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Wyden Hearing On Taxol Agreements Mangles Facts In Attempt To Protect 'Public Interest'

A hearing on the agreements between Bristol-Myers Squibb and the federal government for the development of taxol, intended by Congressman Ron Wyden (D-OR) to demonstrate his subcommittee's concern about cancer patients who might be the victims of price gouging

(Continued to page 2)

In Brief

Moon, Love, Head ASPO; $10 Million For Indiana Cancer Facility Included In Energy Dept. Budget

AMERICAN SOCIETY of Preventive Oncology named new officers at its recent annual meeting. President is **Thomas Moon,** director of the Arizona Disease Prevention Center. **Richard Love** is secretary/treasurer; **Thomas London,** is head of governance; and **Marc Micozzi** is 1992 program chairman. . . . **$10 MILLION** federal contribution to the construction of a cancer research facility at Indiana Univ. Medical Center in Indianapolis has been approved by a House-Senate conference committee. The funds were requested by **Rep. John Myers** (R-IN) and are contained in the FY 1992 appropriations for the Dept. of Energy. The money is to be matched by nonfederal sources. . . . **STRANG CANCER** Prevention Center innaugurated its new facility and affiliation with the New York Hospital-Cornell Medical Center. . . .**CLARIFICATION:** An article on studies of GM-CSF and G-CSF in the July issue of "Cancer Economics," the supplement to **The Cancer Letter,** inadvertently omitted reference to Immunex Corp., the licensed manufacturer of GM-CSF and lead marketer of GM-CSF in the U.S. The story referred only to the firm's co-marketing partner, Hoechst-Roussel. Immunex holds the product license and is the sole manufacturer of yeast GM-CSF, and sells the product under the brand name Leukine. Immunex provides Hoechst-Roussel with all of the GM-CSF that company sells under the trade name Prokine. . . . **CORRECTION: P50 GRANT,** an NIH grant mechanism which NCI has proposed for its new Specialized Centers of Research Excellence, has been used rarely by NCI in the past 20 years, but not never, as indicated in **The Cancer Letter,** July 5. Peter Wiernik, professor and chairman of the Dept. of Oncology, Montefiore Medical Center and head of the Div. of Medical Oncology at Albert Einstein College of Medicine, pointed out in a letter: "When the Baltimore Cancer Research Center was jettisoned from the NCI intramural program into the extramural program, its first extramural funding was by means of a three year P50 grant of which I was the principal investigator." P50 historians, take note.

Wyden Hearing On Taxol Agreements Mangles Facts, Misses The Mark

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and about preservation of an important natural resource, did neither. Instead, the hearing was a classic demonstration on stretching or mangling the facts, or disregarding them completely, in attempting to fire up an issue that might look good on television.

There were plenty of TV cameras grinding away last week when Wyden's Subcommittee on Regulation, Business Opportunities, and Energy, of the House Small Business Committee, heard testimony on "The Government-Industry Partnership to Produce Taxol-Based Anticancer Drugs: Is the Public Interest Protected?"

As a member of Congress from Oregon, Wyden represents a state that will provide much of the yew tree bark from which taxol is derived. He has a legitimate interest in protecting the yew as a resource, and in protecting the forest lands and environment in general. He also acknowledged the public interest in what may turn out to be the most important anticancer drug yet discovered. However, if he has his way, and the agreements between Bristol-Myers Squibb (BMS) and the government are renegotiated, development of taxol could be needlessly delayed, with little if anything to be gained.

The agreements Wyden is challenging are:

--The Cooperative Research and Development Agreement (CRADA) between NCI and BMS, in which NCI gives BMS exclusive access to its clinical and preclinical data on taxol for use in obtaining approval for the commercial marketing of the drug; BMS agreed to undertake the production of taxol and all other work required to gain FDA marketing approval.

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Editor: **Kirsten Boyd Goldberg**
Associate Editor: **Lisa M. O'Rourke**
Contributing Editor: Jerry D. Boyd

Editorial/Subscriptions Office
PO Box 15189, Washington, DC 20003
Tel: (202) 543-7665 Fax: (202) 543-6879

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--Agreements between BMS and the Depts. of Agriculture and Interior for access to yew trees in U.S. Forest Service and Bureau of Land Management properties, which make up the bulk of federally owned land in the Pacific Northwest.

