
Loma Linda Says Yes: Anatomy of a Decision

Bruce Branson

The following essay is based on an address by Bruce Branson, M.D., chairperson of the department of surgery at Loma Linda University, to the Washington, D.C., chapter of the Association of Adventist Forums, held at Takoma Academy, and to the Kennedy Institute of Ethics at Georgetown University in November 1984. Also participating in the Takoma Park discussion was Richard Sheldon, M.D., chairperson of the Institutional Review Board, Loma Linda University.

—The Editors

On Friday morning, October 26, 1984, Baby Fae became the first infant to receive a primate heart transplant. She did not suffer an immediate rejection. In fact, Baby Fae survived 20 days—longer than the first human heart transplants in Cape Town and at Stanford University, and five times longer than any previous primate-to-human heart transplant.

Around the globe, radio, television and over 8,000 newspaper articles followed her progress, discussed the scientific validity of the research conducted by Leonard Bailey, M.D., and explored the ethical questions raised by the operation. Recognizing the public's valid interest when bold new therapy is introduced, Loma Linda University and its Medical Center carefully considered both the science and the ethics of the primate-to-human transplant. The extensive institutional preparation for Baby Fae's operation is the subject of this article.

The first pertinent fact was the extent of need. When babies are born with an aorta, aortic valve and left heart structures that fail to develop normally, most die during the first week of life; very few survive as long as one month and all die if surgery is not performed. In North America, this condition, hypoplastic left-heart syndrome (HLHS), is the cause of 25 percent of all deaths from heart disease during the first month of life.

Another factor is the outcome of alternative therapies for this condition. Over the years, several different types of surgical reconstructions have been attempted by various investigators, but only brief temporary benefit with isolated short-term success has been achieved.

In an editorial in the November 1, 1984, issue of *The American Journal of Cardiology*, William C. Roberts, M.D., summarized the situation by stating, "Operative therapy, thus far, has been unsuccessful. Cardiac transplantation is probably the only useful operative procedure." Attempts to transplant newborn human hearts into infants had been made twice in the United States prior to the Baby Fae operation—once in New York and once in Texas. In each case, the infants lived only a few hours.

Human newborn heart donors are rarely found. Most adult human heart donors come from individuals who have sustained brain death as a result of accidents. Since traumatic brain death rarely occurs in newborns, human infant heart donors are vir-

tually unobtainable. Bailey proposed to study the possibility of using animal donors as a source for heart replacement.

Bailey received his specialty training in general and cardiothoracic surgery at Loma Linda University. During further training in pediatric heart surgery at the Hospital for Sick Children in Toronto, Canada, he became deeply concerned with the inevitable deaths of infants born with HLHS. When he returned to Loma Linda University Medical Center from Canada, Bailey set up a special intensive care unit for infant heart surgery patients. Loma Linda University Medical Center became designated by the state as the referral center for high risk obstetrical patients and neonatal intensive care. Its current average census of over 50 neonatal infants in its intensive care unit makes it one of the largest in the western United States. Consequently, an exceptionally large number of infants with congenital heart disease have been referred to Loma Linda. Bailey, subsequently joined by John Jacobson, M.D., who also trained in Toronto in pediatric heart surgery, achieved survivals in progressively smaller newborns and even in infants born prematurely. Bailey's technical virtuosity and personal

attention to every detail of the postoperative management were key elements in the survival of these extremely small infants.

At the same time, Bailey pursued his research interest in the possibility of perfecting cross-species (xenograft) heart transplantation. Over a period of seven years, Bailey performed nearly 150 animal heart transplants, some between different breeds of goats, and others between sheep and goats. Normally, such transplants of foreign tissue are strongly rejected, but Bailey's hopes for overcoming this barrier were based on

- (a) the relative immaturity of the newborn immune system,
- (b) better control of rejection by newly-available Cyclosporine,
- (c) supplementary doses of steroids and other immunosuppressants, and
- (d) careful monitoring of Cyclosporine blood levels to minimize toxicity.

