Report of the National Institutes of Health

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—The Editors

Background

On Oct. 26, 1984, Leonard Bailey, M.D., and the staff of the Loma Linda University Medical Center (LLU) performed a baboon-to-human infant cardiac transplant operation. The human infant recipient, known as Baby Fae, was born with hypoplastic left heart syndrome. At the time of the surgery, the infant was 14 days old. Baby Fae survived 20 days after surgery. Although the procedure was not funded by the National Institutes of Health (NIH), it was governed by policies set forth in the LLU Assurance of Compliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR 46). The Assurance document, approved by the Office for Protection from Research Risks (OPRR) on May 17, 1984, sets forth the LLU commitment to carry out all research involving human subjects, irrespective of the source of funding for the research, in accord with HHS regulations for the protection of human subjects. OPRR exercises responsibility on behalf of HHS for ensuring implementation and compliance with these regulations.

Shortly after the transplant operation, the director and assistant director, OPRR, had several discussions with the chairperson of the LLU Institutional Review Board (IRB) and the LLU chairperson of the department of surgery. Following these discussions, Harrison S. Evans, vice president for medical affairs, LLU, invited OPRR to conduct a site visit at LLU for purposes of consultation and review of LLU Institutional Review Board (IRB) procedures in connection with the Baby Fae surgery and the cardiac xenograft transplantation program. In response to this invitation, several members of the OPRR staff, accompanied by the NIH legal advisor and two non-federal consultants, visited LLU on Dec. 10 and 11, 1984.

Objective of the Site Visit

The objective of the site visit was to review the baboon-to-human xenograft transplant protocol at LLU in order to determine whether it was reviewed, approved and conducted in accord with the HHS regulations for the protection of human research subjects (45 CFR 46). In order to make this determination, the site visit was designed to focus primarily on the review procedures of the LLU IRB and the informed consent process followed in the conduct of the transplant procedure. The regulations require that the IRB determine that risks to subjects are minimized, that the risks are reasonable in relation to anticipated benefits, that selection of subjects is equitable, and that informed consent will be sought and documented in accord with the regulations. (See 45 CFR 46.111, 46.116 and 46.117)

Therefore, the site visitors were to carefully evaluate the information reviewed by the LLU IRB and assess whether that information and the IRB's review of it were sufficient to enable the IRB to make the determinations which are a prerequisite to IRB approval. Further, the site visitors were to determine whether the research was conducted in accord with the requirements stipulated by the IRB.

Facts

Before permitting the baboon to human xenograft transplant research to proceed, the necessary review and approval of the research by the LLU IRB was obtained. In August 1983, Leonard Bailey submitted a research protocol entitled, "Orthotopic Cardiac Xenotransplantation in the Newborn with Diminutive Left Heart Syndrome," along with its attendant informed consent document to the LLU IRB. The protocol was initially reviewed by the IRB in September 1983, but action on it was tabled because Bailey was out of the country and, therefore, unable to answer questions raised by the IRB. In October 1983, the IRB reviewed the protocol and requested submission of additional data on the sheep-to-goat xenotransplants performed by Bailey. In November 1983, after receiving and reviewing the requested information, the IRB approved the protocol, subject to scientific and ethical review by the hospital ethics committee, the department of surgery, the department of pediatrics, the executive committee of the medical staff of LLUMC, and the advisory committee to the LLU vice president for medical affairs. These reviews were primarily scientific in nature, with the exception of the review by the hospital ethics committee.

In December 1983, the IRB reviewed the consent document and informed Bailey that changes would have to be made in order to obtain IRB approval. The IRB also requested and received information from officials of the LLU Medical Center regarding LLU's willingness to approve the project and provide for the costs associated with it. Later in December 1983, the IRB approved the revised consent document. The IRB stipulated that any changes in either the protocol or consent document would require approval by the IRB. Furthermore, the IRB required that Bailey submit a progress report at the end of one year (i.e., December 1984) at which time the protocol would undergo another IRB review, in accord with HHS regulations.