--FDA's award of orphan drug status to taxol for treatment of ovarian cancer.

"Giving Bristol-Myers Squibb significant taxpayer owned resources to corner the market on an important new drug may be a fast way to get taxol to some cancer patients," Wyden said in his opening statement. "But the chair observes that in the government's crash efforts, it cannot close its eyes to potential problems in these agreements. The fact is, these agreements as written simply are not in the public interest."

Wyden asserted that the agreements "do not assure a reasonable level of commercial fair play. They do not assure responsible management of a natural resource. They do not stimulate the transition from dependence on that natural resource to an alternative supply. Most importantly, there's absolutely no assurance in these agreements that patients will have broad access to these drugs, or that the drugs will be reasonably priced."

Wyden's attack on the agreements amounted to an attack on the Technology Transfer Act of 1986, although he did not present it that way. The taxol agreements are a straightforward implementation of that act, and they include language that addresses each of the points Wyden made. When witnesses pointed that out and offered other information refuting Wyden's contentions, he disregarded them.

Bruce Chabner, director of NCI's Div. of Cancer Treatment, responded to Wyden's concerns, along with representatives of BMS, Hauser Chemical Co. (which contracts with BMS to harvest yew bark and extract taxol from it), the Forest Service and Bureau of Land Management. They explained how provisions in the agreements and various competitive factors would protect the public interest.

Wyden refused to accept those explanations and repeated his charges that the public interest was not being served.

Points made by Wyden, and the response:

▶ That BMS will "have a virtual lock on the market," permitting it to "gouge" cancer patients. "The chair is concerned by the high price, high profit commercial development of anti-AIDS drugs [AZT] by Burroughs-Wellcome through inventions originated in federal laboratories. Orphan drug status protects BMS from competing taxol based products for treatment of ovarian cancer for seven years, Wyden said.

Chabner pointed out that the CRADA includes a provision requiring the company to establish a fair price for the drug. If NCI is not satisfied that the price is fair, the CRADA can be canceled and awarded to someone else. He acknowledged that that might not be a practical solution, but pointed out that BMS rights under the agreements are only for taxol as a treatment for ovarian cancer. Others are free to develop taxol for treatment of other malignancies.

Chabner also noted that other companies are working on taxol related compounds, at least one of which is in clinical trials. He declined to identify that drug at the hearing, but later confirmed that it was taxotere, a product developed from leaves or needles of yew or yew related trees by the French firm, Rhone-Poulenc-Rorer. Other organizations in the U.S. are developing taxol products either from plant cell lines or yew needles (**The Cancer Letter**, July 5). Chabner contended that the market forces represented in those products, plus the possibility of revoking the CRADA, should work to keep the price competitive.

The taxol situation is not comparable to that of AZT, Chabner pointed out. Burroughs-Wellcome owned the patent on AZT; taxol, in development for 30 years, is not patentable.

▶ That the agreements do not assure sound management of the Pacific yew.

A subcommittee staff report states, "Although the agreements indicate that all parties profess a common desire for long term sustained yield management of the species, and individually the parties have at least a limited self interest in maintaining this valuable species, there is little in place within the agreements to guarantee such an outcome."

James Overbay, deputy chief of the National Forest System of the Forest Service, described conservation and management guidelines for bark collection and long term survival of the Pacific yew in the national forests of the Northwest. These cover collection permits, timber sales, site preparation techniques that promote sprouting, regeneration using seed and cuttings, and inventory assessments. Further, the agreement with BMS requires the company to contribute millions of dollars to support research on the ecology, silviculture, and management of the Pacific yew and associated species. The Forest Service will determine how much yew is growing on its lands, how much can be harvested without adversely affecting long term survival, how it can be harvested without adversely affecting the habitat needs of other plant and animal populations, and whether the yew can be more quickly reproduced in a nursery setting than by natural regeneration of the forest.

Michael Penfold, assistant director for land and renewable resources of BLM, reported similar arrangements under its agreement with Bristol-Myers Squibb. The agreement "is fully consistent with the policy, resource management principles and environmental safeguards employed in the BLM forestry program in general," Penfold said. "In fact, additional funding provided under the agreement will accelerate needed inventory and development of management and conservation guidelines to ensure long term sustainability of the Pacific yew."

