THE CANCER LETTER

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Vol. 5 No. 30

July 27, 1979

Subscription $125.00 per year

VIROLOGY CONTRACT PHASEOUT TO CUT $5 MILLION IN FY 1980; BIGGER REDUCTION COMING IN 1982

In what at one time seemed to be an endless debate on "contracts vs. grants," the extramural portion of NCI's Viral Oncology Program was inevitably singled out by critics as the classic example of how the contract mechanism is misused at the expense of investigator initiated research.

Much of the criticism was quieted with implementation of the Zinder Committee's recommendations, which separated the intramural and

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In Brief

HARRIS SAYS SHE WON'T EASE UP ON CALIFANO'S ANTISMOKING CAMPAIGN – IT COST HIM HIS JOB

PATRICIA HARRIS, who will replace Joseph Califano as HEW Secretary following wholesale firing of cabinet officers by President Carter, told reporters not to expect any softening of the HEW antismoking efforts initiated by Califano. Califano was fired because his abrasiveness offended some White House staff members, and they convinced Carter he was a political liability in the South largely because of his antitobacco campaign. Harris, who turned out to be a strong and effective head of the Dept. of Housing & Urban Development, also has left some scars on the Georgia mafia but is considered a political asset because of the fact that she is a woman and is black. . . . **CALIFANO'S IMPACT** on the Cancer Program was significant. He personally selected Arthur Upton as NCI director, and also chose six of the members of the present National Cancer Advisory Board. Although long and unnecessary delays in making those appointments didn't help the Program, Califano more than made up for it by coming down so hard against smoking. He was the first HEW secretary with the courage to do that; the fact that it cost him his job demonstrates why none of his predecessors would take such a strong position. . . . **CIPRIANO CUETO**, chief of the Toxicology Branch in NCI's Bioassay Program, has joined Litton Bionetics as associate director of toxicology. . . . **ALBERT GUNN**, assistant director for hospitals of the University of Texas System Cancer Center, has been named assistant dean of admissions at the UT Health Science Center Medical School in Houston. He will divide his efforts between the new medical school post and his current duties as medical director of M.D. Anderson's rehabilitation center. . . . **O.F.E. MUEHLBOCK**, who for many years was head of the Dept. of Biology at the Netherlands Cancer Institute, died last month after a short illness. . . . **NATIONAL CONFERENCE** on Breast Cancer, sponsored by the American Cancer Society, will be held Sept. 6-8 at the Waldorf-Astoria in New York. Attendance will be limited to physicians and medical students. Contact ACS local divisions or Breast Cancer Conference, ACS, 777 Third Ave., New York 10017.

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VIROLOGY CONTRACTORS WILL COMPETE SUCCESSFULLY FOR GRANTS, NCI FEELS

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extramural components of the program and established strong peer review of contract proposals.

Criticism also was considerably muted when it became apparent that the contract program was supporting some superb basic research and that it had grown far beyond the search for a human cancer virus.

With all of the program's accomplishments, however, it now seems that the critics—at least those who felt the massive contract sums should be moved into grants—have won. NCI Director Arthur Upton's decision to phase out contracts supporting basic research and increase support for grants affected none more than the Viral Oncology Program.

The real impact of that policy has yet to be felt in a major way by the program's contractors, 18 months after it was announced by Upton. A substantial number of contracts had just been renewed or were in negotiation, and they will not be phased out until the 1982 fiscal year. But 28 of 80 contracts supporting what is considered basic research will expire at the end of the 1980 fiscal year, worth a total of about $5 million a year. That will reduce the total budgeted for contracts in viral oncology from $32.1 million in fiscal 1979 to $27 million in 1980.

Although the analogy is far from perfect, the Viral Oncology Program may have been the NCI activity which most resembled NASA's Apollo Program. Directed by John Moloney, it included hundreds of the world's top virologists (not all of them—NCI supported some virology research through grants, which until Upton's reorganization last year were administered by another division independently of Moloney's operation). The contracts were coordinated and monitored closely by Moloney and his staff. Moloney brought them all together once a year at Hershey, Pa., to discuss problems and progress. Scientists from industry and independent research institutions participated, as well as those from the academic world.

