Infectious Diseases in Latin America and the Caribbean: Are They Really Emerging and Increasing?

During 1995, infectious disease epidemics in Latin America and the Caribbean received wide publicity: dengue throughout the region, Venezuelan equine encephalitis (VEE) in Venezuela and Colombia, and hemorrhagic fever in Nicaragua. Increased awareness of these diseases followed extensive reports in the scientific community about the threat of emerging infections (1,2). Are infectious diseases increasing in the region or are we simply seeing the results of better reporting of persistent problems? Analysis suggests that both factors are at work.

Dengue and Dengue Hemorrhagic Fever

During the 1950s and 1960s, under the leadership of the Pan American Health Organization (PAHO), most countries in the Americas successfully reduced or eliminated infestation with *Aedes aegypti*, the principal vector of dengue and urban yellow fever. As a result, much of the Americas became free of dengue. Dengue transmission, however, persisted in many Caribbean islands and in some countries of northern South America that failed to control the vector; therefore, several outbreaks occurred during the 1960s and in subsequent decades (3).

Ae. aegypti eradication programs, however, were not sustained and the mosquito reinfested all Latin American countries except Chile and Uruguay. As a consequence, dengue spread throughout the region, causing severe epidemics or even pandemics during the 1970s and 1980s. Currently, dengue is endemic in virtually all countries with *Ae. aegypti*, and epidemics occur periodically.

Between 1968 and 1980, only 60 suspected or confirmed cases of dengue hemorrhagic fever (DHF) were reported, all by five countries in and around the Caribbean. After the 1981 DHF outbreak in Cuba, reports of DHF in the Americas markedly increased. The Cuban epidemic was the most notable event in the history of dengue in the Americas: almost 400,000 cases of dengue, over 10,000 cases of DHF, and 158 deaths were reported. The Cuban authorities implemented a successful vector control program and the country is still virtually free of *Ae. aegypti*. After this outbreak, cases of DHF continued to occur in the Americas, although at relatively low levels, until 1989 when another large epidemic with 2,500 cases of DHF occurred in Venezuela. Since then, Venezuela has reported large numbers of DHF cases every year, and in 1995 the country reported the largest outbreak of dengue/DHF in its history: almost 30,000 dengue cases and 5,000 DHF cases. Since 1968, 25 countries of the Americas have reported more than 35,000 confirmed or suspected DHF cases and approximately 500 deaths.

In 1995, dengue and DHF activity in the region was higher than in any year except 1981. As of November, countries in the Americas had reported more than 200,000 dengue cases and 6,000 DHF cases, and approximately 90 deaths. Brazil has had the largest number of dengue cases, but more than 80% of the DHF cases occurred in Venezuela. The reinvasion of the Americas by dengue virus type 3, which had been absent for 16 years, has increased the threat of large epidemics and consequent risk for DHF (4). This serotype was isolated in Panama and Nicaragua at the end of 1994, and in 1995 it spread to other Central American countries (except Belize) and Mexico, causing severe outbreaks. High levels of infestation with *Ae. aegypti* are common from the United States to Argentina, making it likely that dengue epidemics will increase in frequency and severity.

Cholera

Another disease reemerging in the Americas is epidemic cholera, which had been absent from this hemisphere for approximately 90 years before it was introduced into Peru in January 1991 (5). Since then more than 1 million cases of cholera have been reported in 20 countries in the region. Only Uruguay and the islands of the Caribbean have been spared. Though the annual total of reported cases has decreased since 1991, the disease is persistent and problematic in several Latin American countries.

Venezuelan Equine Encephalitis

An outbreak of human infection with VEE virus associated with a large number of equine cases and deaths was detected in northwestern Venezuela in April 1995. The disease spread to the adjacent Colombian state of La Guajira in September (6). Unusually heavy rains during 1994 and 1995 contributed to the epidemic by

increasing breeding sites for the mosquito vectors *Ae. taeniorrhynchus* and *Psorophora confinnis*. Viral strains with epizootic and epidemic potential appear to have emerged from enzootic strains maintained in enzootic rodent-mosquito cycles (7). In addition, failure to immunize wild and domestic equine populations allowed the virus to amplify and spread. By mid-October 1995, reported human cases totaled 26,500 in Venezuela and 22,300 in Colombia, with 24 deaths in the latter. Attack rates in severely affected communities were 18% to 57%.

This epidemic of VEE is the largest since that of 1962-1971, when the disease extended from northern South America through Central America and Mexico to the United States (8). Intensified vector control (including application of adulticides and larvicides), equine vaccination, and restriction of equine movement appear to have at least temporarily controlled the epidemic.