▶ The agreements do not encourage BMS to develop other sources of taxol or to support research on development of analogs that would not require yew bark harvesting. Also, they permit BMS to control availability of yew bark and other parts of the yew tree to other organizations interested in developing taxol analogs.

In fact, a tremendous amount of research along those lines is already under way, much of it supported by BMS. NCI has a number of programs, including the imminent award of 10 or 11 grants in response to the RFA issued last year. As Chabner noted, companies all over the world are involved.

Zola Horovitz, vice president for licensing of BMS, said the company "takes very seriously" its responsibility to explore alternative sources of taxol. "During the six months since the signing of the CRADA, we have implemented a comprehensive strategy to identify alternative sources capable of yielding adequate quantities of taxol in future years. As part of this effort, the company is actively exploring the use of twigs, needles, and other renewable parts of the Pacific yew, the cultivation of large numbers of Pacific yew in commercial plantations, and the identification of other plant species from which taxol and its precursors may be extracted. We are also supporting a number of research projects designed to investigate the possibilities of producing taxol from plant cell culture, or through semi or total synthesis. Much work remains to be done in these areas, but we are confident that our efforts will yield meaningful results, and that our reliance on Pacific yew bark will be reduced substantially within several years."

Wyden inferred that BMS and its contractor, Hauser Chemical Research, have tried to discourage collection of yew bark and yew branches, needles, and twigs by other companies. These were left on the harvest sites until other firms expressed interest in collecting them for their R&D purposes. It was only then, Wyden said, that Hauser collected those items and stored them in their warehouses.

The subcommittee staff report says, "Despite recent statements by the Forest Service and Bristol-Myers that other private entities will have access to this species, subcommittee staff continues to hear complaints from potential collectors and taxol distillers that tree harvesting on federal forest lands is practically impossible. There are complaints of uncooperative Forest Service managers, and of anticompetitive practices by the House Chemical Co. . . Since Bristol-Myers has right of first refusal for yew on public timberland, there is considerable concern that the company may high grade available resources--cut the largest and most accessible trees for themselves and leave the smallest and most costly to harvest for the competitors."

Here's Horovitz' response: "The Pacific yew grows throughout the Pacific Northwest on private, state, and federal lands. The cooperative agreements simply grant Bristol-Myers Squibb a right of first refusal to Pacific yew available for harvesting on certain tracts managed by the Forest Service and the Bureau of Land Management. The agreements do not cover all federal lands, and they do not apply in any way to private or state lands. Thus, substantial quantities of Pacific yew biomass should be available for purchase, under usual market conditions, by any interested party.

"Furthermore, even as to those tracts subject to the cooperative agreements, the Forest Service and the Bureau of Land Management retain discretionary authority to provide reasonable quantities of biomass to other interested parties for legitimate taxol research. They also retain full authority to dispose of any material Bristol-Myers Squibb does not accept.

"Finally, representatives of Bristol-Myers Squibb have publicly announced their intent to cooperate with other parties who wish to obtain Pacific yew twigs and needles collected from lands under the jurisdiction of the Forest Service or the Bureau of Land Management in order to pursue valid research and development of taxol. Interested parties may pursue this option either by procuring the appropriate permits from federal agencies and collecting the twigs and needles themselves, or by making arrangements to secure them at cost from Bristol-Myers Squibb."

On the issue of pricing, Horovitz said that it is too early to predict the ultimate investment the company will make in taxol but that "it most likely will be the most expensive research and development program of any anticancer agent currently available." He called attention to the company's indigent patient program initiated in 1973, through which needy patients may obtain oncology products free of charge. "We are committed to continue that program."

▶ The Northern Spotted Owl and Robert Wittes.

Those two species don't have anything in common, except that Wyden and his staff converted them into the species known as "red herring."

The Northern Spotted Owl is an endangered species because of the impact of timber harvesting in its habitat, and possibly other factors, of which harvesting yew trees is not one. It is extremely unlikely that, if every yew tree in the Pacific Northwest were to be cut down, the owl would even notice. It does not nest in the yew and only occasionally sits in one. Yet Wyden said, "The issue before the subcommittee today has the potential of combining the worst aspects of the Northern Spotted Owl/old growth forests debate with the firestorm which surrounds the patenting and marketing of AZT."