Richard Sheldon, M.D., the IRB chairperson, was in close communication with

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representatives of the other committees that reviewed the protocol. Through Sheldon, the IRB was informed of protocol changes required as a result of other committee reviews. Each of the committees reviewing the protocol was fully aware that all required protocol changes would need to be reviewed and approved by the IRB before the final protocol could be implemented.

The LLU hospital ethics committee does not have the authority to approve or disapprove research protocols, but serves to raise issues and provide advice. The ethics committee, and selected members of the LLU Center for Christian Bioethics, reviewed the xenotransplantation protocol in March 1984. At that meeting, the primary issues raised were the probability of survival and quality of the life of the recipient and whether further animal studies should precede a transplant to a human. Although the committee did not meet again on the topic, the chairperson of the committee, Jack Provonsha, M.D., Ph.D., participated in the subsequent review of the protocol by the executive committee of the medical staff of LLUMC. At the time of the site visit, Provonsha indicated that any reservations expressed by the hospital ethics committee had been sufficiently eased by information supplied by Bailey and Sheldon prior to the transplant and that he had so stated at the meeting of the executive committee.

The department of surgery instructed Bailey and his staff that the surgery facilities could not be used for the purposes of surgery under the protocol until the department of surgery approved the protocol. The department of pediatrics insisted on approval by the pediatrics ad hoc neonatal cardiac transplantation committee, as any infant to be involved in the project would be a patient under the care of the department of pediatrics. Additionally, each of these departments required that Bailey obtain scientific review of the protocol from medical experts at other institutions. Consequently Stuart Jamieson, M.D., a transplant surgeon from Stanford University, and Sandra Nehlsen-Cannarella, Ph.D. a transplant immunologist from Montefiore Medical Center, were consulted.

Jamieson recommended that LLU perfuse several baboon hearts with human blood in order to rule out the possibility of hyperacute rejection. Nehlsen-Cannarella reviewed the protocol and the preliminary work and offered suggestions for studies prior to an actual transplant, as well as recommendations to assure cross-species compatibility. The results of laboratory studies suggested by Nehlsen-Cannarella and Jamieson were encouraging. (Subsequently, in August 1984, Nehlsen-Cannarella accepted an invitation from LLU to become an immunology consultant for the xenograft protocol.)

The site visitors were impressed with the candidness of the LLU administrators, researchers and staff, all of whom exhibited significant sensitivity to the ethical, social and scientific issues.

The department of pediatrics developed selection and exclusion criteria to be incorporated into the protocol and required changes in the consent document. The studies recommended by Jamieson and Nehlsen-Cannarella resulted in further changes to the protocol. The revised protocol and consent document, as approved by the department of surgery and by the department of pediatrics, were submitted to the IRB for review in October 1984.

As indicated above, the protocol was also reviewed by the executive committee of the medical staff of LLUMC, consisting of LLU and LLU Medical Center administrative officials. This committee examined the financial, academic, ethical and scientific aspects of the protocol. Final approval by the executive committee was granted several days prior to the transplant.

The infant Baby Fae was not born at LLU Medical Center, but was transferred there from Barstow Memorial Hospital soon after

birth. The infant was examined by several pediatric specialists from cardiology and neonatology and diagnosed as suffering from a severe case of hypoplastic left heart syndrome. The mother was informed of Baby Fae's severe heart abnormality and informed that hypoplastic left heart syndrome is usually fatal within the first week of life. LLU staff doctors explained treatment options to Baby Fae's mother, including the Norwood procedure, a palliative two-stage surgical procedure, available in Philadelphia or Boston. The possibility of a xenograft cardiac transplant was not mentioned to the mother at this time. After completion of the examination and the discussion of options, the baby's mother left the LLU hospital with the baby. Four days later a LLU pediatrician called the mother and informed her that Bailey was interested in exploring the possibility of a xenograft cardiac transplant. The mother, accompanied by the maternal grandmother, a friend of the mother and Baby Fae, returned to LLU Medical Center and met with Bailey for approximately seven hours.