In transplants between different breeds of newborn goats, Bailey showed that the transplanted heart grows and matures in the recipient and that the circumference of a sutured vessel expands to meet the needs of a growing animal. Subsequently successful heart transplants were obtained between newborn sheep and newborn goats with sur-

Overview of Primate-to-Human Transplant

In the early 1960s, Keith Reemtsma, M.D., at Tulane University, transplanted chimpanzee kidneys into humans; one patient survived for more than six months with a functioning kidney. Thomas Starzl, M.D., at the University of Colorado, transplanted baboon kidneys into humans and obtained survivals of a few weeks. These early cross-species transplants led James Hardy, M.D., of the University of Minnesota, to perform the first primate-to-human transplant in a patient dying of end-stage cardiac disease; the small primate heart could not handle the circula-

tory load and ceased functioning in a few hours. In South Africa two subsequent primate-to-human heart transplants were attempted in 1977 by Christiaan Barnard, in an attempt to keep patients alive until a human donor could be found. Barnard reported that the primate hearts functioned adequately for two days in the first patient and three-and-a-half days in the second, but both patients died from multiple system failure. Neither Cyclosporine nor current advanced tissue typing techniques were available when these varied cross-species heart transplants were attempted.

vivals up to five-and-a-half months. These extended survival times in cross-species newborn heart transplants are unprecedented. Bailey gave periodic reports on his research to the department of surgery at Loma Linda University and to a series of national and international conferences on cardiac surgery.

1983

Bailey's increasing success in xenograft heart transplants led him in August of 1983 to submit a proposal to Loma Linda University's Institutional Review Board (IRB) that he transplant size-matched immature primate (baboon) hearts into infants born with fatal HLHS.

The IRB at Loma Linda University was organized in the early 1970s according to guidelines established by the National Institutes of Health. The task of the IRB is to ensure that research involving human subjects offers appropriate data in proportion to potential risks and that careful, legally effective informed consent is obtained from the subject or the subject's legally authorized representative. The board is made up of physicians, dentists, lawyers, nurses, dietitians, psychologists, administrators, ethicists, medical record librarians, chaplains, educators and sociologists. The IRB is made up of Adventists as well as non-Adventists, and includes individuals not connected with Loma Linda University as well as university employees.

Between August and November 1983, the IRB debated Bailey's proposal to begin clinical trials. They requested more data on his animal research and suggested improvements in the proposed consent form. Initial one-year approval was granted in early November 1983 by a majority vote of the IRB with the provision that any substantive changes or additions to the research protocol be resubmitted for review and approval. In that same month, Cyclosporine, so important in preventing rejection, was released by the Food and Drug Administration for clinical use. Previously, Cyclosporine had been limited exclusively to research investigation.

On November 23, 1983, the first of a number of institutional, departmental and academic committee reviews took place. At an administrative meeting called by Harrison Evans, M.D., vice president for medical affairs at Loma Linda University, Bailey requested and received assurance from the administration of Loma Linda University Medical Center that it would fund five xenograft heart transplants for newborns dying of HLHS. At this meeting, a review of the protocol by external scientific consultants was advised. Subsequently, key executive members of the board of trustees of Loma Linda University Medical Center were informed by private and informal discussion of the proposed xenograft operation.

Over the next few months, the departments of surgery and pediatrics again reviewed the scientific merits of Bailey's clinical research proposal. John Mace, chairperson of the department of pediatrics, appointed an ad hoc committee to work with Bailey on criteria for the selection of a recipient of the proposed heart transplant and on details of nonsurgical pediatric care. The group included neonatologists, pediatric cardiologists, nephrologists, allergists, neurologists, and a specialist in pediatric infectious diseases. At the invitation of the pediatricians, Robert Ettinger, M.D., transplant immunologist from the University of California at Los Angeles, conducted an external review and made a number of recommendations.

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Winter/Spring 1984

In early February 1984, as chairperson of the department of surgery, I asked Jack Provonsha, M.D. Ph.D., chairperson of the hospital ethics

committee, to consider several areas of ethical concerns, including the financial costs in relation to institutional resources, the future quality of life of the research subject and the potential difficulty of explaining scientific concepts to parents in an understandable manner so they would be able to provide an adequately informed consent. Hospitalization for four to six weeks was expected to cost approximately \$30,000 for each transplant, about the same as adult heart transplants at Stanford University. However, complications which might occur could significantly increase that figure. Long-term Cyclosporine medication to control cardiac rejection might also be complicated by kidney damage, which over a period of time might eventually require kidney transplantation.

We also wondered about the emotional impact on the parents. Would it be harder for the parents if their child were to die within six or nine months from graft rejection rather than a few days after birth, before they became strongly attached to the infant? Of course, the possibility of obtaining a human heart donor for an infant six months of age would be much greater than for a newborn; therefore, the primate-to-human heart transplant might serve as a bridging operation until a human heart donor might be found.