The staff report, in support of the assumption that BMS has such an edge over potential competitors that it probably will discourage others from developing taxol or analogs, includes this information (Wyden did not refer to this item in his statement):

"In November of 1988, a key NCI administrator who oversaw NCI's therapy evaluation program during the 1980s, was hired by Bristol-Myers as senior vice president in charge of cancer research. Eighteen months later, this research administrator returned to NCI as chief of medicine, shortly before NCI issued its request for proposals for the taxol CRADA. It is unclear what advantage, if any, this gave to Bristol-Myers in drafting its winning proposal. But at the very least, this situation reopens criticism of the revolving door between government technology agencies and private industry, and advantages which may benefit companies which hire strategically placed laboratory executives."

Anyone who really wanted to know if Wittes' job as director of the Cancer Therapy Evaluation Program, ending in November 1988, and his present position as chief of the Medicine Branch had anything to do with the CRADA could have found out in about a minute and a half by talking with either Chabner, Wittes, present CTEP Director Michael Friedman, Developmental Therapeutics Program Director Michael Grever, or Saul Schepartz, special assistant to Grever who is working on NCI's taxol procurement efforts. Dale Shoemaker, chief of the Regulatory Affairs Branch in CTEP, initially headed the taxol program, mostly during the time when Wittes was gone. Wittes was back at NCI when the CRADA was competed, but was in the Medicine Branch, which is part of the intramural Clinical Oncology Program, with no responsibilities for or influence over extramural

research or drug development and procurement.

To suggest that Wittes, Bristol-Myers, and NCI were in some kind of a conspiracy to channel the CRADA to BMS is unfair to all parties, and reflects the sloppiness of the subcommittee's investigation. NCI was fortunate that it could get a person of Wittes' caliber to return to head a very important clinical research program. The brain drain is usually the other way.

NCI carried out an open competition for the CRADA. Three companies in addition to BMS submitted proposals--LyphoMed Inc., Unimed Inc., and Rhone-Poulenc-Rorer.

The staff report adds the information that "companies which decided against making formal bids included Hoffmann-LaRoche, Burroughs-Wellcome, Sterling, Eli Lilly, Smithkline, Merck, and DuPont. Executives from some of those companies interviewed by the subcommittee staff indicated that overall competitive advantages enjoyed by Bristol-Myers in this field soured their ardor for taxol."

BMS' facilities, marketing prowess, reputation, and experience in oncology products does make it a formidable competitor, but those others named in the report are not without resources either. It is difficult to believe that any responsible executive from those companies would admit he couldn't compete with Bristol. The only competitive edge BMS might have had that was mentioned by Wyden and his staff was orphan drug status for taxol in ovarian cancer, and that was not granted until after the CRADA competition.

▶ Does Hauser have FDA's GMP seal of approval or not?

Hauser CEO Dean Stull said in his statement that "Hauser's process and facility meet the rigorous standards imposed under the Food and Drug Administration's good manufacturing practices guidelines."

Wyden said that the subcommittee had been informed by FDA that it had evaluated Hauser's plant extraction process last January and had been judged as meeting the GMP guidelines. However, "that was for extracting vanilla from vanilla beans. Mr. Fromer of FDA indicated that no one at FDA was aware you are extracting taxol from yew bark. Does that surprise you?" he asked, directing the question to Horovitz.

"No," said Horovitz, who could be forgiven if he was thinking that nothing FDA did or said would surprise him. He explained that FDA does not require GMP approval for a particular product until the submission of a new drug application. However, "Our process has been submitted to FDA with NCI data for the taxol IND, and has been approved."

Wyden interrupted. "FDA says they don't know anything about that."

"There are different levels at FDA," Horovitz said.

"You all are touting GMP status for taxol," Wyden insisted. "FDA says they don't know anything about it."

"When they reviewed us in January, we told them we are extracting taxol from yew bark," Horovitz said.

"In our discussions with FDA, we told them all along that Hauser was extracting the drug," Chabner added.

"Don't you think that Mr. Fromer is a responsible agent of FDA?" Wyden asked. "He's head of their congressional liaison."

Wyden was wrong all the way on that issue.

Morton Fromer, who did not attend Wyden's hearing, is assistant director for congressional operations at FDA, not the head of that office. Also, he told **The Cancer Letter**, "We know all about Hauser." He added that FDA knew about taxol and Hauser's role in its production.