The expected benefits of the procedure appeared to be overstated; specifically, the document stated that "long-term survival" is an expected possibility, with no further explanation.

Bailey explained his research to the mother, the grandmother and the friend, informing them that he could give no guarantee of success since this type of transplant had never before been attempted in a newborn. He provided an in-depth explanation of the xenograft protocol as well as information regarding his work with animal transplants. The explanation included a slide presentation as well as a description of the Norwood procedure. Bailey told them that it was unlikely that a human heart would be available for a transplant, since size-matched and histocompatible human infant hearts are rare. At the end of the session with Bailey, the mother gave permission to begin preliminary blood tests on the infant to ascertain histocompatibility with the immature baboons then available at LLU and then left to discuss the xenograft transplant with the baby's father. The mother returned with the father the next day and Bailey repeated his in-depth explanation of the xenograft protocol. During the next few days, the parents met several times with Bailey to discuss his protocol.

On Oct. 23, 1984, the parents signed the consent document expressing their permission for Baby Fae to receive the xenograft transplant. Eighteen hours later the parents were again asked for their permission, and they again signed the consent document. The IRB was aware of the ongoing discussion between Bailey and the parents, as well as the condition of Baby Fae. The IRB was also informed of the results of the studies recommended by Jamieson and Nehlsen-Cannarella, including the immunological findings. (The tissue match between the infant and the baboon was described to the site visitors as extraordinarily close.) Final IRB approval of the revised protocol was granted on Oct. 24, 1984.

The parents were made aware that they could withdraw their permission anytime prior to the surgery. They were also informed of measures to be taken to protect the confidentiality of the family. The names of the parents have never been released by the hospital, and the hospital provided the mother with a nearby place to stay and a special entrance to the hospital so that she could avoid the large number of reporters as well as animal rights activists attracted to the hospital by the xenograft. The parents have stated in published accounts that they at no time felt they were coerced into participating in this research endeavor.

On the morning of Oct. 26, 1984, Bailey performed the xenograft transplant operation. Subsequent to the transplant, a clinical team, comprised of the approximately 20 individuals most directly involved in the care and treatment of Baby Fae, met daily to

Baby Fae Consent Form

Your new baby has been born with a very serious group of malformations involving the left side of his/her heart. Your baby's diagnosis is hypoplastic left heart syndrome. It is clear from past experience with many such babies that without surgical help, it is extremely unlikely that your baby will live beyond the first few days or weeks of life. Temporizing operations to extend the lives of babies like yours by a few months have generally been unsuccessful. We believe heart transplantation may offer hope of life for your baby. Laboratory research at Loma Linda University over the past seven years, including over 150 heart transplants in newborn animals, suggests that long term survival with appropriate growth and development may be possible following heart transplantation during the first week of life.

Drug treatment is used to reduce risk of rejection of the transplanted heart and mininize infection. A new drug known as Cyclosporin-A has, for the first time in history, made it possible to transplant hearts between very dissimilar animals with expectation for long term survival. This drug will be used to treat your baby. Other antirejection drugs will also be necessary during the early weeks and months following your baby's surgery. These other drugs increase risk of serious infection. It is hoped that use of these additional drugs can gradually be discontinued as your baby adjusts to its new heart. Steps to prevent infection will be used and any known infection will be treated vigorously.

Since size-matched human heart donors are not available we recommend use of an immature primate (baboon) donor heart. We believe we have sufficient positive experimental evidence and experience to justify this type of transplant.

You should understand that surgery of any kind for your baby is very uncertain and highly experimental. Results in humans are unknown.

This experimental heart surgery should not result in any additional expense to you as a family. Your baby will be cared for in much the same manner as any other infant undergoing open heart surgery, except that your baby will require 8-12 weeks of additional in-hospital observation. Routine laboratory studies including: chest x-rays, electrocardiograms, ultrasonic heart analysis (echocardiograms), heart biopsy, and certain blood tests will be done at periodic intervals to look for serious systemic infection or rejection of the new heart. Your baby will be treated with great care and empathy. Every effort will be made to minimize pain, discomfort, and anxiety associated with postoperative recovery following heart surgery.

