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President and Director

October 18, 1993

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Dear Dr. Mittal:

This letter is in response to your request for a written report addressing the concerns outlined in your letter to me of August 17, 1993 and in a letter from Dr. John M. Pesando to the Office for Protection from Research Risks ("OPRR") dated May 14, 1993. It is unclear to us why Dr. Pesando has chosen to make these allegations some ten years after the events occurred. However, his recollection of events is incomplete and inaccurate based on the documented history of the research in question. Accordingly, this letter will first provide a detailed summary of critical events and will then address the specific questions raised in the letters from you and Dr. Pesando.

To assist you in your review, we are enclosing in an appendix certain key documents referenced in this letter and the current IRB training manual used at Fred Hutchinson Cancer Research Center ("FHCRC"). In addition, as you requested in your letter, we are making the following IRB records available at Hogan & Hartson:

1. Protocol file on Protocol 159 (file no. 1);
2. IRB agendas and minutes on Protocol 159 (file no. 2);
3. Protocol file on Protocol 126 (file no. 3);
4. IRB agendas and minutes on Protocol 126 (file no. 4);
5. Graft Versus Host Disease ("GVHD") meeting minutes regarding Protocol 126 (file no. 5);
6. Protocol file on Protocol 387 (file no. 6); and
7. Protocol file on Protocol 402 (file no. 7).

Some documents have been redacted to eliminate specific patient identifiers as well as information pertaining to protocols which are not at issue. As agreed in discussions between Dr. Puglisi of OPRR, Barbara Mishkin of Hogan & Hartson and Doug Shaeffer, Fred Hutchinson's General Counsel, the complete records are being delivered to Hogan & Hartson. We understand you will make arrangements with Ms. Mishkin to review them there.

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This letter is organized as follows:

A. SUMMARY OF CRITICAL EVENTS

1. Introduction

The events on which the allegations in Dr. Pesando's letter are based took place ten years ago during 1983 and 1984. This letter will focus principally on this time period in order to respond directly to those allegations. At the end of the letter (Section C) is a discussion of additional procedures which have evolved subsequently through the cooperative efforts of FHCRC's clinical staff and IRB and are currently in place to further ensure the protection of human research subjects at FHCRC.

Although this letter addresses both Protocol 126 and Protocol 159 as you requested, the allegations in Dr. Pesando's letter relate principally to Protocol 126. While Protocol 159 is referenced by Dr. Pesando, there were no unanticipated deaths due to graft failure for patients treated on Protocol 159. Section B.4 of this letter will address certain of the allegations made by Dr. Pesando which concern Protocol 126 specifically and the results of that Protocol.

Finally, in considering Dr. Pesando's allegations it is important to bear in mind that the study of which both Protocol 126 and 159 were a part was peer-reviewed and approved by an NCI Clinical Cancer Program Project Review Committee in 1981 and, in the case of Protocol 126, again in 1986 in connection with FHCRC's Adult Leukemia Center ("ALC") Research Grant (No. CA18029). Relevant pages from the committee's report and critique are included at Appendix 1. Notwithstanding Dr. Pesando's personal view of these studies and their design, the Project Review Committee clearly felt that these studies were well designed and scientifically meritorious.

2. Background On Marrow Transplantation

Marrow transplantation takes advantage of the fact that leukemias and lymphomas exhibit fairly steep dose-responses to alkylating agents, such as cyclophosphamide, and to radiation. However, these agents are also very myelosuppressive. With the technique of marrow transplantation, patients with recurrent leukemia and lymphoma who may have no other chance for cure, can be treated with extremely high doses of alkylating agents and total body irradiation and then rescued from the otherwise lethal myelosuppressive effects of the treatment by infusing bone marrow after the therapy. In general, three sources of marrow have been commonly used: identical twin (or syngeneic) marrow, marrow from an HLA-matched sibling (allogeneic marrow) or one's own marrow (autologous marrow) which was previously removed and cryopreserved at a time when the patient's marrow was in remission.

Although many patients who would have otherwise died have been saved by the technique of marrow transplantation, it was at the time these protocols were originally written (1982) and remains today an imperfect approach. For patients with leukemia or lymphoma resistant to conventional chemotherapy, cure rates with transplantation were in the 15%-20% range in 1982 and, unfortunately, have not changed much. Two major problems of transplantation are disease recurrence after the transplant and graft-versus-host disease ("GVHD"). Both are problems of considerable magnitude. Patients transplanted for resistant leukemia or lymphoma have a greater than 50% chance of their malignancy recurring posttransplant. Currently, even with our best available methods of prevention, GVHD develops in approximately 50% of patients over the age of 30 receiving grafts from matched siblings, and in 80% of recipients of mismatched or unrelated marrow.

Protocols 159 and 126 attempted to deal with these problems using monoclonal antibodies. It is important to note that neither Protocol used monoclonal antibodies for *in vivo* treatment of patients. In both protocols the antibodies were used to treat marrow *in vitro* before the transplant. Protocol 159 concerned patients with malignant lymphoma who were to undergo autologous marrow transplantation. One aim of that study was to see if marrow could be treated *in vitro* with monoclonal antibodies directed at lymphoma cells with the goal of lowering relapse rates after autologous marrow transplantation by removing this potential source of relapse. Protocol 126 concerned patients undergoing allogeneic marrow transplantation who were known to have a high risk of developing GVHD. Animal studies had shown that graft-versus-host disease was initiated by T cells within the marrow graft and that the removal of T cells from the graft could prevent this reaction. Protocol 126 was designed to test the *in vitro* treatment of human marrow.

3. History of Protocol 159

FHCRC Protocol 159 "Autologous Marrow Transplantation for Treatment of Malignant Lymphoma" was written in 1982 with Dr. Fred Appelbaum as the principal investigator. It was written in collaboration with Dr. Ron Levy and Dr. Saul Rosenburg of Stanford. The study was developed after several small pilot studies performed in Seattle had demonstrated that patients with recurrent malignant lymphoma could in some cases be cured if treated with very high dose chemoradiotherapy followed by syngeneic, allogeneic, or autologous marrow transplantation. See Appendix 2. The protocol was for *in vitro* use of monoclonal antibodies only.