Fromer insisted, however, that Hauser has not been inspected for any drug. That technical point may have misled the subcommittee staff. The facts are that Hauser's facilities were inspected by FDA in 1988; the company, in 1990, submitted to FDA a drug master file type 2 on taxol, resulting in the release of its first batches of taxol; and the company provided information on its process as required for the IND, which FDA approved.

As Horovitz said, FDA does not require GMP approval until the NDA is submitted.

Jerry Rust, a member of the Lane County Board of Commissioners in a section of Oregon near forests with yew concentrations, made a case for renewable harvest of needles and tree trimming rather than cutting down the tree (bark harvest kills the tree, so it is routinely cut down for that purpose).

Contending that new extraction processes make it feasible to use needles and twigs (which are yet to be proven), Rust described how gathering and extraction facilities might provide a significant amount of taxol from renewable resources and also provide an asset to the local economy.

That scenario, however, depends on development of a proven process, and it is clear NCI is not going to delay taxol production from the one process already proven. Also, the Dept. of Agriculture's Agricultural Research Service and Cooperative State Research Service are supporting research efforts involving plant cell culture and the use of ornamental yew shrubs, efforts which may make gathering of wild yew

material, needles and twigs as well as bark, obsolete. CSRS plans to sign an agreement for a partnership among the Zelenka Nursery of Michigan, Univ. of Mississippi, and Ohio State Univ. for that project. NCI will contribute $250,000.

NIH Ordered To Create Strict System For Human Subjects Protection

In the wake of a 10-month investigation of collaboration between NCI scientists and French vaccine researcher Daniel Zagury, NIH's Office of Protection from Research Risks has ordered NIH to create a new, stricter system for protecting human subjects involved in studies conducted intramural researchers.

The Office of Protection from Research Risks (OPRR) charged in a report that collaborations between Robert Gallo, chief of NCI's Laboratory of Tumor Cell Biology, Bernard Moss, chief of the Laboratory of Viral Diseases at the National Institute of Allergy and Infectious Diseases, and Takis Papas, chief of the Laboratory of Molecular Oncology at NCI's Frederick Cancer Research & Development Center, with Daniel Zagury, a researcher from the Univ. of Pierre and Marie Curie in France, violated U.S. regulations on the use of human subjects in research.

The OPRR's Div. of Human Subject Protections began the investigation last summer after John Crewsdon, a reporter with "The Chicago Tribune," alleged in a letter to the NIH Communications Office that NIH scientists had provided assistance and materials to Zagury for nine vaccine studies in humans in Zaire and France without receiving clearance for these activities as required by Dept. of Health and Human Services regulations.

An independent panel assembled by the OPRR, after conducting several interviews with the researchers and reviewing results of the studies, found "a general failure on the part of the NIH Intramural Research Program to provide adequate protection for human research subjects involved in these studies."

The panel also recommended restrictions on the research of some of the scientists involved.

However, the OPRR panel said, the problems with protection of human subjects extend beyond this single incident. The panel said its investigation revealed that NIH's system for monitoring its intramural scientists' use of humans in research was "disjointed" and "compartmentalized."

After receiving a preliminary draft of the OPRR findings and recommendations on May 31, NIH Director Bernadine Healy and NIH's acting deputy director for Intramural Research, Carl Kupfer, said NIH would take "urgent and immediate actions," including the establishment of an Office of Human Subjects Research under the authority of the Office of Intramural Research.

The NIH director's office also placed special restrictions on Gallo, Moss, and Papas that severely curtailed their ability to conduct domestic or foreign research using human subjects.

However, Charles McCarthy, director of the OPRR, stressed in a memorandum accompanying the July 3 version of the report that the OPRR had not yet shut the book on the investigation.

McCarthy said his office will not take "final action" until it receives more information on the "nature and degree of harm that may have been experienced by human subjects in the research," and until NIH presents a comprehensive plan for how it will improve its system for protecting human subjects.

Multiple Collaborations

Under an HHS regulation called the "NIH Multiple Projects Human Subjects Assurance," NIH intramural scientists must obtain approval for the use of human subjects, or even the use of small amounts of blood or tissue from human subjects for in vitro studies, from NIH's Institute Clinical Research Subpanel (ICRS).

The regulation extends to any NIH scientist's work with foreign subjects in studies approved by the foreign institutions in which they are conducted.