Should you have any questions regarding the propriety of your participation in this research program, you may contact Hospital Patient Representative, Glenn Sharman at (714) 824-0800, extension 3122, for information. Your doctor to contact is Dr. Leonard Bailey at 714-824-4371 if you have any additional questions or concerns about your participation in this study. You will be given a copy of this consent form.

The information obtained in this study is confidential and your name and identity will not be disclosed without your consent in any published document.

This research is an effort to provide your baby with some hope for immediate and long term survival. We recommend that you consider this proposal for at least 6 hours before re-signing the consent for cardiac transplantation.

AUTHORIZATION: I have read and understand the consent form and agree to participate with my new baby in this research. The purpose, potential benefits, risks and discomforts have been explained to my satisfaction. I have had the opportunity to ask any questions concerning this study.

	Procedure	
Mother and/or Father or Legal Guardian	10-23-84 / Date	12:17 AM Time
Witness	10-23-84 / Date	12:17 a.m. Time

I have reviewed the contents of this form with the person signing above. I have explained potential risks and benefits of the study.

Primary Physician	10-23-84 / Date	12:18 AM Time
Mother and/or Father or Legal Guardian	10-23-84 / Date	6:02 pm Time
Primary Physician	10-23-84 / Date	6:02 pm Time
Witness	10-23-84 / Date	6:02 pm Time

CONSENT FOR NEONATAL CARDIAC TRANSPLANTATION

LOMA LINDA UNIVERSITY MEDICAL CENTER

PATIENT IDENTIFICATION

F / 10/14/34 W

exchange information, discuss the baby's progress and determine any appropriate action. On Nov. 15, 1984, 20 days after surgery, the infant died.

At the time of the NIH visit, LLU advised the site visitors that the autopsy reports were incomplete, as a definitive cause of death had not as yet been established. Preliminary reports, however, have shown that Baby Fae's heart graft did not show the usual typical evidence of cellular graft rejection. The mandatory annual review and approval of the xenograft transplant protocol has been tabled by the IRB pending Bailey's planned submission of a revised protocol which will include information obtained from the first transplant. There is consensus at LLU that a second transplant should not be attempted until the Baby Fae operation has been thoroughly evaluated.

Determination

The site visitors were impressed with the candidness of the LLU administrators, researchers and staff, all of whom exhibited significant sensitivity to the ethical, social and scientific issues associated with the xenograft protocol. The internal reviews of the protocol by the ad hoc committee of the department of surgery, the pediatrics ad hoc neonatal cardiac transplantation committee, the hospital ethics committee, the executive committee of the medical staff of LLUMC, and the advisory committee to the LLU vice president for medical affairs, in addition to the required IRB review, demonstrated to the site visitors that the institution accepted responsibility for the xenograft procedure and allowed it to proceed only after appropriate issues and concerns had been explored, discussed and resolved.

The site visitors, as a result of discussions with the IRB chairman and members and an examination of the IRB file, concluded that the IRB review of the xenograft protocol was appropriate and in accord with the regulatory requirements of 45 CFR 46. The IRB considered the expected quality of life of the infant recipient as well as the psychological impact that an implanted animal heart might have on the family and the recipient. The IRB determined that economic and staff resources were adequate to provide intensive and supportive long-term care if necessary. The IRB also carefully considered the potential toxicity of Cyclosporine (approved by the Food and Drug Administration for clinical use in November 1983) in infants.

The site visitors determined that the requirements of the IRB were followed by Bailey and others and that the IRB had sufficient information to make the determinations required by the regulations.