Cutbacks in the program started well before Upton's reorganization. From a peak of about $44 million in 1975, contract funds dipped to $37.4 million in FY 1978, under pressures generated by level appropriations (in terms of constant dollars) for NCI. Adding to the pressure was the growing feeling that the Viral Oncology Program had done its job in stimulating development of the field to the point where there were enough good investigators with enough good new ideas working in nearly every area of virology. They should be permitted to seek funding for those ideas through the peer reviewed, grant supported process, the critics said. Moloney's budget became the No. 1 cutback target.

The decision to phase out basic research contracts, and the reorganization which moved virology grants into the Div. of Cancer Cause & Prevention side by side with the Viral Oncology Program, spelled the end of that effort as a program. In its dismantling, Moloney left it for a position in Upton's office.

Those with basic research contracts have been told that eventually they will have to compete for grants if they expect to continue receiving NCI support.

With all the uncertainties involved, one might expect the morale of the participants in the program to be shattered. But DCCP Director Gregory O'Conor said that the "transition is working quite well. Most investigators are sympathetic with the needs of the institute and recognize the change the field has taken. . . . I think the scientific community recognizes that the contract program is not needed anymore. Most are confident they can be adequately supported through the grant mechanism."

O'Conor, who became director of the division only a few months before the reorganization was announced and was never involved with the Viral Oncology Program (he is an epidemiologist), has been lavish in his praise of its accomplishments. "It succeeded in really moving the science," he said. "Study of the mechanisms of carcinogenesis was greatly furthered by the Viral Oncology Program. But the character of the program has changed, from the search for a putative virus to the mechanism of carcinogenesis. That field uses techniques developed in the program, in exploring how cells through interaction of environmental agents with genes can be involved in carcinogenesis."

Emphasis now is on "using molecular, immunologic and recombinant DNA techniques for the study of transformation and gene control," O'Conor said. "This is very exciting and can be supported through the grant mechanism."

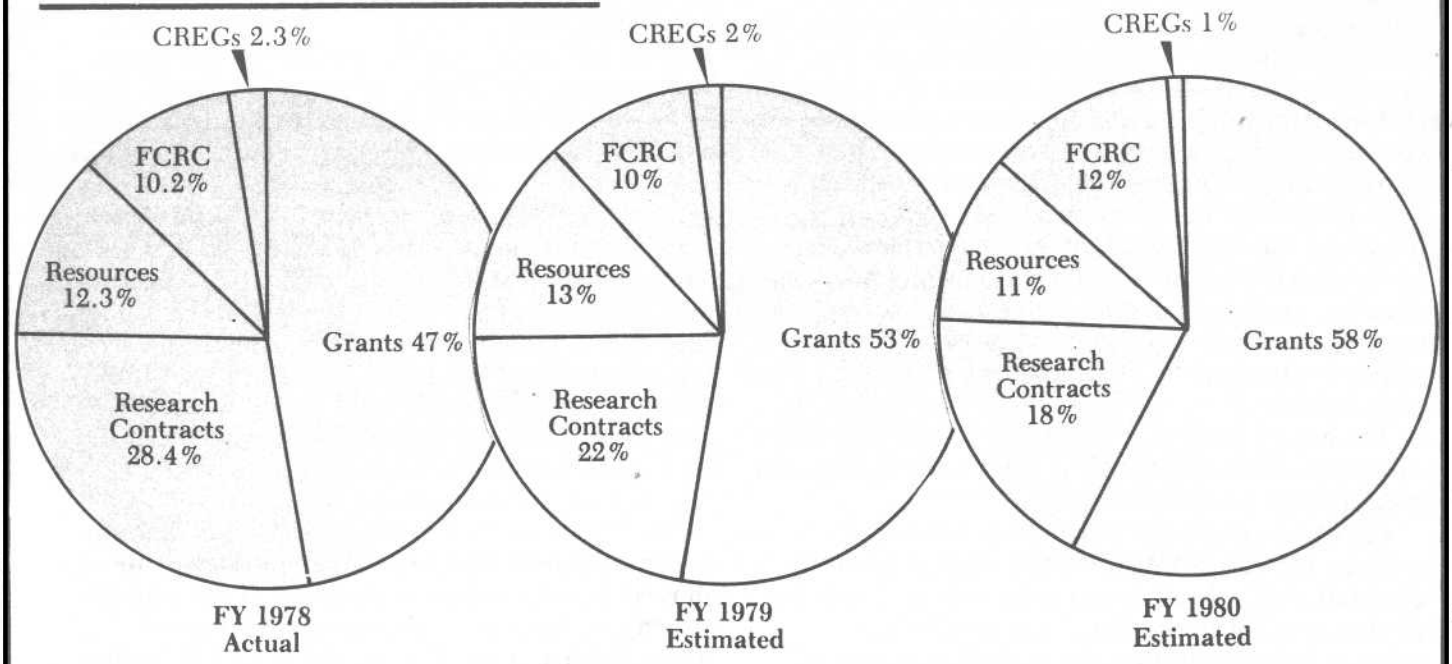
O'Conor pointed out that the more applied aspects of viral oncology, particularly some of the work directly related to humans, and also DNA virus research, will continue to be supported through contracts. Commercial organizations also will have to continue with contracts, since they are not permitted to receive grants.