I also mentioned other questions that were being raised by some scientists who perceived the higher primates as being closer to humans and therefore in a different category from animals raised for food. Does a group steeped in the sacrificial system of the Judeo-Christian tradition have less sensitivity to the idea of sacrificing an animal for the benefit of a human than a scientific humanist or a follower of Eastern ideologies and philosophy?

The alternative, of course, to attempts at surgical repair of HLHS is certain death for the infant.

Provonsha has reported that as it considered these difficult questions, the ethics committee held paramount the concept that

the benefit from new clinical research must outweigh the potential risks. Ultimately it seemed to the committee that a primate xenograft offered at least as great and possibly greater therapeutic hope than previous rarely-successful surgical reconstructions (such as the Norwood procedure) or a human heart transplant for which newborn heart donors were virtually nonexistent. Most important was to insist that therapeutic goals be sought in addition to purely experimental ones.

Meanwhile, Bailey submitted an abstract of his xenograft heart transplant research to Jack G. Copeland, M.D., professor and chief of the section of cardiovascular and thoracic surgery at the University of Arizona and president of the International Society for Heart Transplantation. In a letter dated February 17, 1984, Copeland wrote that Bailey's paper on cardiac xenotransplantation had information of great merit and stated: "... I think infant heart transplants should be tried and see no reason that they should fail."

The transplant committee of Loma Linda University Medical Center met on February 21, 1984, to consider clinical details of Bailey's proposal for cardiac xenotransplantation. Theodore Mackett, M.D., chairperson of the transplant committee, submitted to the department of surgery a report of the committee's discussion, which included moral and ethical considerations, analysis of the animal research data, and a suggestion that either Norman Shumway, M.D., or Stuart Jamieson, M.D., from Stanford University conduct a site visit to review the project.

Six days later, on February 27, 1984, the department of surgery again reviewed the progress of Bailey's research. Bailey noted the xenograft efforts by other pioneers such as James Hardy, M.D., Keith Reemtsma, M.D., and Thomas Starzl, M.D., and reviewed recent advances in immunology, tissue matching, and newer methods of rejection control. During vigorous and challenging debate, members of the department of surgery made a number of sugges-

tions, including the possible benefit of irradiating the donor heart, the advisability of performing cardiac transplants between two different species of primates before moving to the human, and the possibility of testing human-primate transplant tolerance by transplanting a cadaver human newborn heart to a baboon.

Bailey noted that transplantation between the baboon and other species of primates was difficult since most other primates were considered endangered species and were thus not available for experimentation, with the possible exception of the chimpanzee. However, the chimpanzee breeds very poorly in captivity, and since one of the bases for Bailey's expectation for success included the relative immaturity of the newborn immune system, the likelihood of obtaining adequate numbers of immature chimpanzees for cross-species transplanta-

tion was remote. The suggestion for transplanting a cadaver newborn heart to a baboon would be difficult to carry out because of the great size disparity between the larger human newborn heart as compared to the newborn baboon heart, and successful transplantation from human to baboon would not necessarily ensure success of transplantation in the opposite direction. Bailey's surgical colleagues, who had contributed the bulk of the funding for his research, urged him to continue his program but not to proceed with clinical implementation until review by consultants from outside Loma Linda University.

On March 7, 1984, Stuart Jamieson from Stanford University made a site visit to Loma Linda. At Stanford, Jamieson has worked for many years with Shumway in the adult heart transplantation program. He has also done extensive laboratory research in

Research Reports by Leonard Bailey

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cardiac and heart-lung transplantation in primates. Jamieson reviewed Bailey's work in detail and in a written report to Bailey stated:

"I am . . . enthusiastic about your ambitious proposal which I do *not* believe is ill-conceived or irresponsible. Clearly at a time when we are facing a critical shortage of donors, and in particular donors in the pediatric group are almost impossible to obtain, it behooves us to investigate the possibility of once more turning to xenotransplantation."

Jamieson advised that it would be important to prevent a baby's immediate death as a result of rejection of the baboon heart by pre-formed antibodies in the baboon to the human model. In previous experiments in cross-species transplantation, immediate (hyperacute) rejection had sometimes been noted in which the transplanted organ was rejected violently within hours, or even before the operation could be completed.

