

Special Virus Cancer Program: Travails of a Biological Moonshot

Can basic research be targeted? The assumption that it can or ought to be has proved increasingly attractive to politicians and budget makers disenchanted with science for science's sake. Yet despite the importance of the issue, little attention has been given to a uniquely ambitious attempt at targeting basic research toward a specific goal, the Special Virus Cancer Program (SVCP) of the National Cancer Institute (NCI). The SVCP, now in its eighth year, has from the start relied heavily on the planning techniques used in space and military programs, and, for a biological undertaking, it has made similarly lavish use of resources. How well has the SVCP's moonshot approach succeeded in forcing the pace of scientific advance?

On the face of things, there has been much progress made since 1964, when the SVCP was launched with a \$10 million budget. Much new knowledge has been acquired about tumor viruses and their role in causing cancer in animals. Within the last few months, the SVCP seems to have come within reach of a major goal, the isolation of viruses presumed to cause cancer in man. Discovery of one such virus was announced this July by SVCP-supported scientists at the M. D. Anderson Institute in Houston, and two more eureka's were sounded earlier this month by SVCP teams at the University of Southern California and

at Georgetown University. With a tally of no less than three viruses, each announced as a probable human cancer agent by its discoverers, the SVCP might seem well on target in its goal of developing a human cancer vaccine or other antiviral magic bullet.

Although this is how the public and Congress may see it, the SVCP is held in rather lower esteem among the scientific community, particularly by those best qualified to assess the program's contribution.* "The SVCP has been extremely ineffective and maybe has even had a negative effect," says one distinguished cancer researcher. "I hear nothing but complaints about the SVCP. Its main trouble is that it doesn't have much of an intellectual base; it has Huebner's enormous energies, one very good person—George Todaro—but most of the contractees are pretty mediocre"—runs the verdict of a well-established biologist. An eminent West Coast virologist complains, "The SVCP is a masquerade; they make continuous proclamations of progress to justify the vast amounts of money being spent. But the nature of the program is that it excludes people who are highly critical. It has created a kind of stampede in which everyone

* Apart from officials of the SVCP, almost all scientists interviewed for this article asked that their names not be mentioned, many citing the risk of being denied funds, since, as one scientist said, "the NCI has a history of vindictiveness." Almost without exception the scientists quoted are both eminent and active in virology or related fields.

rushes lemming-like in the same direction, and critical discussion, points of obvious contradiction, are ignored."

Several virologists blame the moonshot-style approach of the program for what they see as its lack of evident intellectual underpinning. The present emphasis on finding a human cancer virus is regarded by some virologists as more a political than a scientific goal, designed to impress politicians and sustain the program's funding momentum. (For unless human cells differ from mouse and chicken cells, it is already clear that their genetic inheritance includes the specifications for a virus; the physical isolation of a human-derived virus will not lead to an understanding of the fundamental aspects of cancer and cell biology, which are given less attention by the SVCP.)

The success or otherwise of the SVCP is of topical interest not just because of the fanfare over the recent human virus claims, but also because of the impending reorganization of the NCI hierarchy caused by the new cancer funding. (There are also signs that the programmatic approach of the SVCP is likely to be extended to other areas of cancer research—the NCI has let a \$800,000 contract to a firm of systems analysts to develop a "national cancer plan.") The major criticisms made of the SVCP are that it uses a wasteful method of supporting research, allows too much power to individual scientists to channel resources in a single direction, has failed to develop an intellectual base for its overall research strategy, and excludes critics and outside advice.

The SVCP has its admirers and positive achievements, but the existence of criticisms such as these, whether justified or not, shows that the program has not won the hearts and minds of the academic world. Yet the

administrators of the SVCP seem to have little inkling of the dissidence in the world outside, or at least have taken no steps to cope with it. Officially, everything is running as smoothly as the arrows on the SVCP master plan, an assortment of interconnected boxes that bear labels such as "decision point" and "immunological control," and which embody the "research logic flow" for licking cancer.

The program was launched in 1964, largely on the strength of the association then coming to light between the African cancer known as Burkitt's lymphoma and the herpes-type virus named after Epstein and Barr. But the methodology and intellectual approach of the program, which until 1969 was called the Special Virus Leukemia Program, was inherited from the NCI's chemotherapy program. With the unwritten motto "Nothing too stupid to test," the chemotherapy program has handed out some \$330 million since 1955 in the search for a magic bullet against cancer, yet has managed to miss discovering many of the more useful anticancer agents in current use. Nevertheless, NCI officials decided to model other aspects of cancer research on the chemotherapy program, and since the contract mechanism was an essential feature of the planned approach—how else can a planner be sure of finding others to follow his ideas?—contracts were built into the ground plan of the cancer virus program.

