent areas of research and therapy, takes note of areas that previously have gone unnoticed—such as patient rehabilitation—and makes a firm promise that, as a result of the national crusade against cancer, the very best of existing therapies will be made available to all of the people. It has a reassuring tone to it and gives the impression that something is happening.

Acknowledging criticism that the emphasis on cancer is draining resources from other areas of research, Rauscher points out that "Just as research seemingly unrelated to cancer can result in knowledge vital to the cancer effort, the converse is equally valid." His report highlights the major areas of cancer research, including cell biology, virology, and immunology. Epidemiology is said to be important, as is work to identify chemical carcinogens. It says we need improved methods of diagnosing cancer early and of treating it once it develops. Each of these points is discussed in reasonable detail, with particular attention to the idea that combination drug therapy and combination therapies employing surgery, radiation, and drugs look very promising as means of controlling several forms of cancer.

Nothing in all of this is terribly new —not that it should be—and it indicates that, under the new national cancer program, things are proceeding very much as they have before. There is, however, one facet of the war on cancer that does constitute a change from the way things were, which can be directly attributed to the national program. Rauscher emphasizes it in his report, as he does consistently in his speeches and personal conversations—it is this matter of "delivering research results to the people."

Much has been made of the fact that there are today ten types of cancer* that can be controlled through drugs in a significant number of patients. Much has also been made of the fact that effective use of chemotherapy is a sophisticated and tricky business and that, unless a patient is in the hands of the right doctor, he is not going to derive any benefit at all from the progress that has been made. Under the new cancer program, therefore, a lot of attention will be paid to spreading knowledge around.

The issue came up recently at the White House's Federal Focus on Health seminar (*Science*, 27 July), at which

* Burkitt's lymphoma, choriocarcinoma, acute lymphocytic leukemia, Hodgkin's disease, other forms of malignant lymphomas, Ewing's tumor, embryonal rhabdomyosarcoma, testicular tumor, retinoblastoma, and Wilm's tumor.

The Goals of the National Cancer Program

Objective 1:	Develop the means to reduce the effectiveness of external agents for producing cancer.
Objective 2:	Develop the means to modify individuals in order to minimize the risk of cancer development.
Objective 3:	Develop the means to prevent transformation of normal cells to cells capable of forming cancers.
Objective 4:	Develop the means to prevent progression of precancerous cells to cancers, development of cancers from precancerous conditions, and spread of cancers from primary sites. [Approaches (one of four) Interfere with the process of tumor initiation following cell transformation, including interference with development of stromal and blood vessel elements and other host responses. Approach Elements (one of seven) Interfere with progression of neoplastic transformed cells to cancer through elimination or control of cancer microfoci by chemotherapy.]
Objective 5:	Develop the means to achieve an accurate assessment of (i) the risk of developing cancer in individuals and in population groups and (ii) the presence, extent, and probable course of existing cancers.
Objective 6:	Develop the means to cure cancer patients and to control the progress of cancers.
Objective 7:	Develop the means to improve the rehabilitation of cancer patients.

Rauscher announced the selection of seven "primary" hospitals† that will be part of a cancer treatment control or demonstration project. These seven are to collaborate with some 120 community hospitals in their respective areas for the treatment of acute lymphocytic leukemia, Hodgkin's disease, and various types of lymphomas.

Taking acute lymphocytic leukemia as an example, Rauscher said that, a year ago, only 25 to 30 percent of the estimated 4500 children in the United States who develop this disease each year had access to "best effort treatment." Today, he says, about 50 percent do, but that still is not enough. Presumably, this cancer control project will help, if practicing physicians cooperate.

The issue is terribly touchy, particularly because of its implication that not all doctors are equal. One reporter at the White House seminar put it this way: "Dr. Rauscher, are you saying that right now in this country there are some sweet little children who go to the wrong hospital and die 6 months later, who, if they went to another hospital, would be allowed 5 years?" Said Rauscher, not wanting to offend every doctor in America, "I am not saying that at all." But privately he and other NCI officials concede that that is exactly what they are saying.

Along with cancer control programs such as this—and one with the American Cancer Society to screen women for breast cancer—the plan calls for the establishment of 15 comprehensive cancer centers, geographically distributed across the country. These centers, which are required by law, are supposed to conduct research, train scientists, offer patients sophisticated therapy, and work with the community in which they are located.