Jamieson suggested that such a possible hyperacute rejection could be ruled out by perfusing an isolated baboon heart with oxygenated human blood using a heart-lung machine. If the baboon heart could be kept beating for 12 hours with perfusion by human blood without showing signs of immediate rejection or abnormal microscopic findings suggesting rejection, then there would be hope for legitimate clinical application. In a later interview with a reporter from the *New York Times*, Jamieson stated that he was impressed by the work that the team at Loma Linda University had done. He felt the problem had been approached systematically and conscientiously and he strongly supported the scientific procedures used by the Loma Linda doctors. Elsewhere Jamieson has stated that his suggestion for the isolated baboon perfusion was one of the few recommendations he made because Bailey's animal research had been so extensive.

Over the next few weeks, Bailey carried out the experiments proposed by Jamieson and, utilizing blood donated by various

members of the research team, demonstrated that the isolated baboon heart could be perfused with human blood without sign of the feared hyperacute rejection.

While Bailey was carrying out Jamieson's research recommendations, a medical meeting was being held in China in the spring of 1984, which was attended by Ralph Harris, M.D., a nephrologist on the ad hoc committee of the department of pediatrics. While attending the China medical meeting, Harris heard Sandra Nehlsen-Cannarella's discussions on complex problems in immunology. Nehlsen-Cannarella, Ph.D., had

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**—Stuart Jamieson, M.D.
Stanford University**

trained under Sir Peter B. Medawar, who received a Nobel prize in 1960 for his studies on modification of the rejection of skin grafts between species. During a private conversation, Harris sought Nehlsen-Cannarella's opinion on the immunological aspects of Bailey's research proposal. Upon her return to New York, Nehlsen-Cannarella sent a long letter to Loma Linda in which she supported Jamieson's proposal for isolated perfusion of the baboon heart with human blood and also suggested a number of additional specialized serum and cellular tissue matching studies.

In May 1984, Bailey presented his cardiac xenograft research to the Western Thoracic Surgical Association in Maui, Hawaii. Craig Miller, M.D., associate professor of cardiovascular surgery at Stanford University,

subsequently notified Bailey that his paper on sheep-to-goat heart transplantation had been accepted for publication in the *Journal of Thoracic and Cardiovascular Surgery*.

Summer/Autumn 1984

During the last week in August 1984, Nehlsen-Cannarella presented a seminar at Loma Linda University on the subject of transplantation immunology and agreed to participate in ongoing laboratory and clinical research. During the next three months, the results of the preliminary tissue typing studies suggested by Nehlsen-Cannarella proved to be most encouraging. The blood bank of San Bernardino participated by screening units of blood for anti-baboon antibodies and identifying units of human blood which could be safely used during the primate-to-human xenograft heart transplant. Bailey reviewed and completed treatment and procedure protocols with the cardiac surgery nursing staff, the operating room nurses, the department of anesthesiology, the public relations office and the infectious disease committee. He conferred with campus security regarding protection of the animal quarters housing the baboon colony. The updated research protocol and revised consent form were submitted to the IRB in late October 1984 and were approved.

During the third week in October, a baby with congenital heart disease was referred to the Loma Linda University Medical Center from Barstow. An echocardiogram confirmed the diagnosis of HLHS. The neonatologist, Douglas Deming, M.D., explained the lethal nature of this congenital heart deformity to the mother, along with the limited options available, including the rarely successful two-stage palliative Norwood procedure. Bailey was out of town at the time, but when he returned, the mother was contacted by phone. She was offered the

additional option of returning to Loma Linda to discuss with Bailey the possibility of primate-to-human heart transplantation.

On October 19, 1984, after consultation with the pediatric department and with concurrence of the School of Medicine and Loma Linda University Medical Center administration, the chairperson of the department of surgery authorized Bailey and his team to proceed with the necessary tissue typing in anticipation of performing the transplant. I consulted with the anesthesiologists and informed them and the operating room personnel that the operating room was cleared for Bailey's cardiac xenotransplant, and the detailed procedure protocols were set in motion.

Nehlsen-Cannarella flew out to Loma Linda from New York and supervised the meticulous week-long process of tissue typing and comparing Baby Fae's tissues with individual baboons in the primate pool, using human volunteers and the infant's parents as controls for comparison. During this same week, while Baby Fae was placed on life support systems, Bailey had a series of extended discussions with the baby's family regarding the operative and nonoperative options available. With the assistance of slides and drawings, Bailey explained the primate-to-human heart transplant proposal. He also offered the mother the option of the experimental Norwood procedure. In an interview given to the press at the time of the Baby Fae transplant, Norwood stated that he had done approximately 100 first-stage procedures for HLHS. While it is true that he obtained a 45 percent survival rate of the first stage, of those 45 survivors, only four had become candidates to undergo the second stage; and of those four, two had survived the second-stage procedure. At the time, therefore, only two percent of the original 100 had survived both stages. Aside from Boston, no other pediatric heart surgery center has been able to achieve significant numbers of survivals using the Norwood procedure. Baby Fae's mother indicated that she did not wish to

pursue that type of experimental option.