O'Conor said there have been some problems with the phaseouts in the Chemical Carcinogenesis Branch. "Some of the contractors didn't really believe it was going to happen to them," he said. "In many cases, it was our fault, due to the unstable condition of the Carcinogenesis Program. People were behind schedule and found themselves with their contracts running out but not in the grant cycle. We were able to work with them, get some extensions, to permit them to complete their projects."

James Duff is chief of the Biological Carcinogenesis Branch. He agrees with O'Conor, that those who do high quality research will be able to compete successfully for grants. It will take some getting used to, however.

"The problem with grants is that funding is cut off

Biological Carcinogenesis Branch



at a priority score of 235 (or whatever the funding level is)," Duff said. "With contracts, it is yes or no."

Also, priority scores tend to reflect study section views of what is important. "Right now, molecular studies are red hot," Duff said. "Work with the less popular viruses may have a more difficult time."

Suppose a contractor is doing some of the less popular work and can't score high enough with a grant to get funded. If NCI considers the work important, would the contract be renewed or a new RFP generated?

The answer is yes, Duff said, provided the DCCP Board of Scientific Counselors approved at its annual concept review. There have been no such instances yet, but the Board will be considering DCCP staff recommendations for contract supported projects at its November meeting.

The first test of whether Viral Oncology Program contractors could move successsfully into grants came with the grants reviewed in June by the NIH study sections. Those grants will go to the National Cancer Advisory Board in October (those that are over $35,000).

The results were mixed, Duff said. Some received priority scores better than 235, which will assure their funding; others did not. Duff feels this was not a valid test, since these were the contractors with the shortest notice and least amount of time to prepare grant applications.

Frank Lilly, at Albert Einstein, and Norman Davidson, at Cal Tech, were two contractors who succeeded in getting grants to continue their studies. Davidson's work is for studies of tumor virus nucleic acids, and Lilly's for studies of genetic and immunological factors in viral leukemogenesis.

Many of those who will not be funded will be encouraged to resubmit, Duff said.

There have been problems with some of the larger projects which have been funded under one contract. At least one is putting together a program project grant application to cover portions of the work while other components will have to compete for support through individual R01 (traditional) grants. Another will receive a grant for basic research, with the rest of the project to be recompeted as a contract.

There is no guarantee at all that the $5 million which will be phased out of Biological Carcinogenesis contracts by the end of 1980 will be added to the $37.5 million in grants which the branch is supporting in 1979. That depends on how well those contractors compete, NCI institute wide priorities, and what study sections do with budget requests.

Moloney remains a defender of the contract mechanism as it was used in the Viral Oncology Program. "I still feel it is an ideal way to initiate and coordinate a major research effort," he said. "We never looked at it as directed research."

Answering those who have pressed for increased emphasis on investigator initiated research, Moloney said, "People in the universities are not the only ones with bright ideas." People in the universities have said the same thing about people in Bethesda, Moloney acknowledged. "But I don't believe that things will always happen if you just give scientists enough money and get out of their way."

The Biological Carcinogenesis Branch, according to DCCP's description of its mission, "plans, initiates, coordinates, evaluates, and maintains an extramural basic and applied research program on the role of biological agents as possible etiological factors or cofactors in cancer and on the control of these agents and their diseases; plans, develops, allocates and main-

tains research resources necessary for the conduct of the coordinated research program, including selection of appropriate contractors and management of resources contracts; develops and maintains computerized management information systems; plans and conducts appropriate scientific meetings and workshops to further program objectives; establishes program priorities, evaluates program effectiveness, integrates the activities of the various elements, represents the biological program area, and provides advice in management and scientific decision making meetings within the division; and provides project officer for monitoring collaborative research activities of the division."