The Roswell Park Memorial Institute in Buffalo, N.Y., the M. D. Anderson Hospital and Tumor Institute in Texas, and the Sloan-Kettering Memorial Institute in New York, were immediately designated as comprehensive centers. Hospitals such as the ones named earlier as places where one should go for treatment of acute leukemia are what the NCI calls specialized centers. Cancer control is more an idea than a place. Therefore, a cancer control project could be run out of a center but does not necessarily have to be.

Rauscher's report is preceded by a letter of transmittal to the President. "The Program is making excellent progress, driven by the dedication and the determination that infuse the cancer science and medical community of this country," he said. "Moreover, our way is made easier by the advice and counsel of your Panel and the National Cancer Advisory Board. The problems that exist are manageable. . . . We are deeply grateful for your strong personal commitment and the sense of urgency you impart to the Program." That bit of rhetoric was composed on 31 January. Eight months later, there are not many people who take it seriously.

In assessing the cancer program so far, one inevitably asks what is going on now that was not taking place before. Primarily, it is the emphasis on patient care—the NCI insists it is running "demonstration projects" rather than delivering care in a strict sense. Until the cancer act was passed, the NCI, like each of the other institutes, did very little in the way of treating large numbers of patients. Its new sense of mission is a tremendously expensive one which does not have the full support of the advisory board. Many of its members feel that money is merely being wasted on the centers and cancer control programs. It is particularly dissatisfied with the requirement in the law that comprehensive centers be established. For fiscal 1974, NCI requested more than $84 million for its centers programs and $34 million for cancer control. It asked for $99 million for regular research grants. Rauscher believes that this distribution of funds is in keeping with what Congress wants but it has not made the scientific community happy.

After leaving Rauscher's office, the cancer plan did not go straight to the White House as many people erroneously assumed it would. It went, instead, to the HEW bureaucracy, like any other NIH document, and there it began its journey through what Secretary Caspar Weinberger calls the "various loops" of administrative approval. The plan also went to the Office of Management and Budget (OMB) for scrutiny.

One of the obstacles to getting everyone to go along with the plan was money. The planners carefully spelled out what they believed they would need in terms of manpower, facilities, and money for the next 5 years, basing their projections on what they believe the scientific possibilities to be. The original version of the plan went to pains to point out that the program was being defined "in terms of the minimum research necessary" and that the science base "*does not* include *all available* scientific knowledge regardless of its relationship to the cancer program. It *does* include only that research deemed necessary for an effective at-

† Children's Hospital of Los Angeles; Children's Hospital Medical Center, Cincinnati; Dartmouth Medical School, Hanover, N.H.; University of Alabama Medical Center, Birmingham; Children's Hospital of Denver; New York Hospital–Cornell Medical Center; and Mount Sinai School of Medicine, New York City.

tack on the disease of cancer." In other words, the cancer planners were trying to reassure the Administration that they were not going to pull a fast one and support all of basic research in the name of cancer. They said they could use 11,500 to 15,000 professional scientists and somewhere between $1 billion and $2 billion a year to get on with the job.

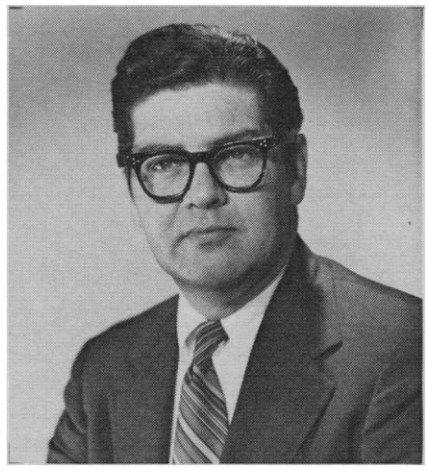
The Administration simply would not buy that. Weinberger recently told *Science* that even in fighting a war on cancer, one could not forget the necessity of keeping the total federal budget in bounds. And assistant secretary for health Charles C. Edwards lets his opinion be known when he talks about the need for restoring balance in biomedical research (*Science*, 31 August). OMB officials are also unconvinced that the cancer program should be funded at the level that the NCI would like.

