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Dear Dr. Puglisi;

Thank you for your recent advice. Per that discussion, I have outlined the conflict of interest problem that I mentioned and provided copies of relevant documents. Basically, senior clinicians at the Fred Hutchinson Cancer Research Center in Seattle conducted clinical trials with high therapy-induced mortality rates while they were major stockholders in the company with commercialization rights to those therapies. The Director of the FHCRC was notified of this situation at that time but apparently did little to correct it.

While a junior clinical faculty member at the FHCRC in the fall of 1983, I was drafted to serve on its newly reconstituted Institutional Review Board charged with reviewing clinical protocols "to assure that ethical standards for patient care are met." Our committee quickly became concerned by the sloppy design of many studies which used locally prepared monoclonal antibodies (MAb). For example, some previously approved protocols did not even state which MAb they were using, let alone their possible adverse effects. IRB efforts to review and regulate these protocols (a burdensome and unwelcome task) met with stiff opposition from the senior medical staff, as best typified by the 10/14/83 letter from Dr. E. Donnall Thomas, Chief of the Clinical Service, to the IRB stating "I would have to object to arbitrary restrictions of our research activities ... I think that Committee members have not only an obligation to review the ethical aspects of this work, but also an obligation to assist us and not impede our research." Dr. Thomas had a fearsome reputation - you crossed him at your peril.

It soon became obvious that at least one FHCRC clinical study (Protocol #126) involving MAb was causing very high mortality rates in patients who otherwise stood a good chance of cure by bone marrow transplantation. Moreover, the IRB learned of problems with this protocol through its own members, and not from the study's principal investigators nor from FHCRC staff. Protocol #126 involved use of MAb to remove T lymphocytes from donor bone marrow in an attempt to prevent graft-versus-host disease. While this protocol was causing many patient deaths, FHCRC senior staff insisted on its continuation. Final numbers are unavailable, but it is safe to say that protocol #126 was

directly responsible for at least two dozen patient deaths (Blood 66: 664-672, 1985; Blood 72: 1978-1984, 1988). Most deaths resulted from failure of the donor marrow graft (normally a rare event), but there was also an extremely high (and fatal) leukemic relapse rate in patients with chronic myelogenous leukemia.

At issue in 1983/1984 was whether the conflicting opinions of the IRB and FHCRC senior medical staff regarding continuation of protocol #126 simply reflected the superior vision and judgement of the medical staff, the inexperience of the IRB, or something more. The atmosphere during IRB discussions of this matter was literally one of fear and disbelief. It is also noteworthy that protocol #126 continued to enroll patients even after an alternative successful prophylaxis for graft-versus-host disease was published by FHCRC staff in the New England Journal of Medicine in early 1986.

It was common knowledge in 1983 that the biological agents used in protocol #126 and other studies at the FHCRC were licensed to the Genetics Systems Corporation, a local biotechnology company where one of the principal investigators of protocol #126 (Dr. John Hansen) served as Medical Director and the other (Dr. E. Donnall Thomas) served as a scientific advisor. The IRB was concerned with rumors that Drs. Hansen and Thomas both held large blocks of stock in this company and sought to resolve the issue of possible conflicts of interest. At the same time, the IRB was concerned with preventing potentially harmful conflicts of interest for IRB members (whose jobs and careers were controlled by the principal clinical investigators of the studies being reviewed) and therefore sought to have these clinical protocols reviewed by independent outside examiners. Some of these IRB efforts are summarized in communications from Dr. Henry Kaplan, IRB Chairman. In a unique written response to IRB concerns in a letter dated 10/14/83, Dr. Thomas flatly denied the existence of conflicts of interest.

Some IRB members met with Dr. Robert Day and senior FHCRC medical staff on January 17, 1984 to discuss these issues. At that time Dr. Kaplan and I successfully lobbied to remove those patients having the most favorable clinical prognosis (AML in first remission, CML in chronic phase) from the list of candidates for protocol #126 on the grounds that these patients especially had too much to loose from inclusion in this study. However, the FHCRC resisted our efforts to have clinical research protocols involving biological agents reviewed by independent outside examiners. Some of the items discussed at this meeting are contained in Dr. Day's memo of February 23, 1984. In contrast to Dr. Thomas' statement of 10/14/83, Dr. Day then indicated that both Drs. Thomas and Hansen had "substantial holdings of founders stock in GSA," (Genetics System Corporation).

With this meeting, the IRB felt that it had exhausted its options and hopefully discharged its responsibilities in dealing with these problems, having informed Dr. Day and senior medical staff of the nature and seriousness of its concerns and having been reassured by Dr. Day that he would deal appropriately with the matter. It should be remembered that the IRB operated in a regulatory void without the necessary authority or guidelines to perform its purported function of protecting patients from their physicians. Moreover, no one on the IRB had any experience in regulatory matters.

Despite Dr. Day's promises, protocol #126 and its derivatives continued, the death toll mounted, and the IRB remained poorly informed as to the progress and complications of these clinical studies. Meanwhile, other bone marrow transplant centers now began to report high graft failure rates in patients receiving T cell-depleted bone marrow (21% in a British study and 40% in one from UCLA). As the IRB completed its two year term, there was growing awareness that most of its objectives regarding design, review, and conduct of clinical protocols using locally produced biological agents remained unmet. Thus on 5/17/85 the IRB again requested Dr. Day to establish an independent committee of outside investigator to review all such clinical protocols.

I finally appreciated the seriousness of this problem when I read the chapter dealing with Drs. Day, Thomas and Hansen and the Genetic Systems Corporation in Grant Fjermedal's book Magic Bullets. While a somewhat desperate IRB in 1984-85 placed its trust in Dr. Day, Mr. Fjermedal's description of Dr. Day's behavior at this time suggests that Dr. Day had another agenda. Mr. Fjermedal indicated that Drs. Hansen and Thomas owned 250,000 and 100,000 shares, respectively, of stock in the Genetic Systems Corporation while the aforementioned clinical studies were in progress and at the time the IRB's initial inquiries were being made. Dr. Day appears to have done nothing about this situation. Regardless of the wisdom and clinical judgement that may or may not have been shown in pursuing protocol #126 for a multiyear period in the face of its disastrous early results, there can be no question that those conducting this study should not have had a financial interest in its pursuit and favorable outcome.

I have much anger regarding this matter. There is no question that our actions saved many lives and prevented much suffering, but a price was paid. Only a fool would fail to realize the dangers inherent in opposing the wishes of superiors and employers, and we were well aware of them in 1983/84, despite reassurances from Dr. Day on 1/17/84. A great many people, then as now, simply will not make the personal sacrifices currently required to even attempt to correct abuses of this kind, even when human lives are at stake. Thus similar abuses are all but guaranteed to continue.

We live in a most imperfect world, but I believe that we must draw the line between what we deplore but tolerate and what is simply intolerable. The seriousness of this issue and its implications for future patient care continue to make it very difficult for me to take the expedient course of doing nothing.

Thank you for your help.

Sincerely,

John M. Pesando M.D., Ph.D.

cc: Dr. Claudia Blair, Institutional Affairs Office, NIH
Mr Grant Fjermedal
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