Zagury headed five studies in Zaire starting in 1986: an immunotherapy trial in eight HIV-positive patients; a trial of an experimental vaccine in 18 healthy children; a trial of another candidate vaccine in 30 healthy adults; a study of HIV infection rates using blood samples from military personnel and their families; and a study of peripheral blood lymphocytes taken from subjects in the second vaccine study.

Scientists from the Universite Pierre et Marie Curie in France and the Cliniques Universitaires de Kinshasa and the Institut National de Recherches Biomedicales in Zaire worked with Zagury on these studies.

In France, either Zagury or his colleague, researcher Odile Picard, headed three studies: a vaccine immunotherapy trial for 28 HIV-positive patients at the Hospital St. Antoine; a trial of synthetic HIV peptides in healthy volunteers; and a study to produce vector-expressed HIV envelope polypeptides that involved some samples of sera from HIV-positive individuals.

Three patients in the first French trial died following the experimental treatment, the report said.

For the ninth project, an immunotherapy trial, NCI scientists planned to provide Zagury with HIV-1

proteins and peptides, but NCI has not approved the collaboration.

The OPRR investigators found that during these projects, NCI scientists had "trained study personnel, performed laboratory analyses, and supplied critical biological reagents for and reviewed data from studies involving human subjects."

In particular, said the OPRR report, NIAID's Moss supplied a recombinant vaccinia virus that Zagury used in his first three Zairian studies and his first French study.

When Moss later learned that Zagury was using the vaccinia material in human subjects, the report said, he refused to supply additional vaccinia, but did continue to supply Zagury with plasmids and technical support.

Moss and Gallo were listed as co-authors of the publication resulting from the first French trial, in which three of the subjects later died.

In addition, said the report, Gallo assisted in the sequencing of blood samples from subjects in the fourth Zairian project and he and NCI researcher Jay Berzofsky were named as co-authors in the publication resulting from the fifth Zairian project.

Takis Papas collaborated with Zagury in the production of HIV polypeptides and the study of HIV-positive sera for the eighth research project, the report said.

NIH scientists denied direct involvement in the French project in which healthy volunteers were vaccinated, said the report. However, Zagury told the OPRR "that reagents supplied by NIH scientists have been used for in vitro analyses of the blood samples [from] which data from this project are derived," the report said.

The OPRR panel went on to note that Gallo was listed as a co-author with Zagury "on no fewer than 14 scientific publications reporting research that appears to have involved human subjects."

Restrictions on Research

In a letter to OPRR director McCarthy after the preliminary version of the OPRR report was released at the end of May, Zagury insisted that "the French Minister of Health concluded...that my team and myself complied with all...ethical rules. In the same period, the Embassy of France in Zaire confirmed ... that all...regulations, both of France and of Zaire, had been respected in clinical tests performed in by myself in Kinshasa."

But compliance with foreign standards was not enough, the OPRR said. "While some may argue that the contributions of the individual intramural scientists...did not constitute 'collaboration,'" the report said, "NIH is responsible for the protection of human subjects in these projects at a level commensurate with both the individual and the collective involvement of its scientists."

NIH scientists and Zagury indicated to OPRR "that such activities...have usually been undertaken freely and informally, most often with no written agreement to define the obligations or responsibilities of the parties involved," the report said.

For each project, the OPRR panel documented the failure of NIH scientists either to obtain approval from the ICRS or to complete written agreements with Zagury stipulating that materials provided through NIH could not be used for human subjects without approval.

In February, while the investigation was still in progress, the OPRR placed restrictions on "collaborative research with any foreign scientists or institutions by any...Div. of Cancer Etiology [which includes Gallo's laboratory] intramural scientists" and on collaborations between intramural scientists and any of the French or Zairian institutions connected with Zagury's studies.

Under these restrictions, the OPRR had to give special approval to any project involving any of these entities.

After a the OPRR sent a preliminary draft of its report to NIH Director Bernadine Healy at the end of May, Healy informed Gallo, Moss, and Papas in memoranda dated June 21 that "effective immediately, any proposed collaborations involving human subjects by you and your staff with scientists or institutions outside the NIH, domestic or foreign, will require review and approval by the Office of Intramural Research (OIR) after the Institute Clinical Research Subpanel and the Director, NCI, have approved the project."