The budget of the SVCP had climbed to \$36 million by fiscal 1971, accounting for nearly two-thirds of the funds available to the NCI's etiology division, and this year's budget for SVCP is \$49 million. Formally, the SVCP is the extramural research pro-

gram of the NCI's Office of Viral Oncology, but the same people, though in different capacities, operate both program and office, and the two are, for practical purposes, inseparable. The NCI scientific director for viral oncology and chairman of the SVCP is John B. Moloney. Under Moloney serve three branch chiefs, Robert Manaker, Robert J. Huebner, and George Todaro. The names of the three branches, which, by and large, differ from one another as much as do their respective functions, are the viral biology branch (Manaker), the viral carcinogenesis branch (Huebner), and the viral leukemia and lymphoma branch (Todaro). The three branches conduct some in-house research, which is distinct in theory but not in practice from the extramural research supported by the SVCP. In fact, a fair fraction of SVCP funds are used to support industrial laboratories that serve simply as extensions of the branch chiefs' in-house research facilities. These sums seem to amount to about \$5.5 million for Huebner's laboratories, \$1.8 million for Todaro's, and none for Manaker's. The purpose of this arrangement is to provide operational flexibility and avoid the restrictions on NIH hiring.

The SVCP is divided into eight segments, each of which is supposed to have a specific research objective. Each segment is presided over by a chairman and advisory working panel that reviews contracts. Contracts are directly supervised by project officers, but a segment chairman may act as his own project officer, particularly for contracts that are extensions of his in-house research. The largest of the eight SVCP segments are the developmental research segment chaired by

Manaker, which in fiscal 1971 controlled \$10.1 million of the \$31.6 million available to the program, and the solid tumor virus segment chaired by Huebner, which disposed of contracts worth \$9.6 million. In addition, the branch chiefs control their in-house research budgets, which in fiscal 1971 amounted to a total of \$4 million.

The total amounts controlled by each branch chief fluctuate quite widely from month to month as contracts are let, axed, or swapped, but a current estimate given by Frank J. Rauscher, scientific director for etiology and Moloney's predecessor as head of the SVCP, is that Manaker controls \$9 million, Huebner \$7.5 million, and Todaro \$6 million. Probably few individuals in the history of biological research have had such unfettered control over so much money.

The unusual power wielded by the three branches is one focus for criticism from the academic community; but the strongest objections are to the contract mechanism of supporting research and what is perceived as the program's insulation from outside advice. "They have purposely isolated themselves from the scientific community because they have been so much on the defensive," says a virologist acquainted with NIH affairs. According to a scientist on contract to the SVCP, "The program is structurally not open. The methods by which decisions are made are designed to concentrate power within the SVCP." Although all contracts awarded by the SVCP are reviewed by the segment working groups, on which outside scientists are represented, these committees are said to function as rubber stamps for decisions already made by SVCP administrators.



John B. Moloney



Robert A. Manaker



Robert J. Huebner



George J. Todaro, Jr.

Almost universal is the criticism that, for lack of outside advice and the checks and balances that govern other research programs, the principal officers of the SVCP have too much power. "I feel enormous uneasiness about the power the branch chiefs wield," says a virologist under contract to the SVCP. "It's just plain wrong. If some check cannot be put on them, then we are going to see an incredible fiasco should their judgment prove wrong." Huebner, Todaro, and Manaker each control sums of money that equal or exceed the \$6 million disposed of by the entire NIH virology study section in fiscal 1971.

Almost all research supported by the NIH is financed by grants, which are allocated by a system of peer review and are not tied down to specific objectives. By contrast, the SVCP distributes all its monies in the form of contracts, which are not subject to peer review. This applies not only to clearly definable projects such as the preparation of viruses or the collection of human tissue specimens, but also to research work that, in many instances, is no different in kind from that supported by the grant system. The SVCP's exclusive reliance on contracts is considered one of its more unpopular features in the academic world. One virologist explains, "Most of the people making the top decisions at the SVCP are not top scientists. They are allocating enormous amounts of money on the basis of relatively little knowledge. But to make scientific decisions of this nature is a complicated and chancy business. The reason why the peer review system grew up is that no one individual can make these decisions intelligently."