The objectives of Protocol 159 were two-fold. The first major objective was to define the cure rate using a single preparative regimen of cyclophosphamide and 12 Gy Total Body Irradiation ("TBI") followed by autologous marrow transplantation for patients with recurrent malignant lymphoma of various histologic subtypes including lymphoblastic lymphoma, Burkitt's lymphoma, diffuse histiocytic lymphoma and Hodgkin's disease.

A second objective of the protocol was to test the feasibility of restoring hematologic function using autologous marrow that had been manipulated *in vitro* in an effort to remove tumor cells. No *in vivo* treatment of patients was conducted under this protocol. Numerous studies had documented that malignant lymphomas at presentation and at relapse frequently involved bone marrow. This raised the concern that reinfusion of unmanipulated autologous marrow might also result in the reinfusion of tumor cells after the transplant. Studies in animal models had demonstrated that lymphoid cells could be removed from autologous marrow without endangering hematopoietic function. See Appendix 3. This initial study was designed to test whether the same held true for human marrow. This study was peer-reviewed and approved in 1981 and in connection with FHCRC's ALC Grant. See Appendix 1.

In order to safeguard patients, the first 10 patients on this study had two aliquots of autologous marrow stored, one of which was treated *in vitro* with the monoclonal antibody in question and the second of which was not manipulated. Only those patients who previously had their tumors screened to determine if they reacted with specific monoclonal antibodies were eligible to have their marrows treated *in vitro*.

This protocol was sent to the FHCRC IRB in September 1982. Two consent forms were included. One outlined the potential toxicities of the cyclophosphamide and total body irradiation. The second dealt specifically with the issue of the use of monoclonal antibodies to treat marrow *in vitro*. The second consent form (159B) which accompanied

the protocol clarified for the patient the experimental nature of the study and the potential risks of the use of *in vitro* marrow manipulation. This protocol was sent to the IRB and reviewed and approved in December of 1982, for the period December 30, 1982 through September 20, 1983.

A renewal was submitted on September 20, 1983. At that time, FHCRC had treated five patients on the protocol, all of whom engrafted normally and three of whom remained alive and in complete remission. Following this submission, a letter dated September 28, 1983 was sent from the IRB to Dr. E. Donnall Thomas concerning Protocol 159 and the use of monoclonal antibodies generally. See Appendix 4. In that letter Dr. Kaplan, as chairman of the IRB, asked 1) for information concerning the decision making process by which the Clinical Division decided which monoclonal antibodies were suitable for clinical application, 2) whether the Clinical Division had established controls for monoclonal antibody production, 3) the division's guidelines for screening monoclonal antibodies as to their biologic activity, and 4) what checks and balances were in place to deal with potential conflicts of interest. Responses were written to this letter and sent back to the IRB on October 14th and October 28th of 1983. See Appendix 5. These responses included an explanation of the decision making process for choice of monoclonal antibodies, a description of the established controls for production of antibodies, and the methodology used to determine biologic activity. In addition, an appendix was included which explained in detail the monoclonal antibody production and testing facility. Finally, the Center's conflict of interest policy was discussed. The IRB reviewed the responses and granted approval on November 31, 1983 for the period from December 1, 1983 through November 30, 1984.

On November 30, 1983, I received a memorandum from Dr. Kaplan requesting the formation of a new, independent scientifically based group to consider the scientific merit of monoclonal antibodies proposed for use in studies. See Appendix 6. In response to Dr. Kaplan's memo and concerns which he raised in his earlier letter to Dr. Thomas, I appointed a Monoclonal Antibody Advisory Group composed of individuals with a strong background in immunology with no reported conflicts of interest arising from ties to biotechnology companies who could provide advice about the scientific merit of the individual studies, the choice of monoclonal antibodies and address concerns about potential conflicts of interest. This Advisory Group, which included Drs. Appelbaum, Cheever, Kaplan, Storb, Sullivan, and Pesando, met initially on January 17, 1984 at which time it was decided that the committee would act as an independent review committee for the IRB whenever asked. Minutes of the January 17, 1984 meeting are included as Appendix 7.

The Advisory Group was subsequently renamed the Scientific Review Committee and became a standing committee. It next met on June 25, 1984 at which time the use of monoclonal antibodies in 7 different protocols was reviewed, including Protocols 159 and 126. Approval of these protocols had been withheld by the IRB pending review by the Scientific Review Committee. Those present at the meeting included Drs. Appelbaum, Cheever, Day, Storb, Sullivan, and Pesando. At that meeting the use of monoclonal antibodies in Protocol 159 was reviewed and approved. The minutes of the June 25, 1984 Scientific Review Committee meeting are included as Appendix 8. On December 1, 1984 renewal for Protocol 159 was requested and granted by the IRB through November 30, 1985.

In a letter dated December 17, 1984, Dr. Kaplan again wrote to me concerning Protocol 159 and what the IRB perceived to be ongoing problems in the review mechanism at FHCRC. See Appendix 9. Specifically Dr. Kaplan and the IRB felt that protocols should be reviewed and approved by a statistician prior to submission to the IRB. This suggestion was implemented and is still FHCRC's policy. The IRB also felt that all protocols at FHCRC should be reviewed by experts external to FHCRC who were experts in the particular field. As discussed more fully in Section B.2.a below, because most FHCRC protocols are externally peer-reviewed in connection with grant application and by the full Clinical Research Division of FHCRC an additional layer of review was unnecessary questions specific to monoclonal antibody use were addressed to the Scientific Review Committee. Specific questions concerning Protocol 159 were addressed in a letter from Dr. Appelbaum and a letter from Dr. C. Dean Buckner, who was the principal investigator of the grant that funds the autologous marrow transplants. See Appendix 10.