So, the cancer plan that was finally released is a more modest one than it might have been. While stating that $1 to 2 billion would be nice, its actual projections call for much less: $500 million for fiscal 1974, rather than the $640 million Rauscher says he needs and Congress, in the 1971 act, said he could have. Progressive increases go up to somewhat more than $800 million in fiscal 1978.

There is reasonable consensus that NCI needs that much money to do the things it has planned. However, even among the cancer board members, there is no consensus that it has its priorities straight. In fact, some of them believe that if the focus of the cancer program were reset, significant progress could be made on the $500 million.

The Heart Plan

Although the heart program is not without its problems, it seems to be less embattled than the cancer program. The plan was laid with less trauma, in far less time, and cost little more than half of what the cancer plan has cost so far. Theodore Cooper, director of the National Heart and Lung Institute, diplomatically says that, in part, this is because the heart planners had the cancer planners' experiences to draw on. Furthermore, the heart act spelled out areas to which the NHLI was to address itself and solved some of the problems of setting priorities by requiring that 15 percent of the budget be spent on lung disease research and 15 percent for work that is related to blood.



Frank J. Rauscher

Theodore Cooper

To get the encyclopedia of scientific information needed to construct a plan, Cooper appointed only four panels‡, in contrast to the NCI's 40, and let the members of those panels solicit the counsel of their colleagues as they saw fit. Altogether, Cooper estimates, as many scientists contributed to the heart plan as did to the cancer plan, but there was no equivalent to the cancer planners' Airlie House conferences. The panels' reports went to the National Heart and Lung Advisory Council, which subsequently drew up its own report. From these, Cooper himself made an assessment of the available options, which are summarized in his report. Arteriosclerosis, or hardening of the arteries, and hypertension will receive considerable attention. The former is thought to be responsible for 84 percent of deaths from heart and blood vessel diseases, Cooper says. The latter affects an estimated 23 million adult Americans, is the most important factor contributing to the development of strokes, and accelerates the development of atherosclerosis, a narrowing of arteries and veins.

The plan clearly spells out ways of attacking these diseases with a sense of putting first things first. The approach to arteriosclerosis is representative. Cooper begins by noting that a great deal is already known about the causes of arteriosclerosis—high levels of lipids in blood, genetic makeup, physical inactivity, and heavy smoking among them—and calls first for an emphasis on studies of its etiology "within existing research programs." In other words, there will be more basic research along existing lines since they seem to be the right ones. And, there will be more large clinical studies intended to show whether it does any good to change the dietary, exercise, or smoking habits of individuals at risk.

But a decision has been made to push for something new as well. The NHLI will "stimulate" the development of noninvasive techniques of detecting arteriosclerotic changes in vessels so that, in a couple of years, it might be possible to actually see what changes are taking place as disease progresses. As one member of the heart council pointed out, the very expensive large clinical trials involving thousands of persons are fine if, after 8 or 10 years, you want to know how many of them are dead. "But if we want to know why, we have to really know what is going on inside those vessels." Cooper, like others, believes that noninvasive techniques will help in this regard and that the technology for appropriate instruments is sufficiently advanced that a concerted effort for further development will pay off.

Throughout, the heart plan highlights areas such as this that can be programmed with some expectation of success and there is reasonable agreement that they are good ideas. Nevertheless, many of the heart people, like many of the cancer people, are still unconvinced that one can really plan for the thing that, ultimately, counts most—a substantive step forward in understanding through basic research.

There are other dissatisfactions among the heart planners that parallel some of those which are prevalent among cancer researchers. One is the matter of money. The Administration is unwilling to go along with the funding

‡ Heart panels were established to consider heart and blood vessel diseases, lung diseases, blood diseases, and blood resources.

levels the Congress has said it will approve. Cooper says that the heart plan is an attempt to state "what we can do in terms of the real world" but the real world seems to be shrinking. The plan, for fiscal 1974, calls for $311 million. The President's budget calls for $265 million. And, several members of the council contend that they need that extra money in view of the fact that, as things stand now, large clinical surveys and demonstration projects will be

Heart Plan Calls for "Professorships"

The national heart plan proposes that the federal government establish a "research professorship" in every medical school in the United States and that it support 50 small "professorial research groups" of individuals devoting their full energies to research on heart, blood, and lung diseases. The idea is to introduce some semblance of stability into the research environment which is currently plagued by fiscal uncertainties. The two programs together would cost $25 million a year. According to members of the advisory council to the National Heart and Lung Institute (NHLI), who made the proposal in their report which is volume II of the plan, this kind of research support is essential to the ultimate success of the national crusade to conquer heart disease.