Academic scientists point out that most of the important discoveries in cancer virology made in recent years have come from scientists working on grants, not SVCP contracts. "If you delete most of the work financed under contract to the SVCP, we would be almost as far along the road as we are now," is the verdict of one well-known virologist. "There have been lots of advances lately, but I don't know if I could assign any of them to this particular program," says a scientist intimately acquainted with the program's affairs. Another intimate of the SVCP concludes that nothing done on contract could not have been done on research grants at one-sixth to one-tenth of the cost.

Many outside scientists criticize what

they consider to be the waste and poor quality of much contract research. The standard of SVCP contracts seems to have improved markedly in the last few years—many eminent virologists now have contracts with the program—and it probably no longer happens that applications considered not worthy of support by the NIH virology studies section receive SVCP support. But many of the 120 contracts currently let by the SVCP still arouse less than unanimous enthusiasm.

Three Look-alike Branches

How does the SVCP look from the inside? To the untutored eye there is little difference in the character of the contracts controlled by the three branch chiefs, and everyone concerned gives slightly different answers. According to Rauscher, Manaker looks after resources and research on herpes-type viruses, Todaro is concerned with the molecular biology of C-type viruses, and Huebner's interests are in viral serology, epidemiology, and chemical-viral cocarcinogenesis. According to Manaker, "My segment is tapered towards investigations involving specifically human problems. Huebner started off with DNA viruses, then shifted to RNA viruses and has spent a considerable amount of his time looking at the natural history of cancer." Huebner's perspective is that he and Todaro do not do the same things but "leapfrog" each other; Manaker is responsible "for herpes, for a lot of resources, and for Spiegelman." Todaro says that his program puts more emphasis on basic molecular biology than the other branches do. He denies that there is any duplication between his program and Huebner's—"Huebner and I do in practice coordinate our work, and if there is any competition with Huebner's branch it is a very healthy one." Another opinion, given by a scientist close to Huebner's part of the program, is this: "There is hardly any difference in subject matter between the three chiefs. You might say Manaker was more into herpes, but it isn't really true. The real difference is one of style. Huebner feels that scientific input should come from in-house, meaning largely him, and he is exceptionally good at suggesting ideas for people to do and at seeing that his contractors communicate with each other. So his segment is really rather well controlled. Manaker manages contracts where no particular scientific input is required from him.

His contracts are a hodgepodge—if they interconnect, no one has ever seen the interconnection." The same scientist adds: "The bulk of the program is still a bunch of really worthless junk, such as injecting monkeys with God knows what and other holdovers from the early days of the program."

As far as this reporter has been able to discern, there are, in effect, two different SVCP's, neither of which has very much to do with the other except for the sharing of resources. Both programs have their good points, but both are probably the worse off for being largely closed to genuine outside review. One program is that administered by Huebner and Todaro, both of whom actively participate in the research they direct and have clear ideas of the direction in which they wish the program to go. ("The SVCP is how I feel about cancer," says Huebner.) The other program is that directed by the scientist-administrators such as Rauscher (when he was chairman), Moloney, and Manaker. All three are distinguished scientists, though none is still active in the laboratory as are Huebner and Todaro.

Indications that the two camps operate largely independently are not hard to find. The three recent claims to have found candidate human viruses are a case in point. The candidate human cancer virus announced in July this year was discovered in the laboratory of one of Manaker's contractors, Leon Dmochowski of the M. D. Anderson Institute in Houston (the Institute's contract is at present \$600,000 a year; since 1965 it has received some \$2.7 million from the SVCP). Whereupon laboratories in the Huebner-Todaro program quickly proved to their own satisfaction that the virus was in fact a mouse virus that had contaminated the cell culture. (Independent tests now make this verdict rather less certain.) Huebner is said to have obtained samples of the Dmochowski virus after writing a memorandum to Carl Baker, director of the NCI, urging that, because of the numbers of people dying daily of cancer and the research funds being expended thereon, Dmochowski not be allowed to sit on his virus. Earlier this month, scientists at the University of Southern California medical school, which holds a \$1,600,000 contract from Huebner, announced that they had released a candidate human virus after growing human cancer cells in cats. Scientists in the other camp

naturally refer to the USC virus as a cat virus, but more serious evidence of rivalry was a second claim to have discovered a human virus, announced simultaneously and in direct reaction to the USC claim by scientists at Georgetown University under contract to another segment chairman, W. Ray Bryan. (Both claims were announced before appearing in the scientific literature.) Although it would doubtless be inapposite for SVCP management to try to control the release of information by their contractors, closer coordination between the two rival camps could at least establish a set of minimum criteria for announcing a human cancer virus.