By October 1985, 42 patients had been treated on this protocol of whom 38% were alive and in complete remission. In addition, among those patients whose marrow had been treated *in vitro* with monoclonal antibodies, engraftment had been normal and complete in every case. At that point two decisions were made. The first decision was to limit enrollment on this study to patients in first relapse or second remission since these patients were doing well on this study. However, patients treated for later stages of disease had a high relapse rate, and it was decided to study more aggressive preparative regimens in those patients. The second difficult decision concerned what to do with the *in vitro* marrow treatment. By this time, the study had satisfied its initial specific aim of establishing that one could treat marrow *in vitro* without endangering engraftment. Other studies supported this conclusion. It was less certain whether the *in vitro* marrow treatment afforded patients any advantage by decreasing the relapse rate. On the one hand, there was good theoretical evidence this might be so but there was no data to

prove it. Unfortunately, on the other hand, the rate of accrual on this study would not permit the performance of a randomized study to determine the efficacy of *in vitro* marrow treatment. After much discussion among the members of the clinical group it was decided that *in vitro* marrow treatment would continue to be offered to patients whose tumor immunophenotype was known on the basis that such treatment might offer the patient some advantage and all of the evidence suggested it posed no danger.

This protocol was continued with annual IRB approval through July of 1993 when it was closed. Even to this day, no randomized study of *in vitro* marrow treatment has been performed. However, with large numbers of patients treated, comparisons to historical controls suggest that *in vitro* marrow treatment is of some advantage. Perhaps more convincing are the studies recently published in the New England Journal (Gribben et al.: New England Journal of Medicine, 325:1525 (1991) which demonstrate that if one can treat marrow *in vitro* with monoclonal antibodies and remove all evidence of contaminating tumor cells as evidenced by a negative signal using PCR for the 14:18 translocation, the outcome of marrow transplantation is superior to those cases where marrow is not treated *in vitro* to remove the signal or where *in vitro* treatment is unable to remove all evidence of the 14:18 translocation.

4. History of Protocol 126

a. Summary of Clinical Trials.

Protocol 126 was motivated by the clinical need for better prevention of GVHD after allogeneic marrow transplantation. The ability to prevent GVHD by removing T cells from donor marrow had been demonstrated in numerous experimental models. Impetus for testing this approach for preventing GVHD in clinical trials came from the development of a variety of methods for selective depletion of T cells in human marrow. Data from animal models indicated that the need for posttransplant immunosuppression could be entirely circumvented by T cell depletion. This led to the anticipation that the risks of mucositis, delayed engraftment, renal impairment, infections, and other complications could be diminished by avoiding the necessity of GVHD prophylaxis with methotrexate, cyclosporine, anti-thymocyte globulin, prednisone or cyclophosphamide. It was hoped that more effective GVHD prevention would lead to improved survival.

Protocol 126 embodied several distinct clinical trials of T cell depletion beginning on May 11, 1981. This study was peer-reviewed in 1981 and again in 1986 in connection with the FHCRC ALC Grant. It was approved on both occasions. See

Appendix 1. Dr. John Hansen was the original principal investigator for Protocol 126. Dr. Paul Martin became the principal investigator in 1983.

Following is a brief summary of each of the clinical trials embodied in Protocol 126.

1. The first trial involved simple incubation of donor marrow with T cell-specific monoclonal antibodies alone. The study enrolled nine patients and was discontinued when it became apparent that this approach did not decrease the risk of GVHD. A publication summarizing the results is included at Appendix 11.

2. The second trial involved depletion of T cells in the donor marrow by complement-mediated lysis with a defined mixture of T cell-specific monoclonal antibodies and was approved by the IRB on May 26, 1983. This is the study which is primarily referenced in Dr. Pesando's letter. Patients selected for this study were considered to be at high risk of GVHD because of being over 30 years of age. This study is discussed in detail below. The method of T cell depletion employed in this study was also used in all subsequent protocols except where noted otherwise.

3. The third trial, designated 126.1, implemented several important changes based on the results of the preceding study. Enrollment was limited to patients with advanced malignancies which required higher doses of TBI (15.75 Gy), and posttransplant immunosuppression with cyclosporine was not administered. At the request of the IRB, this protocol was reviewed for scientific merit by an ad hoc committee before any patient enrollment was allowed. This study enrolled eleven patients and was discontinued when two developed graft failure. The precedent of selecting only high risk patients has been continued in all subsequent protocols involving T cell depletion. As with Protocol 126.1, each of the three subsequent studies was also stopped after graft failure in any two patients.

4. The fourth trial, designated 126.2, prescribed the administration of methotrexate after transplantation, based on data from a canine model indicating that this agent could help prevent rejection. After IRB approval on December 11, 1984, twelve patients were enrolled.

5. The fifth trial, designated 126.3, prescribed the combination of methotrexate and cyclosporine after transplantation. After IRB approval on June 21, 1985, nine patients were enrolled. A publication summarizing results of this trial and the preceding three studies is appended. See Appendix 12.

6. The sixth trial, designated 126.4, tested whether graft failure could be avoided by T cell depletion with the use of a CD3-specific immunotoxin developed in collaboration with Ellen Vitetta at the University of Texas Southwestern School of Medicine at Dallas. An IND exemption for testing this immunotoxin was allowed by the FDA (IND #BB-2286). After IRB approval on November 1, 1985, eight patients were enrolled. A publication summarizing results of this study is appended. See Appendix 13.

7. The seventh trial, designated 126.5, tested whether addition of total lymphoid irradiation in the pretransplant conditioning regimen could prevent rejection. After approval by the IRB on December 10, 1985, nine patients were enrolled. Although the protocol remained open until November 30, 1989, no patients were enrolled after September 3, 1987, due to the availability of better alternatives for patients.

8. The eighth trial, designated 126.6, tested whether selective depletion of CD8 cells could prevent GVHD. After IRB approval on October 14, 1986, two patients were enrolled. The study was stopped when it became apparent that removal of CD8 cells was not sufficient to prevent GVHD in HLA-identical recipients who received no posttransplant immunosuppression.