For several years, scientists have been concerned about the disruptive effects budget decreases have had on the research community. While there is no doubt that biologists are asking for more money, it has, perhaps, been less apparent that they are also looking for stability. No one can do spectacular research, the argument goes, if he has to spend half his time worrying about whether he is going to have enough money to keep his laboratory open 1 year.

The instability in the research community that has resulted from generally diminishing levels of support was compounded last January when the Administration announced its decision to do away with the National Institutes of Health (NIH) training grants programs. This decision sent the biomedical community into a state of shock from which it has yet to recover.

There were two things at stake: support for students, usually at the postdoctoral level, and support for their teachers. Although for years people were reluctant to admit it, the NIH training programs, which last year totaled about $130 million, always served a double purpose. The grants, as their name implies, provided stipends to young biologists; they also provided funds to the institutions in which they trained. The money was used to pay faculty salaries and to cover certain other research expenses.

The Administration did not approve. As Health, Education, and Welfare Secretary Caspar Weinberger said during a recent conversation with *Science*, one of the main objections to the old training grants program was its double life. Weinberger said he is not necessarily opposed to institutional support but, he noted, it should not exist under the guise of something else. Nor, he said, does he oppose federal support of young scientists who are planning careers in research. As evidence of that, he cited the government's "new" training grant program which he announced in July (*Science*, 27 July). Under that plan, NIH can spend $30 million this year to provide stipends of $10,000 each to qualified biologists in training. Weinberger's announcement drew no protest, as did the original statement that the training program was out; nor did it elicit much praise from the nation's biologists who apparently feel that this $30 million compromise does not resolve the problem.

For the most part, the protest that was leveled against the Administration was not particularly constructive. Highly reputable scientists went around proclaiming that there would be no new biologists to carry on, and that the lights were going out in laboratories all over America. Their hyperbole amused many Administration officials but did not really convince them of much.

In this context, the proposals made by the heart and lung advisory council have a measure of substance and seriousness to them that deserve attention. Although their proposals are intended to advance the cause of heart and lung research, it is clear that their ideas are applicable to other areas of biomedical science as well.

In its report, the council acknowledges that "To accommodate the needs for both fundamental and mission-oriented research, the National Heart and Lung Institute requires a variety of support mechanisms suitable to a wide variety of investigators." One of those mechanisms, it says, should offer stable support to senior scientists. ". . . [T]he rapid advance of the National Program [to conquer heart disease] requires that more senior scientists dedicate 80 to 90 percent of their time to research." Therefore, the council proposes that the NHLI establish a research professorship in every U.S. medical school. The necessary grants to the schools would be made for 10 years, not just one or two, and would be renewable for additional periods of 10 years. Each grant—about $75,000 per year—would pay the salary of the research professor and provide him with one research fellow and one technician.

(This concept of supporting an individual who could become the focus of a research program within a school is derived from the American Heart Association's "Career Investigator" program which has been in operation since 1951. In its review of the National Cancer Program Plan, a committee of the Institute of Medicine made a similar suggestion for cancer researchers, based on the "Career Development" awards of the American Cancer Society.)

In addition to "research professorships," the heart and lung council would like the NHLI to establish units of several investigators—it calls them "professorial research groups"—at a cost of about $300,000 each. The grants would go to teams of three or four scientists, plus three technicians, who propose a specific research program. Again, the idea is to make a long-term commitment so that scientists could be assured of basic expenses, even though they might have to seek some additional funds. The grants would be made for 7 years at a time.

So far, there has been no response from the Administration that indicates it will buy the council's suggestion. But then, the idea, tucked away in the heart plan, has not yet been pressed very hard either.—B.J.C.

supported at the expense of research.

The heart plan did not run around HEW's loops nearly as long as the cancer plan did, but it ran into trouble because it also contains dollar figures that the Administration will not stand behind. HEW officials wanted to release the plan with the future budgets deleted. Cooper and the council wanted them to stay and, after a struggle, they did. Pressured to get the heart plan through the bureaucracy and over to Congress with some dispatch, HEW released it within 3 months of its receipt. It is apparent HEW officials released it reluctantly.