In a letter to Healy in early July, Moss argued that he had provided the vaccinia virus to Zagury only for use in animals and had refused to provide more once he learned that Zagury was using it in Zairian subjects.

"Since I was not a participant in human research, my behavior did not represent non-compliance with [HHS regulations for the protection of human subjects]," he said.

Moss also noted that contrary to the statements in the OPRR preliminary report, he had obtained the approval of the OPRR before providing the vaccinia materials to Zagury for his French immunotherapy trial.

Papas also wrote to Healy arguing that the claims in the preliminary report about Zagury's eighth research project were incorrect.

"We never collaborated with Dr. Zagury in any studies that involved, him or us, using any HIV-positive sera," Papas said.

"I agree...that the NIH guidelines and directives need to be clarified...however, since I did not do anything to disregard those guidelines, I feel I should not be subject to any greater restrictions than any other NIH intramural scientist," he said.

Gallo did not respond to the preliminary report or to Healy's restrictions on research with human subjects.

OPRR did not remove the disputed allegations about Moss and Papas from the July 3 version of its report. However, at the end of that report, the OPRR said the restrictions involving "all human subjects research activities...with investigators outside the NIH" would still apply to Gallo until he had "established a record of strict compliance with HHS regulations."

The OPRR also said the February restrictions placed on the Div. of Cancer Etiology and on collaborations with scientists affiliated with the French and Zairian institutions in question would remain in effect until NIH improved its system for protecting human subjects.

A Failure of the System

To the OPRR panel, perhaps the most disquieting facet of the entire investigation was the picture that emerged of an oversight system that was characterized by a "lack of centralized and authoritative oversight of research activities covered by HHS human subjects regulations [that resulted in] uncertainty at all levels of the intramural community regarding individual and institutional responsibilities."

The investigators reported, with a note of incredulity, that the scientists they spoke to "were uninformed about their responsibilities [concerning] the protection of human research subjects under the HHS regulations. These scientists...assumed that they had no responsibilities in this area as long as they did not directly inject human beings with experimental materials.

"Some seemed to believe that compliance with foreign standards was all that was required. There appeared to be virtually no realization that in vitro experiments utilizing human materials may constitute research with human subjects under HHS regulations."

When the OPRR began its investigation last summer, it first requested information from Saul Rosen, who, as acting director of NIH's Clinical Center, was the person responsible for ensuring that intramural scientists complied with HHS regulations on human subject protection.

However, the OPRR was shocked to find that Rosen "exercised authority almost exclusively within the clinical center itself....[and] had no direct authority over (and little opportunity to influence intramural scientists who were not who were not actually conducting research in the NIH Clinical Center."

A few months later, Edward Rall, NIH's deputy director for intramural research at the time, took over Rosen's oversight duties regarding human subjects.

Overall, said the OPRR report, the NIH system for ensuring the protection of human research subjects in intramural research is "inadequate" and required "modifications."

In its July report, the OPRR said that NIH must "create a unified system of human subject protection that extends across all relevant NIH institutes, centers, and divisions and has clear authority over the entire intramural community."

In doing so, NIH must fulfill four specific requirements. NIH must identify a central official responsible for compliance by all intramural scientists and develop a program to educate all relevant intramural scientists about protection of human subjects.

The OPRR said NIH must also establish procedures to ensure that the new oversight system was capable of identifying, initially reviewing, and periodically checking all pertinent intramural research projects and, in addition, any activities of extramural program personnel that involved research human subjects.

NIH officials must outline their plan for fulfilling these requirements in a "comprehensive plan of action" presented to the OPRR within 60 days of the July 3rd report.

However, NIH officials jumped to correct the problems with the review system as soon as they saw the preliminary report at the end of May.

Kupfer said in a letter to the OPRR that NIH would create the "unified system" called for in the report and would also create a "parent Institutional Review Board," that would "significantly strengthen the surveillance of human subjects research," partly by overseeing the reviews conducted by the current ICRSs.

To corroborate the information Zagury provided on the results of the nine studies, OPRR's Div. of Human Subjects Protection is trying to obtain medical and research records through diplomatic channels to determine the effects of the Zairian and French research projects on the human subjects involved, the report said.

The OPRR will not lift the restrictions on human subjects research that it imposed earlier this year until it approves NIH's final plan for improving the review system, the report said.