9. The ninth trial, originally designated 126.7 and later amended as 126.8, tested whether the addition of 2-chlorodeoxyadenosine to a conditioning regimen of high dose cyclophosphamide and single fraction TBI would prevent rejection of T cell depleted HLA-mismatched marrow. This study was sponsored by the Cancer Therapy Evaluation Program of the NCI and was reviewed by FDA. After IRB approval on May 30, 1991 a single patient was enrolled. The study was closed after the initial patient rejected the graft.

b. The Second Trial.

The events referred to in Dr. Pesando's letter relate principally to the second trial under Protocol 126. The protocol for the second trial was originally submitted to the IRB on April 4, 1983 and was approved on May 26, 1983 after modifications recommended by the IRB were made. The first patient was enrolled on June 24, 1983. On September 23, 1983, one of the patients developed marrow hypoplasia together with cytogenetic changes indicating recurrent myelodysplasia after transplantation. The first two unambiguous rejections occurred on November 23, 1983 and January 11, 1984. The first patient engrafted after a second marrow transplant but later died on April 22, 1984. The second patient died on January 27, 1984 after a second transplant. One other patient developed severe neutropenia on January 25, 1984 but recovered spontaneously.

In accordance with FHCRC's normal practices, these events were discussed in detail by members of the Division of Clinical Research at regular GVHD weekly meetings on February 2, 1984 and February 8, 1984. There were two members of the Clinical Research Division on the IRB at the time including Dr. Pesando. The IRB administrator was also invited to these meetings, however, it doesn't appear whether or not she was present at these particular meetings. Minutes of the first discussion were not recorded, but minutes of the second discussion are appended. See Appendix 14. After careful review, the group decided to continue the study until twenty patients had been enrolled. Copies of minutes of the GVHD meetings were provided to the IRB administrator as part of FHCRC's normal procedure.

The complications associated with Protocol 126 were discussed again at an IRB meeting on February 14, 1984. In response to an inquiry from the IRB, Dr. Martin summarized the events and results of the discussion by staff members during the proceeding two weeks. See Appendix 15. Enrollment of twenty patients was reached on March 16, 1984, and the protocol was suspended for observation.

An IRB renewal application was submitted on March 28, 1984. IRB approval was granted on April 17, 1984 contingent on revisions which were submitted on April 20, 1984. After further revisions made at the suggestion of the IRB on May 3, 1984, the protocol was approved on May 9, 1984 and circulated to members of the Division on May 14, 1984.

Members of the Division of Clinical Research discussed the results in the original twenty patients during regular weekly group meetings on May 9, 1984 and on May 16, 1984. Minutes of these discussions are included at Appendix 16. These minutes were provided to the IRB. On May 23, 1984, an addendum to the protocol was submitted to the IRB and was subsequently designated 126.1. This addendum was approved by the IRB on June 5, 1984, contingent on review by the Scientific Review Committee. As discussed previously, the review of the Scientific Review Committee was conducted on June 25, 1984 and resulted in a request for clarification of protocol entry criteria. See Appendix 8. The changes were submitted on July 10, 1984, and approval was granted on July 11, 1984. Protocol enrollment was started on August 2, 1984. At the time, continuation of studies involving T cell depletion was justified by the reduced risk of GVHD and by the fact that graft failure had occurred in only one of nine patients who had received 15.75 Gy TBI before transplantation. A publication describing the results in these 20 patients is included at Appendix 17.

B. RESPONSE TO OPRR AND PESANDO LETTERS.

1. The IRB Was Qualified and Trained and Had Authority to Fulfill Its Obligations Under FHCRC's Assurance and Applicable Federal Regulations.

In your letter at page 2, you ask that we address the questions raised about the competence and authority of our IRB. Federal Regulations require that an IRB be comprised of members from diverse backgrounds, that members be sufficiently qualified through experience, expertise and diversity to promote respect for the IRB's advice and counsel and that members include men, women and diverse professions and that they include at least one member who is not affiliated with the institution and one member whose primary expertise is in a nonscientific area. 45 CFR 46.107. See, also, July 27, 1981 Assurance at p. 11 (Appendix 18). Included at Appendix 19 is a list of IRB members during the period of 1983-1985 including resumes for many of these individuals. During this time period the IRB included several physicians, scientists, nurses, and administrators and an attorney and a minister. While we have not been able to locate all of these resumes because of the time that has passed, the ones enclosed demonstrate that these individuals were highly qualified to serve on the IRB and otherwise satisfied all of the criteria contained in FHCRC's assurance and the applicable federal regulations.

The IRB members also received training when they began their service on the IRB. We have included for your information a copy of our current training manual for IRB members which has evolved from the first versions. In addition to receiving this manual, our IRB coordinator conducts an orientation for new IRB members to familiarize them with their responsibilities as IRB members. At this class they are shown a video provided by OPRR entitled Evolving Concern - Protection for Human Subjects. Other video tapes are made available to them including Balancing Society's Mandates/Criteria for Protocol Review and The Belmont Report/Basic Ethical Principles and Their Application. After their orientation, the IRB administrator continues to send IRB members relevant materials which she obtains from seminars including those sponsored by NIH, the FDA and the Applied Research Ethics National Association ("ARENA") and from publications including updates to any applicable regulations.

Concerning the IRB's authority, it is clear from reviewing the correspondence from the IRB and the protocol files for Protocol 159 and 126 that rather than being intimidated by Dr. Thomas or any other person on the FHCRC clinical staff, the IRB remained actively involved in reviewing and monitoring the two protocols in question. As discussed in more detail below, because of IRB involvement and dialogue with the clinical staff, several changes to these protocols and to general procedures at FHCRC were made. Rather

than evidencing an IRB without competence or authority, the dialogue and subsequent actions of FHCRC in response to that dialogue indicate that the IRB at FHCRC was at the time and continues to be a respected and effective part of the research effort at FHCRC. Neither Protocol 126 nor 159 was ever allowed to proceed without IRB approval.