A more serious lack of management control is evident in the segment working panels that are supposed to review all SVCP contracts. Rauscher and Moloney point to the existence of these panels as evidence of outside review. Most of the panels draw half of their

members from the NCI staff and half from outside, but in practice it is almost impossible for the outside scientists to vote down a contract of which they disapprove. According to one panel member, whose account is confirmed by a second member of the same panel, the voting procedure on contracts is that a favorable vote may be given without explanation, an abstention counts with the majority (in effect, as an affirmative vote), but negative votes must be justified in writing. Since materials relating to a contract are often distributed only on the morning of the panel's meeting, members have to read and listen simultaneously; thus, the segment chairman, who can usually count on the votes of the NCI members, is rarely overruled. "The outside consultants are likely to end up approving things after the fact," says a former panel member, who indicates that most of the decisions on contracts are taken by segment chairmen before the working panel meets.

Another awkward feature of the working panels as founts of independent advice is the practice of having contractors as panel members. Asked how panel members were selected, Rauscher told *Science* that Huebner, for example, will ask his panel members to suggest names of outside scientists, which are then submitted for approval first to Moloney, then to Rauscher, and finally to Baker. The membership of Huebner's working panel, as approved by Moloney, Rauscher, and Baker, is as follows: Maurice Green, St. Louis University, holder of a \$750,000 contract from Huebner's segment; Leonard Hayflick, Stanford University, holder of a \$175,000 contract from Huebner's segment; Karl Hellstrom, University of Washington, holder of an \$83,000 contract from Huebner's segment; Edwin Lennette, California Department of Public Health, holder of a \$33,000 contract from Huebner's segment; Hans Meier, Jackson Laboratories, holder of

a \$299,000 contract from Huebner's segment; Joseph Melnick, Baylor University, holder of an \$800,000 contract from Manaker's segment; and two NCI staff members. The panel's one independent voice is Wallace P. Rowe of the National Institute of Allergy and Infectious Diseases.

The free-for-all over the candidate human cancer viruses and the setup of the segment working panels raises the question of who runs the SVCP. Several sources state that Moloney, the formal head of the program, cannot control Huebner because of Huebner's close relationship with Baker; Moloney does the best he can within the rules set by Baker, these sources say. In fact, there may be some advantage in the diversity allowed by the lack of central control. Scientists in the Huebner-Todaro camp like to depict the Manaker-Moloney-Rauscher part of the program—called for convenience the administrators' SVCP—as a ragbag of unproductive contracts based on outmoded approaches. This is closer to parody than truth; the administrative part of the program may not have the same drive and sense of direction as the Huebner-Todaro part, but the average standard of its contracts has in the last 2 years improved considerably, scientists both within and outside the program say. This is partly because of the scarcity of funds from other sources, partly because of deliberate efforts to recruit good scientists by Moloney, Manaker, and a member of Manaker's staff, Timothy E. O'Connor. Manaker's contracts now include a number of distinguished scientists such as the group under J. Thomas August at the Albert Einstein College of Medicine (\$498,000), the Hanafusa team at the Public Health Research Institute of the City of New York (\$159,000), George Klein at the Karolinska Institute in Stockholm (\$73,000), Fred Rapp at Pennsylvania State University (\$292,000), and Sol Spiegelman at Columbia University (\$800,000).

The contracts under Huebner differ from Manaker's in that many of them are viewed by Huebner simply as extensions of his in-house laboratories. The unusual arrangement of Huebner acting both as an administrator and as an active scientist is a mixed blessing. On the credit side is that he is well regarded in both roles. "The real trouble with the program is that it has only on Huebner, not five or six," says a prominent critic of the SVCP. "Huebner's contracts have been more successful because he is a good manager and

because he has a very good intuition, which is important in science," this critic adds.

The disadvantage of Huebner's dual role as scientist and administrator is that he is put in the position of awarding or denying research support in a field in which he has an active personal interest. He and Todaro are felt by many scientists involved in the SVCP to be more concerned with the success of their own research interests than with the welfare of the program as a whole. "Huebner is very active at trying to get the best part of every pie. I have heard him pooh-pooh things simply because they weren't part of his program," says one SVCP contractor. Many virologists are alarmed at the "unidirectional" approach of the SVCP, or at least the Huebner-Todaro part of it, which seems designed almost exclusively to provide support for the oncogene theory, a set of ideas that have been vigorously espoused by Huebner.