The branch groups its research activities into three categories—DNA virus studies, RNA virus studies, and special projects (figures are for FY 1979):

• DNA virus studies—26 contracts totaling $5.1 million, 131 grants totaling $13.9 million. Includes elucidation of role of viruses in induction of neoplastic disease; viral associations with neoplasia in humans; characterization and biological activity of oncogenic and suspected oncogenic DNA viruses; intracellular relationships established between DNA virion and intracellular components; virus genome expression and intracellular control; mechanisms of reproduction and induction of neoplasia; inhibition of replication and transformation; development of methods for control of virus infections or prevention of induction of neoplasia in humans and animals.

• RNA virus studies—39 contracts totaling $6.9 million, 135 grants totaling $15 million. Includes detection in case material of activities or components characteristic of RNA viruses; virus isolation and characterization; virus replicative processes; intracellular relationship between virion and cellular components; function of virus genome components in the disease process and cellular control of expression; mechanisms of virus induced cell transformation to malignancy; inhibition of viral replication and cell transformation; interaction between virus and environmental carcinogens resulting in enhanced incidence of neoplasia; host response to the presence of viral information resulting in altered susceptibility to infection/malignancy.

• Special projects—15 contracts totaling $3.8 million, 47 grants totaling $8.6 million. Includes morphogenesis of mouse mammary tumor virus (MuMTV); biological characterization of MuMTV variants; host control of virus expression; mechanisms of mammary carcinogenesis in animal systems; relationship of viral/extrinsic factors; detection of viral information in human breast carcinomas; detection of host immunological response to type B retroviruses; growth and cell control process, mechanisms, and regulation of gene expression in viral and nonviral systems; biogenesis of transformed membranes; molecular dynamics and structure of non-oncogeneic viruses and membrane assemblies; biology of host-virus interactions; relationship of immune function to tumorigenesis.

Seven of the 26 DNA virus contracts will expire by the end of the 1980 fiscal year (which ends Sept. 30, 1980); 15 of the 39 RNA virus contracts will expire by then, although some may require extensions; and six of the 15 special projects will expire during the same period.

The branch also supports 26 contracts for research resources, worth $8.6 million in FY 1979; one contract for data management and information, $300,000; and two contracts under the Litton Bionetics management of Frederick Cancer Research Center, worth $7.4 million, for a multifaceted, comprehensive biological carcinogenesis program including basic and applied viral oncology research and associated research support activities.

The resources, data management and FCRC contracts will not be affected by the emphasis on grants and will be recompeted as contracts at the appropriate times. However, resources contracts were trimmed from 36 to 26 from 1978 to 1979, with a $200,000 reduction to $8.6 million, and will drop further, to 17 contracts and $7 million in 1980. The data management contract will remain approximately the same. FCRC support will go up slightly, from $7.4 to almost $8 million, but that will still be $1 million less than the branch supported in 1978.

Under the original budget for NCI submitted by the Administration to Congress, the total number of viral oncology grants in 1980 was estimated at 309, compared with 313 in 1979 and 282 in 1978. However, Congress has added money specifically for investigator initiated grants which could increase that number somewhat. Again, those numbers also depend on how well viral oncology grant applicants compete against other NCI programs.

There were 56 competing renewals in 1979; the estimate for 1980 dropped that total to 29. However, the number of continuations rose from 193 to 242, and that factor is responsible for the drastic reduction in numbers of new and competing renewals despite an estimated increase from $37.5 to $38.9 million for grants.

The branch supports 283 R01 grants in FY 1979, totaling $24 million, and estimated that will drop to 278 next year with an increase to $26.2 million. There were two conference grants totaling $100,000 in 1979, and an estimated four at $200,000 in 1980; 12 young investigator grants in 1979 totaling $400,000, with no changes in those numbers estimated for 1980; and 16 program project grants in 1979 totaling $13 million, with an estimated 15 totaling $12.1 million in 1980.

The number of CREGs will drop from 20, at $1.7 million, in 1979, to six, at $600,000. Since the program divisions now are supporting all types of grants, the usefulness of CREGs is diminishing. Most program managers now prefer to publish a request for

applications or program announcement, describing in more general terms the research areas needing emphasis, rather than seek applications through the more detailed CREG route. Applications responding to RFAs and program announcements are reviewed and awarded as traditional grants.