In his letter Dr. Pesando repeatedly implies that the IRB during the period 1983-1985 lacked qualifications and authority to carry out its duties. He suggests that the IRB was intimidated by senior clinical staff. At page 2 of his letter, he describes the atmosphere during IRB meetings as one of "fear and disbelief". As evidence of this intimidation by senior medical staff he cites a single sentence from Dr. Thomas' letter to the IRB of October 14, 1983. See Appendix 5. In that sentence, Dr. Thomas expresses his concern over restrictions on research, specifically a 60-day limitation on the approval for Protocol 159. However, the letter is a detailed response to concerns raised by the IRB. In the letter Dr. Thomas states that he and other members of the Clinical Division are "willing to spend a great deal of time in assisting the committee members". See Appendix 5 at p. 1. Rather than suggest "stiff opposition" the entire tenor of the letter indicates a willingness to cooperate with the IRB. Furthermore, in spite of Dr. Thomas' concern over the 60-day restriction on Protocol 159, all information requested by the IRB was provided before the approval was extended beyond that time period. See Protocol File for Protocol 159.

Dr. Pesando further implies that IRB members were intimidated because their jobs were controlled by the principal investigators for Protocol 126 and 159, presumably Dr. Thomas and Dr. Hansen. However, neither Dr. Thomas nor Dr. Hansen was a principal investigator of these Protocols during the period in question. More importantly, there were only two members of the IRB that were even in the Clinical Division. Many members, including the chairman, Dr. Kaplan, were employed by independent institutions and were not in any way dependent on Dr. Thomas or Dr. Hansen for future employment.

At page 3 of his letter, Dr. Pesando also states 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." It is not clear what Dr. Pesando means by a regulatory void since NIH did have regulations in effect concerning the operation of IRB's, copies of which were provided to members. In any event, the physicians, scientists and lawyers on the committee clearly had expertise to address any regulatory matters that might have arisen or to obtain appropriate assistance.

2. Protocols 159 and 126 Were Only Allowed to Continue With IRB Approval After Providing All Information Requested by the IRB and Implementing All Procedures Required by the IRB.

The central theme of Dr. Pesando's letter is that FHCRC refused to comply with IRB requests to establish an independent scientific review procedure for protocols using monoclonal antibodies or to address conflicts of interest involving Dr. Thomas and Dr. Hansen. Similarly, Question 1 at page 2 of your letter asks why protocols 159 and 126 were allowed to continue a) without following the advice of the IRB for external review and approval; b) without providing information that was requested by the IRB about the monoclonal antibodies used; and c) without resolving the conflict of interest issues raised by the IRB.

As discussed below, each time the IRB requested information concerning Protocols 159 and 126 it was provided and each time the IRB recommended procedures, substantially similar procedures were implemented which were satisfactory to the IRB.

a. FHCRC Provided an Independent Review Procedure for Protocols Using Monoclonal Antibodies.

The formation of a new independent scientifically-based group to consider the scientific merits of monoclonal antibody preparations proposed for study was first proposed in Dr. Kaplan's memo to me of November 30, 1983. See Appendix 6. In response to this letter an advisory committee was organized. The first meeting of this group occurred on January 17, 1984. See Appendix 7. As shown in the minutes of that meeting, the procedures developed by this committee for external review were approved by Dr. Kaplan, the Chairman of the IRB, and Dr. Pesando. This committee ultimately became a standing committee called the Scientific Review Committee, which included Drs. Appelbaum, Cheever, Kaplan, Storb, Sullivan and Pesando.

In May of 1984, at the request of the IRB, all protocols using monoclonal antibodies were stopped until the IRB was satisfied that appropriate reviews by the Scientific Review Committee had occurred. Minutes of the meeting of the Scientific Review Committee on June 25, 1984 are included at Appendix 8. As shown in the minutes, investigators of all protocols using monoclonal antibodies at FHCRC were required to supply detailed information for each antibody, including information on the method of preparation, the source of the antibody and quality control. Both Protocol 159 and Protocol 126 were reviewed by this committee at the June 25 meeting as reflected in the minutes and use of the specified antibodies in these protocols was approved.

On December 17, 1984, Dr. Kaplan wrote to me suggesting two further modifications. See Appendix 9. First, Dr. Kaplan felt that the IRB did not have sufficient statistical sophistication to evaluate protocols and, therefore, suggested that each protocol provide a section and signature line for a statistician before review by the IRB. This suggestion was adopted and remains part of the regular review process.

Dr. Kaplan's second suggestion was that we set up an extramural scientific review of protocols. The suggestion contemplated use of a system similar to manuscript review in which copies of the protocol would be mailed out to experts in the field throughout the country who have agreed in advance to be reviewers. This was not a recommendation which dealt specifically with the use of monoclonal antibodies but with the entire research activity of the FHCRC. The Clinical Research Division discussed this possibility but decided that it was neither necessary nor practical. First, the vast majority of our clinical research is carried out with the support of NIH research grants. Each of these grants undergoes close scrutiny by external reviewers on a periodic basis and thus our research is, in fact, externally peer-reviewed. For example, as discussed earlier, both Protocols 126 and 159 were peer-reviewed and approved in connection with the Center's ALC Grant. See Appendix 1. Second, the question of the scientific merit of each individual research protocol always has been, and continues to be, an internal decision. We know of no other circumstance in which institutions are required or choose to send out every protocol for external review. Third, it was the decision of the Clinical Research Division that such a process would significantly slow down the research process and would be unduly burdensome on external colleagues. Finally, all protocols at the time were reviewed first by working committees of clinical investigators and ultimately by the entire clinical staff at a weekly staff meeting before being sent to the IRB. This procedure is explained in a memo from Dr. Thomas to the IRB dated October 3, 1983. See Appendix 20. This procedure continues today except that review takes place at Clinical Investigator Meeting ("CIM"). For these reasons, it was felt that an additional layer of review was unnecessary.