The publicity-tinged style of Huebner's operation, his practice of signing papers written by contractors in far-distant laboratories (in fact contracting scientists tend to add Huebner's name to their papers on a Herr Professor basis, and Huebner does often contribute significant ideas), a recent incident in which scientists in Huebner's camp (Todaro and Aaronson) risked depriving another scientist (Rowe) of priority for an important technique, and indeed the general style of Huebner's operation, have all engendered a certain sourness toward the SVCP in academic circles. Much of the hostility caused by Huebner's domination tends to fall, unfairly, on the heads of the other administrators. "The real culprit for all this is Baker," says one scientist connected with the program.

Pace of Discovery

The flair of the Huebner-Todaro approach offers a viable and probably necessary alternative to the less *dirigiste* part of the program controlled by the administrators. Nevertheless, it seems open to question, certainly by the academic community, as to exactly what the SVCP has achieved that could not have been done equally well by the grant program. Two lines of research which the Huebner-Todaro part of the program has backed heavily in the last year and a half are work on the reverse transcriptase enzyme possessed by RNA tumor viruses, which was discovered by Howard Temin and David Baltimore

(neither of whom was on SVCP funds at the time, though the program supplied Baltimore with virus) and the group-specific antigens of C-type (gs) viruses first discovered by Huebner and colleagues in 1964.

Huebner states that the pace of discovery is proceeding "10 to 20 times faster than it would without the SVCP." In fact, it is probably too early to say whether the hectic pace imposed by Huebner's methods of massed laboratory attack on a problem will really speed solutions to basic problems. For example, he and other SVCP officials claim that as a result of SVCP emphasis, "The reverse transcriptase story is worked out to an extent that would have taken 10 years under the grant program." But scientists outside the program are not so sure. Rauscher proudly claims that the SVCP made available \$4.5 million of virus for researchers studying the enzyme. "It was because of this that all this terrible work appeared in the last year," says a scientist prominent in the reverse transcriptase field. Several virologists believe that under a grant program the reverse transcriptase would have unfolded at a slower but sounder pace. There seems to be greater consensus that Huebner's fantastically expensive work on viral gs antigens—to make 1 gram of antigen, which is enough to raise antibodies in ten guinea pigs, costs about \$1 million—would stand little chance of being funded under a grant program and is a plus for the contract mechanism.

As for the administrators' part of the SVCP, there have certainly been successes in the past, notably the far-sighted provision for mass producing viruses before the research demand developed. The SVCP supported the work of the Henles on EB virus and mononucleosis, and SVCP contractors (including Huebner before he joined the program) helped to largely rule out DNA viruses, such as the 31 adenoviruses (which are oncogenic in animals), as causes of cancer in man. Because of SVCP support, the number of viruses known to cause cancer in animals now totals more than 100. Yet apart from the SVCP's provision of resources, academic critics of the SVCP are not obviously wrong in claiming that nearly all of these advances could have been supported more efficiently on grants instead of the despised contract mechanism.

Administrators of the SVCP, such as Moloney, Rauscher, and Gio B. Gori, Rauscher's planning director, tend to

discount all outside dissatisfaction with the SVCP by attacking the motives of their critics. Certainly the academic community harbors no natural liking for the contract mechanism and planned research of the type represented by the SVCP. But instead of trying to counter the antipathy by exposing the program to outside advice, the higher echelons of the SVCP hierarchy seem instead to have retreated to a closed world of charts and systems analyses, where cancer vaccines can be developed in

five phases and three subphases. The charts, which are regarded as a harmless absurdity by the active scientists in the program, are symptomatic of the NCI administrators' divorce from reality, of their failure to provide scientific direction for the SVCP, and to straighten out its organizational confusion. But to let outside air into the SVCP, to switch some of the research-type contracts over to a grant mechanism, to start a sensible training program, and to switch more resources to

basic cell biology, are approaches that seem politically foreclosed. Says a virologist close to the SVCP, "The NIH heads have tried so hard to persuade Congress that everything was ready, they are not now in a position to take the long-term view." The moonshot design of the SVCP was from the start a gamble that cancer would prove to have a short-term solution, in the form of a viral cause and a vaccine cure. But many biologists believe a longer-term view is necessary.—NICHOLAS WADE