Although it was clear from discussions with IRB members that all of these issues received attention by the IRB, the site visitors found that the IRB minutes were lacking detail and specificity and a review of the minutes alone would not have revealed the extent and depth of the IRB review. The site visitors found that the IRB spent a great amount of time reviewing the informed consent document. There was a lack of evidence that the IRB devoted the same level of effort to evaluating the entire informed consent process.* Nevertheless the site visitors believe that the process was appropriate, i.e., the parents were given an appropriate and thorough explanation of the alternatives available, the risks and benefits of the procedure and the experimental nature of the

*The informed consent *document* alone should not be confused with the entire informed consent *process*. The document refers to the actual paper that the subject ((or guardian) signs, which explains all relevant information as required by 45 CFR 46.116. The process refers not only to the form but also to the actual interaction between subject (or guardian) and researcher, and the circumstances and manner in which the relevant information is conveyed.

transplant. The site visitors also believe that the explanation was presented in an atmosphere which allowed the parents an opportunity to carefully consider, without coercion or undue influence, whether to give their permission for the transplant.

The site visitors identified three shortcomings in the consent document as printed at the time the consent was made: (1) The document failed to include an explanation as to whether compensation and medical treatment was available if injury occurred, and, if so, what they consisted of, or where further information could be obtained [required by 45 CFR 46.116(a)(6) for all research that is considered to be greater than "minimal risk"]; (2) The expected benefits of the procedure appeared to be overstated; specifically, the document stated that "long-term survival" is an expected possibility with no further explanation; and (3) The document stated that "Since sizematched human hearts are not available we recommend the use of an immature primate donor heart." Although it is true that infant human hearts are generally not available, the protocol did not include the possibility of searching for a human heart, or of performing a human heart transplant at LLU hospital or elsewhere had one been available. The site visitors believe that the document should have clearly stated whether a search for a human heart suitable for transplant into the infant would be made and if there was to be such a search, the arrangements and chances of success for a human heart transplant. If a search would not be made, the reasons should be stated.

In spite of these criticisms, the site visitors believe that as a result of the consent process the parents of Baby Fae fully understood the alternatives available as well as the risks and reasonably expected benefits of the transplant. The informed consent document appropriately explained the experimental nature of the transplant, the extent to which confidentiality would be maintained, whom to contact for answers to questions about the research, and a description of what procedures would be followed and what to expect. A copy of the consent document, with the signatures of the parents deleted, accompanies this report.

The site visitors determined that the requirements of the IRB were followed by Bailey and others and that the IRB had sufficient information to make the determinations required by the regulations.

"We have already corrected the procedure of searching for a human heart at the time of future surgery. We shall incorporate pertinent information in the consent document as suggested. Further, the IRB chairman is taking steps to be sure the consent process is appropriately monitored and documented to insure clarity of communication and avoidance of misunderstanding."

—Harrison S. Evans
Vice-president for Medical Affairs
Loma Linda University

However, not all of the information reviewed by the IRB is set forth in the protocol; much of the information is found in other files, documents, articles and unpublished papers. Consolidation of all of the information relating to all aspects of the protocol would greatly facilitate the establishment of a complete and thorough file on this procedure.

Recommendations

The administrators and clinical staff of LLU assured the site visitors that a second transplant will not be performed until all the information that can reasonably be learned from the first transplant has been collected and carefully considered. The site visitors strongly concur with this decision, believe that it is consistent with the way in which LLU approached the Baby Fae xenograft and note that it will

provide ample time for implementation of the recommendations set forth below.

1. All information associated with the Baby Fae xenograft should be carefully documented, including not only information reviewed by the IRB, but information associated with other reviews of the protocol as well.

2. If another xenograft is to be attempted, the informed consent document must be revised accordingly: (a) to include a statement regarding the availability of compensation and medical treatment in the event of injury, as required by 45 CFR 46.116(a)(6); (b) to more reasonably convey the expected benefits and risks, particularly the possibility of survival; and (c) to clearly state whether a search will be made for an appropriate human donor heart and the risks and benefits associated with that decision.

These recommendations were conveyed to LLU administrators, staff and IRB members during an exit interview at the end of the site visit and were well received. The LLU staff thanked the site visitors for their input and welcomed the recommendations.

After reviewing a draft of this report, Harrison Evans, M.D., vice president for medical affairs at LLU, thanked NIH for its evaluation and recommendations, indicating that the recommendations expressed in this report will be adopted by LLU.