On May 17, 1985 an IRB subcommittee sent a memo to me recommending the procedures for sign off by a statistician and external scientific review suggested by Dr. Kaplan in his December 17, 1984 letter to me. See Appendix 21. As indicated before, the policy and procedures concerning sign-off by a statistician were adopted. Attached to the May 17 memo is a proposed Institutional Review Board Application which was ultimately adopted by the IRB and used at FHCRC. At page 4 of the form is a section on monoclonal antibodies requiring prior review by the Scientific Review Committee before submission to the IRB. See Appendix 21. A formal policy was adopted by the IRB and incorporated into its review manual on November 7, 1985. A copy of the relevant

chapters are included in Appendix 22. Page 2-5 of the policy requires that monoclonal antibodies used in protocols at FHCRC be approved by the Scientific Review Committee. The committee remains in place today although it is now called the Biologics Committee as discussed in Section C below.

b. All Information Requested by the IRB Regarding Production Procedures, Quality Control and Selection Criteria for Products Was Provided.

In Dr. Kaplan's letter to Dr. Thomas dated September 28, 1983, the IRB first raised concerns about the unspecified use of monoclonal antibodies. See Appendix 4. In his letter Dr. Pesando states that the IRB was concerned by the "sloppy design" of many studies using locally prepared monoclonal antibodies, in particular, the failure to specify which monoclonal antibodies were being used. See page 1 of Dr. Pesando's letter. In his September 28, 1983 letter, Dr. Kaplan references Protocol 159 as an example of a protocol which did not specify which antibodies were being used. The letter then goes on to request certain specific information concerning the use of monoclonal antibody at FHCRC.

Dr. Thomas responded to this letter by a letter dated October 14, 1983 (Appendix 5) which included all of the information requested in Dr. Kaplan's letter including a discussion of the decision-making process by which the clinical staff selected monoclonal antibody, the processes by which controls for monoclonal antibody production were established, standards for toxicity and selection criteria. The letter was accompanied by detailed appendices.

Subsequently, as discussed above, in response to further IRB concerns, all protocols utilizing monoclonal antibodies were required to be submitted to the Scientific Review Committee. In connection with that review, detailed information concerning each antibody being used was provided to the Scientific Review Committee for analysis. See Appendix 8. As shown in the protocol files for 159 and 126, each time a new antibody was used, a separate appendix containing detailed information about that antibody had to be approved by the IRB and the Scientific Review Committee.

Although Dr. Pesando characterizes the design of these studies as "sloppy", the NCI committee that peer-reviewed this study in 1981 felt that they were "meticulously detailed" and notable for their logical progression and careful attention to controls." See Appendix 1A at p. 16.

c. Conflict of Interest Concerns of the IRB Were Addressed Promptly.

As demonstrated by NIH's own efforts to develop an acceptable conflict of interest policy, the issues raised by relationships between private companies and scientific researchers are difficult to resolve satisfactorily. As indicated in the minutes of the first meeting of the Monoclonal Antibody Advisory Group (Appendix 7), Dr. Hansen and Dr. Thomas both had substantial holdings in founders stock of Genetic Systems. Dr. Hansen also served briefly as medical director of Genetic Systems. Dr. Thomas served on the advisory committee for Genetic Systems. These relationships arose in 1980 and 1981 when Genetic Systems was first organized. However, while Dr. Thomas and Dr. Hansen were listed on Protocols 126 and 159, neither was a principal investigator on these protocols or otherwise primarily responsible for conducting the research with respect to them except that Dr. Hansen was the principal investigator on Protocol 126 in 1982. Dr. Paul Martin became the principal investigator on Protocol 126 in 1983 and had a small amount of Genetic System's founders stock (10,000 shares out of approximately 15 million shares outstanding in 1983) issued to him in 1980 when the company was formed. He did not receive any consulting fees from the company. Fred Appelbaum, the principal investigator on Protocol 159, held no stock or other interest in and received no fees from Genetic Systems.

In March of 1983 the FHCRC Board of Trustees adopted official policies on conflicts of interest and participation of scientific staff with outside interest designed to prevent inappropriate dealings between the scientific staff and outside interests. Copies of these policies, which are still in effect, are included at Appendix 23. The relationships between FHCRC clinical staff and Genetic Systems were developed prior to the adoption of these policies. Under these policies any involvement of the scientific staff with outside interests must be reviewed and approved by the division director of the division with which that scientist is associated and by the Director of FHCRC. The Director can refer the matter to the Board of Trustees if necessary. The policies are referenced by Dr. Thomas in his October 14, 1983 response to Dr. Kaplan. See Appendix 5, p. 3.

As stated at page 2 of Dr. Pesando's letter, the conflict of interest that most concerned the IRB were the relationships of Drs. Thomas and Hansen with Genetic Systems. Because of this concern and the concerns raised in Dr. Kaplan's letter to me received November 30, 1983, I organized the Advisory Group on monoclonal antibody testing. As reflected in the minutes of the first meeting of that group, one of the principal areas of discussion was conflicts of interest including the conflicts of Dr. Hansen and Dr. Thomas. See Appendix 7. A procedure was discussed under which the group could be called together to review the use of particular antibodies whenever the IRB felt such

review was appropriate. The procedures outlined at that meeting were agreed to by Dr. Kaplan and Dr. Pesando. The Monoclonal Antibody Advisory Committee ultimately became the Scientific Review Committee. In that capacity this committee reviewed all monoclonal antibodies used in both Protocol 159 and 126. See Appendix 8.

It should also be noted that all antibodies used in Protocol 126 and Protocol 159 were produced at the Center with the single exception of antibody B1-1F5 which was produced by Oncogen, a joint venture in which Genetic Systems was involved. While most of these antibodies were licensed to Genetic Systems, the increased use of any of the licensed antibodies for *in vitro* treatment of bone marrow would not have made any significant difference to Genetic Systems financially. At this time there are approximately 5,000 allogeneic transplants performed each year in the United States. In the early 1980's the number was less. For each marrow treatment only 40 micrograms of antibody are used. Even if T-cell depletion was used in every single allogeneic transplant performed in the United States and all of the antibody was obtained from the same supplier, the amount of the antibody used each year in the United States for *in vitro* treatment of marrow would be only 0.2 grams. Additionally, antibodies against T-cells have been produced by a number of institutions with no evidence that any single antibody has superiority over others. As noted in the report of the NCI Committee that peer-reviewed this proposal, "The monoclonal antibodies already produced by this group do not appear to be significantly different from those obtained in other laboratories, but it is evident that they will be put to good use." See Appendix 1A, at p. 25. There are also other methods of removing T-cells that have been developed including lectin binding and elutriation. Therefore, there was no real financial incentive for anyone in the Clinical Research Division to promote antibodies licensed to Genetic Systems.