CITIZENS' COMMITTEE ASKS EMPHASIS ON NEW TREATMENT AT COMP CENTERS

New characteristics for comprehensive cancer centers being developed by the Assn. of American Cancer Institutes and NCI staff for recommendation to the National Cancer Advisory Board should include a requirement that centers participate in developing "newer, better, and less toxic treatments."

That is the position of the Citizens' Committee for the Conquest of Cancer as expressed by one of its co-chairmen, Solomon Garb, medical director of the American Medical Center at Denver.

Responding to suggestions for changes in the characteristics established by the NCAB for comprehensive cancer centers (***The Cancer Letter,*** July 13), Garb said:

"There is an area that seems to have been played down or overlooked by those concerned with the comprehensive center issue—participation in the development of better treatments.

"The report of the National Panel of Consultants on the Conquest of Cancer in 1971, in several places but particularly on page 26 and 27, emphasizes the importance of developing new anticancer drugs and other treatments. Experience since 1971 indicates that this has been the most fruitful and promising part of the Cancer Program.

"It is the position of Citizens' Committee for the Conquest of Cancer that a center which is called 'comprehensive' should have significant, meaningful and productive research programs to develop newer, better, and less toxic treatments. Although clinical trials are of major importance and value, they are not, in our opinion, a substitute for the additional need to develop new treatments.

"It is not clear whether all comprehensive cancer centers are in fact expected and required to have such programs. We know several that do. If they all do, it may be that this area is not mentioned because it is

once a month for three months, and 15 were randomized to receive immunization with antigen and adjuvant once a month for three months. We have also followed 16 concomitant controls.

Significant prolongation of survival has been seen in those immunized compared to those who were not immunized. Of the latter, 11 (total 24) have died (eight before two years) and one is currently receiving treatment for a cerebral metastasis. Of the 28 immunized, five have died of lung cancer (four after two years).

Of the 15 patients who were immunized, only three have had recurrences. One woman had a stump recurrence at 21 months of her large cell anaplastic carcinoma, received cobalt, and is now free of disease approaching her sixth anniversary in June 1979. A man had recurrence around his sleeve resection for squamous cell carcinoma, had a total pneumonectomy 14 months after the primary surgery and is now free of disease three years after the second operation. The third man had tracheal and carinal recurrence in November 1977, 38 months after a primary lobectomy for squamous cell carcinoma. He received cobalt and chemotherapy and is alive with further local recurrence 19 months later.

Two of 13 patients receiving immunochemotherapy have died, at 14 months and at six years.

The favorable results obtained in this study are being tested in two other trials. One is at the Roswell Park Memorial Institute, under direction of Hiroshi Takita. Preliminary survival data conform to our early data. The second is a large multicenter trial in Canada, with hospitals in Chicago and Pittsburgh cooperating, a total of 10 centers. A total of 300 patients will be entered into this large trial.

In order to test for biological activity of the pooled antigens to be used we called back known reactors who had been immunized in the first Canadian trial. Six patients were tested and all showed a strong DHR to the pooled antigen, retaining activity from two to five years after immunization. Histologically these reactions are characterized by intense perivascular and interstitial accumulations of mononuclear cells. Such a strong stromal response to tumor has been correlated with longevity in every solid tumor in man where this has been looked for.

At this point we realized that we were able to induce a strong DHR to cancer antigen derived from the surface of cancer cells. Such an activity lasts for years, up to five years and probably much longer. Since immunization is ineffective in stage 3 lung cancer patients, less effective in stage 2 and since it fails in stage 1 when micro metastases are already present, presumably above a critical 10^6 in the number of cells, the feasibility of prophylactic immunization of adults at high risk for lung cancer becomes an attractive possibility. A very large literature of prophylactic immunization in animal systems exists, with protection against transplantation of taken for granted. Our committee plans to urge that every center which has the comprehensive designation have a significant research program for the development of newer, better, and less toxic treatments. We would like to see this accomplished by consensus if possible."

Characteristic No. 10 presently requires that "each center group sufficient beds for cancer patients to give the program cohesion, identification and favorable facilities for the clinical research program to be carried out. In general, it is expected that existing inpatient facilities will be commited for this purpose."