On October 23, Bailey again discussed with both biologic parents all the issues confronting the baby in the presence of four witnesses, including an attorney, a patient representative and two nurses. Both parents signed the IRB-approved consent form. The following day, the board of trustees of Loma Linda University Medical Center held a transcontinental telephone conference, during which they were told of the impending primate-to-human heart transplantation. At a special meeting of the executive committee of the medical staff of Loma Linda University Medical Center on October 25, Bailey and Nehlsen-Cannarella summarized the week-long blood and tissue typing and immunologic studies on Baby Fae. The tests indicated that one particular baboon out of the pool of available primate donors provided a remarkably close match. The infant's father was the only match better than "Goober," the baboon donor finally chosen. With this encouraging indication of significant therapeutic hope for this particular infant, the executive committee approved the transplant.

The actual operation on Baby Fae went very smoothly. She did not suffer immediate rejection. Bailey directed her postoperative care with the support of specialists from a variety of disciplines in surgery, pediatrics, hematology, immunology, and infant heart surgery nursing care. In keeping with the international outreach for which Loma Linda is known, the daily staff conference included 16 to 18 specialists from the United States, Mexico, South Africa, Vietnam and England. Although the majority were members of the Seventh-day Adventist Church, the team also included representatives of the Buddhist, Congregationalist, Jewish and Mormon faiths. Messages of support came from many of the major medical centers with the most experience in cardiac surgery and organ transplantation, including James Hardy at the University of Mississippi, Keith Reemtsma in New York, Johns Hopkins University, the Cleveland Clinic, the Hos-

pital for Sick Children in Toronto, Stanford University, and centers in Europe and other parts of the world. In an article for the *Cape Times* of South Africa for November 26, 1984, Christiaan Barnard concluded a discussion of Baby Fae's surgery by stating:

"The problem faced by Baby Fae's surgeons is that her situation was desperate. . . . It is lonely out there at the edge of human knowledge, and there are no prizes for losing. Baby Fae's doctors did their skillful best with the odds given them. For that reason, gentlemen, I salute you."

Since the Baby Fae surgery, referrals of potential infant and newborn donors have increased; essentially, a new potential donor population has been identified.

Shortly after Baby Fae's operation, there was a press report that an infant human heart had been available in Los Angeles the day of her surgery, but that Loma Linda University had not sought a human donor organ. Further investigation revealed that the Los Angeles donor heart was not available until 12 hours after the completion of Baby Fae's surgery, that the donor was two months of age, and that the heart was far too large to be used for Baby Fae.

Subsequently, Theodore Mackett, chairperson of the transplant committee, inquired whether a newborn human heart donor had been available during the 12 months preceding Baby Fae's operation. The Regional Organ Procurement Agency in Southern California stated that the availability of newborn hearts was so rare that no statistics had been maintained to date. However, since the Baby Fae surgery, referrals of potential infant and newborn donors have increased substantially; essentially, a new potential donor-recipient population has been identified since the Baby Fae operation. Anencephalic infants have not been

considered to date because of conflicting problems involving the "Baby Doe" legislation, but new criteria for legal salvage of organs from these anencephalic infants might provide a hitherto unused source of newborn human heart donors.

The department of surgery has requested and been granted approval from the IRB for an initial search for a possible human donor to be added to the transplant protocol for infants in the future who may require cardiac transplantation for HLHS.

Many poignant messages have come from parents of infants who have died because of HLHS. In letter after letter, these parents have written how much they would have

given to have had a little more time with their child and have urged Bailey to continue the important research.

The research program will go on. The large amount of information gained from the experience with Baby Fae's operation will be incorporated into updated therapeutic procedures to be reviewed by institutional review committees. As a result, infants born with hypoplastic left heart syndrome will have a better chance of living.

As Bailey said, "The Baby Faes and their parents are the real pioneers. The last thing her mom said to me was not to let this experience be wasted. We should honor that request."