3. <u>The Director Took Prompt and Appropriate Action to Address IRB Concerns</u>.

Your letter inquires as to what I did to address IRB concerns. In paragraph 8 Dr. Pesando states that in spite of my promises, Protocol 126 and its derivatives continued and the death toll mounted and the IRB remained poorly informed of its progress and the complications of these clinical studies. In fact, each time the IRB made recommendations to me, I acted to implement them. The principal concerns expressed to me by the IRB as shown in Dr. Kaplan's letters (Appendices 6 and 9) were the formation of the review committee and addressing the conflicts of interest. As discussed above, these matters were addressed promptly through the formation of an advisory committee. As already discussed, FHCRC determined that an additional layer of external review was unnecessary. Review of protocols using monoclonal antibodies was performed by the Scientific Review Committee.

The other recommendation made by the IRB was sign-off by a statistician. See Appendix 9. This was implemented by FHCRC and is still required.

4. Protocol 126 Was Conducted for Scientifically Appropriate Reasons With Full Disclosure of Risks and Adverse Events to the IRB and Patients.

The majority of Dr. Pesando's allegations are directed at Protocol 126. Dr. Pesando states that this protocol caused very high mortality rates in patients who otherwise stood a good chance of cure by bone marrow transplantation. He also states that the IRB was kept poorly informed as to the progress and complications of this study and that the IRB only learned of complications through its own members rather than the principal investigator or the FHCRC staff. None of these assertions have any basis in fact.

As discussed in Section A.4.a. above, Protocol 126 was motivated by the clinical need for better prevention of GVHD after allogeneic marrow transplantation. Monoclonal antibody technology represented a major scientific breakthrough. Initially, there were few data from animal experiments to indicate that T cell depletion could lead to complications. Early enthusiasm for this approach in humans was evidenced by the widespread testing in many centers. More than 800 T cell-depleted marrow transplants were carried out world-wide during the six year period between 1981, when the initial reports were published, and the end of 1986. This enthusiasm is also reflected in the critique and report of the NCI committee that peer-reviewed and approved this protocol in 1981 and again in 1986. See Appendix 1. Data from the initial studies have confirmed the expectations of decreased incidence and severity of GVHD but have also led to recognition of the problems of increased graft failure, leukemic relapse and delayed immune reconstitution. This recognition has indicated the need for greater understanding of the immunobiology of marrow transplantation, particularly in terms of the relationships between engraftment, GVHD, and immunologic control of malignant cells.

In each case the clinical trials under Protocol 126 were carefully designed and carried out. The protocols were restricted to those patients who stood the most to gain by the potential elimination of graft versus host disease (those over 30 years of age and, more recently, those without a complete match). Furthermore, each of the trials was designed with strict stopping rules. The original protocol stated simply that the study would be stopped if there was cumulative evidence of toxicity. Subsequent protocols stated that the study would be stopped whenever any two patients developed graft failure. This criterion was selected to represent the smallest number of adverse events that could be reliably interpreted to indicate that any new approach being explored would not likely

be successful. This criterion represented the reason for closing protocols 126.1, 126.2, 126.3 and 126.4. Protocol 126.7 and its amended version 126.8 had a highly sophisticated phase I dose escalation design. Under Protocols 126.7 and 126.8, the occurrence of graft failure in the first patient, together with information that became available after these protocols were written, made it clear that the original design was not likely to succeed, and the protocols were abandoned as a result. In its review, the NCI committee that peer-reviewed Protocol 126 in 1986 stated "The hypotheses are reasonable, the selection of an older population of patients at higher risk for developing significant GVHD, and the stopping criteria for any given pilot phase (for example, an unacceptable rate of GVHD or rejection) also seem reasonable." See Appendix 1.B. at p. 29.

The risks of treatment under Protocol 126 were fully disclosed to and discussed with the patients. The consent form for this study states among other things:

> "The use of monoclonal antibody in human patients is still investigational and with any such product there may be unanticipated adverse effects. There is a possibility of an allergic reaction even though nearly all of the monoclonal antibody and the rabbit serum will have been removed. Other possible effects are fever, chills, temporary difficulty in breathing or drop in blood pressure. Your clinical situation will be monitored closely at all times. Treatment of marrow with monoclonal antibody and rabbit serum may damage cells necessary for engraftment, and it is possible that failure of engraftment or graft rejection may occur following such treatment. In this case a second marrow transplant would be necessary."

This form of consent was cited by the IRB to Dr. Appelbaum as a good model for Protocol 159. See memo dated June 19, 1984 from IRB to F. R. Appelbaum at p. 2 in Protocol File for Protocol 159.

Additionally, as indicated in Dr. Martin's letter to the IRB dated February 15, 1984 regarding Protocol 126, (Appendix 15), it was the Center's general policy to inform patients about new results that might affect their willingness to participate in protocols. FHCRC clinical staff reviewed the results of Protocol 126 with new patients. The results were monitored closely by Dr. Martin and attending physicians were kept advised of the results. Dr. Martin personally discussed the results with patients as necessary.

Dr. Pesando states in paragraph three that the IRB learned of problems with this Protocol through its own members and not from the principal investigators or FHCRC

staff. However, as described previously, adverse events and other problems were discussed by the entire clinical staff at GVHD meetings. The IRB administrator was invited to and received the minutes of these meetings. On the occasion referred to in Dr. Pesando's letter the IRB apparently learned of two adverse events involving Protocol 126 through the clinical members of the IRB that participated in these weekly conferences. These problems were not a secret and were openly discussed. It was assumed that these members would inform the IRB of these discussions which they did. When the IRB requested more detail from Dr. Martin he promptly provided it. See Appendix 15. Also, as shown in the Protocol file for Protocol 126, adverse events were reported to the IRB on the annual review form and also in special reports where appropriate. See, for example, Dr. Martin's report to the IRB dated October 1, 1985 in the Protocol file for Protocol 126.

