

Protocol 126 and “The Hutch”

On March 11th, the *Seattle Times* published the first of several stories, editorials, and replies about “Protocol 126” at the Fred Hutchinson Cancer Center (“The Hutch”), in which 20 of the 82 patients enrolled during the 12 years the study was under way reputedly died as a result of the protocol. The articles drew public attention once again to concerns about conflict of interest in research with human subjects, the IRB process, and the adequacy of subjects’ informed consent.

Protocol 126, first reviewed in January 1981, used monoclonal antibodies to remove T-cells from donor bone marrow for transplantation in hopes of preventing graft-versus-host disease (GVHD). Over the next 12 years, the protocol went through at least 9 versions in an effort to reduce the incidence of graft failure, learning in the process that some donor T-cells are necessary for both engraftment and disease-free survival.


In effect, Protocol 126 was a series of 9 related but separate phase 2 studies that incrementally altered the subject entry criteria (sicker), post-transplant immune suppression (first one and then two drugs), radiation (higher dose), and T-cell removal (selecting certain T-cell subsets). As the research proceeded, it became evident that failure to engraft (and thus death from high-dose radiation and chemotherapy) was the most serious toxicity. After a number of patients died from graft failure in the second version (126.0) of the protocol, all subsequent versions were stopped when either one patient (version 126.8) or two patients (versions 126.1-6) failed to engraft. The series was finally terminated in 1993.

Conflict of Interest. The first version of Protocol 126 had no impact on the transplant recipients, given the absence of complement to enhance antibody-mediated destruction of the donor T-cells. The controversial second version of Protocol 126 (numbered 126.0), in which 8 of 20 patients suffered graft failure after receiving a T-cell depleted bone marrow transplant, was in effect from

May 1983 through July 1984. The outcomes were never a secret; the fact that patients on the protocol had died were documented in a 1985 publication. Less well known at the time, however, was the fact that The Hutch and the three investigators (Hutch founder Donall Thomas, John Hansen, and Paul Martin) had close ties to Genetic Systems Corp., the start-up biotechnology company to whom some of the monoclonal antibodies used in the protocol had been licensed. In addition to owning shares of Genetic Systems stock—valued at between \$105,000 and \$1.8 million in 1985—Thomas was a member of the company’s scientific advisory board, Hansen was its medical director, and Martin had a three-year consulting contract.

In June 1983 the Board of Directors of The Hutch had adopted a conflict of interest policy that appeared to preclude Drs. Thomas, Hansen, and Martin from participating in Protocol 126 given their equity holdings in Genetic Systems. It is not clear whether this policy was applied to existing economic interests, or only to those interests arising after June 1983. There is no documented evidence that the decision to continue Protocol 126.0 was influenced by the financial holdings of Drs. Thomas, Hansen, and Martin, but in September 1983 the IRB expressed concern about institutional oversight of conflicts of interest and the impact of such interests on the selection of antibodies for clinical testing. An informal advisory group was established in January 1984 to provide “independent” scientific review and selection of antibodies for testing free of any financial conflicts of interest. Although in a letter dated 10 October 1983 Dr. Thomas denied the existence of any conflict of interest, the advisory group’s 17 January 1984 minutes confirm that both Drs. Hansen and Thomas “have substantial holdings in founders stock from [Genetic Systems].”

Yet the argument presented at a news conference on 15 March this year was that no conflict of interest existed as Genetics Systems (holder of the license and not the patent) would not gain financially from the monoclonal



antibodies. Dr. Hansen nonetheless acknowledged that he should have avoided the appearance of a conflict of interest by removing himself completely from the clinical trial. A distinction was made between general financial benefits accruing to an individual through a licensed product, and any impact on the conduct of a clinical trial. “There have been individuals who have made important scientific discoveries and contributions which have been licensed to industry, ... and for which that individual has received financial benefit. But not because they were running the clinical trial. They would not be allowed to run that clinical trial if they had that substantial financial interest.” This distinction may be difficult to maintain given the extent to which The Hutch was and is involved in biotechnology firms, and the group process that was apparently involved in the February 1984 decision to continue Protocol 126.0, in which, presumably, Drs. Thomas and Hansen participated.

The advisory group minutes also reflect group concern about possible retribution from unnamed senior staff members. Dr. John Pesando, a young investigator who joined The Hutch in 1982 and left in 1987 when he was not promoted, served on the IRB from 1983 to 1985 and was a member of the advisory group. Although his failure to be promoted may reflect an independent assessment of his career trajectory, the documents that are publicly available suggest that fear of retribution and perceived conflict of interest were issues contemporary with Protocol 126.0.