On 24 July, deputy secretary Frank Carlucci, not Secretary Weinberger, sent the heart plan to Congress with a letter of transmittal that said in part: I believe it is important to note that the report has not been fully reviewed within the Executive Branch. As written, it does not reflect a consideration and development of priorities among all of our research objectives but is limited to those within the scope of the National Heart and Lung Institute. The potential danger of looking at only a single research area is illustrated by the fact that the plan's recommendations for heart and lung research, if implemented within the approved 1974 budget levels, would result in a reduction of $46 million in other important research fields. . . . In order to respond to the wishes of the Congress for prompt submission, I am transmitting the plan at this time with the above understanding.

The tone of the letter offended the people who wrote the plan, though Weinberger and Edwards insist that no offense was intended. (Carlucci, who reportedly put into his own words an assessment of the plan that came from Edwards' office, has been on vacation and was unavailable for comment.) The point of the letter, they say, was simply to emphasize to Congress the fact that the request for money comes from the heart institute and not the President.

Congress has let it be known that it is as interested in the wars on cancer and heart disease as it was to begin with and there is every reason to believe that when the appropriations bills are reported out within a few weeks, they will include sums far higher than the President has asked. No one knows what will happen then, or whether the wars to conquer disease will ever get started.—BARBARA J. CULLITON

Insect Viruses: A New Class of Pesticides

Saved countless lives in World War II; won Nobel prize for inventor; became household word throughout world; attacked by Rachel Carson; target of bumper sticker people; banned by the Environmental Protection Agency (EPA). The dramatic rise and fall of DDT is a paradigm of the vicissitudes that have beset the whole class of chemical pesticides. It may also prefigure the career of a radically new class of pesticides that is about to make its commercial debut. The use of viruses to kill off their natural insect hosts is conceptually elegant and, on the face of it, offers minimum interference with nature. Yet, unless viral insecticides are one of life's rare panaceas, they will probably be found in the course of use to have harmful consequences that are now unforeseen or held discountable.

Viral insecticides have the advantage over chemicals that they occur naturally and are apparently innocuous to all but their host species. But development of the viruses for field use has dragged out over more than a decade. Regulatory agencies, understandably enough, have not instantly embraced the idea of spraying viruses over crops intended for human consumption. And wariness of viruses has not been allayed by the emergence of their possible role in cancers or by the knowledge accruing from biological warfare programs. But virus enthusiasts persisted, regulatory officials eventually decided what safety tests they required, and a few months ago the EPA, in a little-noticed announcement in the *Federal Register*, declared for the first time that a particular viral pesticide was safe for use. If the virus is also deemed to be efficacious, a decision that may be taken in the next few weeks, it will be registered for commercial use, the first viral pesticide to attain this status.

The virus in question is the nuclear polyhedrosis virus of *Heliothis zea*, a noctuid moth known commonly as the cotton bollworm. By notice in the *Federal Register* of 30 May, the EPA exempted the virus from the requirement of leaving no more than a minimum residue on crops—a way of saying that the virus presents no hazard to human health.

This landmark decision has been reached with at least the appearance of some casualness. Virologists at the Center for Disease Control in Atlanta, Georgia, the federal agency charged with monitoring health hazards, were not involved in the decision (there is no statutory requirement that they should be) and were unaware that the virus was nearing registration. Nor, as might perhaps have been expected, did the EPA find it necessary to convene an outside review panel of specialists in molecular genetics and other pertinent disciplines.

This is not to say, however, that the EPA has not done its homework. According to Reto Engler, a virologist in the EPA pesticides tolerance division, numerous outside experts have been consulted on an ad hoc basis over the last 5 years, and the safety issue has been reviewed by an international group that met last year under the auspices of the World Health Organization (WHO). (Chaired by C. E. Gordon Smith, former director of the British biological warfare establishment at Porton Down, the group consisted of entomologists active in the viral pesticide field rather than disinterested experts.)

The arguments for and against the safety of viral pesticides are not very evenly balanced. There is a mass of direct evidence for supposing the viruses to be quite safe. The reasons for supposing them to be hazardous to health, on the other hand, are for the most part far out theoretical possibilities for which no hard evidence exists.

Among the many attestations to the