Dr. Pesando states in paragraph 4 of his letter that Protocol 126 continued to enroll patients even after an alternative successful prophylaxis was published in 1986. In fact, only three patients were treated on protocol 126 variants after 1986 and these were patients with extremely high risks of developing graft-versus-host disease despite alternative prophylaxis strategies. Further, it should be noted that there is no uniformly successful prophylaxis for graft-versus-host disease and patients continue to die of this complication despite the regimen published in 1986.

In paragraph 6 Dr. Pesando claims that he and Dr. Kaplan successfully lobbied to exclude those patients having the most favorable clinical prognosis in the list of candidates for Protocol 126. This is untrue. This decision was made by members of the Division of Clinical Research at their regular weekly meetings as shown in the minutes of the meeting. See Appendix 14.

5. Dr. Pesando's Failure to Receive an Appointment at FHCRC was Unrelated to His Involvement with the IRB.

In paragraph 10 of his letter, Dr. Pesando implies that his involvement with the IRB was responsible for his failure to achieve a promotion at FHCRC. He states, "Only a fool would fail to realize the dangers inherent in opposing the wishes of superiors in employers and we were all aware of them in 1983 and 1984."

Dr. Pesando was not promoted to the rank of assistant member and left the Center in 1987. His failure to be promoted is not unique as the promotions process is considered very seriously by the scientific staff. In accordance with FHCRC's normal procedures, a review committee was appointed to make recommendations to the

scientific staff of the Division of Clinical Research. Neither Dr. Thomas nor Dr. Hansen was a member of this committee. The recommendation was not to promote.

This recommendation was based primarily on Dr. Pesando's failure to receive favorable national peer-review in pursuit of his grant requests. Although efforts were made to aid Dr. Pesando in his pursuit of successful national peer-review of his grant applications to NIH, the report of the independent scientific review committees of the NIH who considered Dr. Pesando's grant applications, and the low priority scores that he received after review of these grants, confirmed a generally unfavorable opinion of the nature and rate of his scientific productivity and was the principal reason for his unfavorable review for promotion. This national peer review had nothing to do with Dr. Pesando's allegations about the nature of clinical research conducted at the Center, nor the organization and administration of the Division of Clinical Research, but was based entirely on his scientific capabilities as perceived by individuals who had no involvement with the FHCRC.

Dr. Pesando was assisted materially with startup and continuation funds for his laboratory research pending his ability to secure his principal sources of research support from competitively awarded grants, in which he was unsuccessful. He was treated in the same fashion as any junior member of the scientific staff has or will be treated, namely, startup and initial funding for the member's research with the expectation that the member will be successful in securing support through national peer-review. The substantive component in his review that led to the unfavorable recommendation regarding his promotion was that performed under the NIH peer-review system based solely on grant requests prepared and submitted by Dr. Pesando. This review process has nothing to do with FHCRC or its internal operations such as the IRB. Dr. Pesando's inability to compete successfully nationally was a disappointment to members of the scientific staff who had urged his appointment in the first place as a person with whom they wished to collaborate and someone whom they expected to take a leadership role in aspects of immunology that are obviously of importance in the Division of Clinical Research.

Dr. Pesando had a joint appointment at the University of Washington School of Medicine, Department of Medicine. He requested review for promotion in that department. He was reviewed by the University of Washington Department of Medicine under its customary review procedures and was not promoted. Again, neither Dr. Thomas nor Dr. Hansen were members of the committee that performed this review.

C. CURRENT PROCEDURES FOR REVIEW OF PROTOCOLS USING MONOCLONAL ANTIBODIES.

As monoclonal antibody research at FHCRC has evolved so have the methods of evaluating this research to further protect the human subjects involved in this important research. This evolution has occurred through the interaction and active participation of FHCRC's IRB and the members of FHCRC's Clinical Division and is evidenced in FHCRC's current policies regarding monoclonal antibody research. As already discussed all protocols must be reviewed and approved by voting members of the Division of Clinical Research at FHCRC and by a biostatistician before they are submitted to the IRB. To further facilitate IRB review, FHCRC investigators filed a protocol approved by the IRB on October 16, 1987 describing the methods for production, purification and preclinical testing of the monoclonal antibodies used in any applicable protocols. This IRB file has been included with the records for Protocols 159 and 126 to assist you in your review. See File No. 6, Protocol file for Protocol 387. FHCRC investigators also initiated a separate protocol describing the rationale and methods involved in purging of autologous marrow for patients with lymphoid malignancies. This protocol was approved by the IRB on May 13, 1988. This IRB file has also been included with the other records. See File No. 7, Protocol file for Protocol 402. Additionally, in recognition of the need for improved quality control over biological agents used in clinical trials at FHCRC, FHCRC developed a biologics production facility capable of producing monoclonal antibodies under GLP conditions. The responsibility for ensuring that appropriate safeguards are implemented for clinical studies at FHCRC using noncommercial biological agents is assigned to a standing committee established in 1990 called the Biologics Committee.

D. CONCLUSION.

The records with respect to Protocols 126 and 159 demonstrate that FHCRC fulfilled both the letter and spirit of FHCRC's assurance and the applicable NIH regulations concerning protection of human subjects. As our records demonstrate, the IRB at FHCRC was at that time and continues to be an integral and important part of the research process at FHCRC. While we believe that the IRB review process at FHCRC functions very well, we are always interested in ways to improve it. Accordingly, we would appreciate any comments or suggestions you might have in that regard. Also, we are happy to provide you with any further information you might need in connection with your

inquiry and can also make someone available to answer questions if that would be helpful.

Sincerely yours,

Robert W. Day, M.D.

Attachments