Characteristic No. 1 says that "the center must

disease-free interval or survival without any clearcut effect on increasing the cure rate. Thus, in each of these categories which include the common types of malignancy, activity has been modest, suggesting that immunotherapy must be further developed before it will be a major contribution to our weapons for the treatment of cancer. This makes immunotherapy a prime target for intensive investigation in clinical research studies.

Two other types of human cancer are worthy of special mention. These are malignant melanoma, which is a very aggressive skin tumor which spreads to many organs, including the lungs, liver and brain. The other is acute leukemia. In both of these diseases, BCG as well as other types of immunotherapy have been shown to be active and to prolong survival significantly. It is of particular interest that in primary malignant melanoma where after surgery the recurrence rate is 50% and only half of the patients are cured, a marked improvement in disease-free survival and possibly an increase in the cure rate has been observed when BCG alone or with chemotherapy has been added to surgical therapy. This will have to be confirmed in additional studies before it can be recommended for general use by practicing physicians.

T.H.M. Stewart, Univ. of Ottawa—It became clear in 1969 that crude membrane extracts of cancer cells were unsuitable for sophisticated antigen preparation and analysis. Thus I was delighted to cooperate with Ariel Hollinshead of George Washington Univ. . . . We were able to identify cell surface antigens, tumor associated, in the four main histologic varieties of human lung cancer. This work was done from 1970 to 1973. In March 1973 we were ready to immunize patients who had received curative surgery for lung cancer, but who were at high risk for recurrence and death in the years following surgery, especially in the first two years.

A total of 52 patients, stage 1, were entered into the study until September 1976 and have been followed to the present. Eight were randomized to receive methotrexate once a month, for three months. Thirteen were randomized to receive immunization following MTX using the appropriate allogeneic antigen homogenized with Freund's complete adjuvant, virus and carcinogen induced tumors. A few papers show protection against spontaneous tumors. Cancer antigens have been identified by many workers, using several methods, in lung cancer in man over the past 10 years. We believe that it is now possible to induce specific cellular immunity against lung cancer antigens and that this may allow the deliberate induction of immune surveillance against this tumor before it arises.

Should it be possible to conduct a successful trial of immunoprophylaxis in man, in a population at high risk, then widespread and far reaching repercussions for cancer may result.

Allan Goldstein, George Washington Univ.—Biological response modifiers are the wave of the future in treating cancer as well as many of the other debilitating diseases of aging. Their development needs to be accelerated now by the collaborative efforts of the scientific community, the pharmaceutical industry, and most important, the government.

I am convinced that with the vital help of this committee and the Congress in the form of increased budget support for the development of this area and support from the pharmaceutical industry in providing the means for large scale production and quality control, the fruits of these new discoveries can be quickly translated into new modalities of therapy and have an enormous impact on improving the health care of the American public.

Far-reaching advances in the area of basic immunobiology over the past five years have made it possible for us to understand how the immune system works. With this knowledge (which has come primarily from the lab bench) we have begun to develop new strategies to fight disease. A prime example of the translation of this new information to the clinic is the successful utilization of thymosin in reconstituting the immune systems and prolonging life in critically ill children born without functioning thymus glands, and in prolonging survival of patients with lung cancer in a study that has just become completed. . . .

More than 60 children with a variety of rare life-threatening immunodeficiency diseases have been treated with thymosin and over 30 have responded favorably. . . . In addition to the encouraging pediatric studies, the results of the first randomized trials with thymosin in lung cancer are of potentially major significance. In this first phase 2 trial with thymosin, Drs. Chretien and Cohen have successfully used thymosin in combination with intensive chemotherapy in thee treatment of a difficult type of lung cancer termed "oat-cell carcinoma." What is important about this trial is that it is the first positive utilization of thymosin, or for that matter, any form of immunotherapy, to significantly prolong the life span of patients with oat cell carcinoma of the lungs. If this initial trial can be confirmed by other studies, it will have a major impact on the treatment of this serious form of lung cancer which affects over 20,000 Americans per year. . . .

I would predict that if the basic and clinical programs with thymosin can be accelerated and proven successful that within less than five years, physicians will be able to use thymosin to treat cancer patients who have defective immune systems, in much the same way as diabetic patients are now treated with insulin.

It is my belief that research on the biological response modifiers in general and thymosin in particular is reaching the critical point where other major steps can be made, if more funds are made available to complete the development.