The Review Process. The 1991 publication of *Magic Bullets* detailing the role of Genetic Systems in the development of monoclonal antibodies apparently stirred Pesando to go public with accusations of inadequate IRB review and investigator conflict of interest resulting in the unnecessary deaths of patients enrolled on Protocol 126. The Office of Protection from Research Risks (OPRR) investigated Dr. Pesando’s concerns, issuing a report in 1995 based on a review of the documents submitted by The Hutch. Although the OPRR concluded that communication of research results (presumably including adverse events) to the IRB could have been improved, the written record showed no evidence that the IRB was impeded in the review and oversight of research. However, the flow of information to the IRB appeared to be through Dr. Pesando’s attendance at a weekly meeting of clinical researchers, rather than through the investigators.


Adding to the importance of an independent IRB review of adverse events, Protocol 126.0 appeared not to

have stopping rules for graft failure. At the March 15th news conference, Dr. Fred Appelbaum, current head of the Clinical Research Division at The Hutch stated: “In the first study, we did not know that graft failure was a possibility since in all the animal models and all the studies we had done up to that point—that risk was not seen. As soon as the third patient was found to have graft rejection, the study was stopped.” Yet the 1993 letter to OPRR from Dr. Robert Day, then director of The Hutch, indicates that, after discussion at an 8 February 1984 meeting of the clinical researchers, the study was continued until 20 patients had been enrolled in spite of two (perhaps three) graft failures requiring a second transplant. Dr. Pesando appears to have been in the difficult position of reporting this decision back to the IRB. Although the IRB received a verbal report the following week from Dr. Martin, the principle investigator for Protocol 126.0, the later recollection of Dr. Henry Kaplan, IRB chair at the time, is one of impotence in addressing the conflict of interest. In the end, seven (not three) patients enrolled in Protocol 126.0 suffered irreversible graft failure and died as a result.

Reportedly, during review of the original protocol in 1981 concerns were raised about the study, including the adequacy of prior animal research, subject selection, and the protocol consent form. Changes were requested and the protocol was ultimately approved in April 1981. When the investigators requested approval of major changes in 1983 at least one member of the committee expressed concerns about one of the new antibodies selected for study and argued that the consent form should include notice about the possible risk of new, unexpected cancer it posed. Nonetheless, the committee approved the protocol in May 1983, without substantial change to the consent form.

In September 1983 a new IRB was established at The Hutch. Despite concerns about the protocol among incoming members, the IRB seemingly continued to accept assurances from the investigators and administrators at The Hutch and repeatedly approved further versions until the protocol was finally halted in 1993, when the first patient on version 126.8 experienced graft failure.

Informed Consent? The adequacy of informed consent has also been raised as an issue. During the initial 1981 review, the review committee expressed concern that potential subjects would not be adequately informed of the available alternatives for dealing with GVHD. The committee accepted the investigators’ argu-



ment that there were indeed no alternatives for *preventing* GVHD as opposed to treating GVHD. Meanwhile other patients at The Hutch were being enrolled on a protocol (published in 1986) that established effective prophylaxis against GVHD. Should potential subjects have been told about the choice between these two approaches to GVHD?

In addition, should potential subjects have known the results of the previous versions of Protocol 126 when considering enrollment? The results of prior versions were not shared with subsequent subjects on the rationale, offered in March, that each trial was different and its outcomes unknown. Were the versions of Protocol 126 sufficiently different to justify not sharing the earlier results with potential participants?

Lessons of Protocol 126. I offer the following lessons and observations in closing: (1) the principle investigator should be held responsible for all reporting to the IRB; (2) IRB members should never be placed in a position that invites possible retribution (although an unpopular IRB decision may result in retribution); (3) individuals

who fear possible retribution for IRB decisions should not serve on an IRB; (4) all clinical trials should be insulated from financial conflicts of interest, even if this means removing the trial from an institution with extensive licensing and/or patent involvement; (5) all clinical trials should have monitoring plans, including clear stopping rules for unexpected serious adverse events; (6) accreditation inspections of IRBs should use on-site interviews to explore whether IRB members can review protocols free from fear of retribution; and (7) potential participants in early phase clinical trials should be told about previous results in order to make an informed decision.

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The documents used to prepare these comments can be found on either http://www.seattletimes.newsource.com/uninformed_consent (accessed 2 May 2001) or <http://www.fhcr.org/response> (accessed 2 May 2001).