Leptospirosis

In late October 1995, Nicaragua reported several hundred cases of a hemorrhagic febrile illness in and near the community of Achuapa, approximately 110 km northwest of Managua; eight patients died. The affected communities had experienced unusually heavy rains and flooding during the 2 weeks before the cases were noted. Although dengue was occurring elsewhere in Nicaragua at the same time, that diagnosis was excluded by negative laboratory tests and the absence of *Ae. aegypti* in the local area. In addition, some of the patients had frank pulmonary hemorrhage [not typical of dengue]. By the end of October, the Centers for Disease Control and Prevention had ruled out dengue, other arboviruses, and hemorrhagic fever viruses as causes but had identified leptospira by immunohistochemistry in tissues from four patients with fatal cases. By mid-November, the Ministry of Health reported that 2,480 persons had been ill, 750 were hospitalized, and at least 16 died. (Investigation to define the extent of illness and the responsible serovars was still in progress at this writing.)

Of the examples discussed here, dengue and DHF are certainly reemerging. Dengue has been signaling its return for more than 15 years and DHF since 1989; these diseases will likely persist as epidemic problems unless drastic changes in vector control are achieved. Enzootic VEE has persisted in northern Venezuela and Colombia since the previous major epidemic of 1962-1971. PAHO had urged the countries to increase vaccination coverage of equines because of increased viral activity in 1993 and 1994. The appearance in 1995 of strains similar to these of the 1962-1971 epidemics, with locally intense transmission, raised the possibility that VEE would reemerge as a major epidemic disease. Whether vigorous vector control measures and immunization programs have contained that threat is not yet known, but we must continue to regard the threat as real. Leptospirosis is a persistent, often under-recognized, problem to which the international community has paid relatively little attention. In Nicaragua, public health interest was sparked by concern that the epidemic of a new disease would pose a threat to other communities and countries, but attention waned as that threat diminished. Yellow fever, which is usually present in relatively low numbers in remote areas of South America, reemerged with force in Peru during 1995. At least seven departments of that country have been affected (470 cases and a 40% case-fatality rate by September 1995).

Several factors have contributed to the reemergence of infectious diseases in the Americas. Investments in public health have been decreasing because of economic recession and a shrinking public sector or have been diverted from infectious disease programs to other pressing problems (9). Human populations throughout the region have grown and become increasingly urban, with many living in inadequate housing without sanitation or potable water. At the same time, population and commercial pressures have led to the invasion of forests, exposing people to exotic agents and enzootic diseases, including yellow fever, rabies transmitted by vampire bats, arenaviruses, and others. Human behavior has contributed to epidemic plague in Peru and the rapid spread of diseases such as cholera. To this list can be added the effects of deforestation and habitat and climate change. Unusually heavy rainfall contributed to at least three of the epidemics considered in this commentary (10).

Infectious diseases (whether new or reemerging) are a real and serious problem in Latin America and the Caribbean. To combat the threat of these diseases, PAHO, with the participation of other institutions in the region, has prepared a regional plan to improve surveillance for emerging disease and enhance countries' ability to respond effectively by strengthening laboratory capacity, training, and research and by implementing prevention and control strategies. Ministers of health from countries throughout the region discussed and endorsed the plan at a meeting of PAHO's Directing Council in September 1995. Successful implementation of the plan will require committed action by public health authorities and collaboration and cooperation by many institutions and experts throughout the region.

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Microbial Threats and the Global Society

The public health threat of microbial organisms living in what can be regarded as one large global society was the subject of a recent interactive workshop sponsored by Tufts University's Education for Public Inquiry and International Citizenship 10th anniversary celebration, held at Tufts University in Medford, Massachusetts. The participants* discussed microbes as the harbingers of disease and society as both potential victim and guardian of health. Microbial threats were identified as new, reemerging, and not yet known.

The forum examined the many unanswered questions regarding the origin and causes of infectious disease agents. The failure of traditional treatments due to antibiotic resistance and the ineffective control and continued spread of infectious agents were also discussed. Participants addressed environmental and behavior factors that foster the "amplification" and "spread" of disease organisms: bathhouses conducive to the spread of HIV infection, homelessness and crowded living promoting the spread of tuberculosis, day-care centers that are ideal environments for the spread of drug-resistant pneumococcus.

In the context of the workshop at Tufts, analyses of emerging infectious disease issues generated insights about the political and social framework within which to address these threats to health: A minority group may be particularly affected by a new or reemerging disease, as was the case, for example, of AIDS in the gay population or tuberculosis in the immigrant and homeless population. These groups become valuable resources for understanding the factors leading to the emergence or reemergence of the disease and should be the focus of public health efforts for curtailing its spread. However, as the history of AIDS demonstrates, because of political concerns, investigative efforts are often delayed or inadequate to stop the spread of the disease.

An emerging or reemerging organism, however, propagates and spreads unhindered by the social concerns of its potentially infectable host. To microorganisms, the world is a single entity without borders. Microorganisms have more freedom than we do and also more genetic flexibility. Thus, in the contest between humans and microbes, we are at a disadvantage. We can neither easily acquire resistance mechanisms *against* the organisms, nor rapidly respond to an infectious disease problem in another country. The recent difficulties in dealing with a possible plague epidemic in India are just one example. Moreover, antibiotics which have been a front-line weapon against diseases are becoming increasingly ineffective, and new antibiotics to treat and contain drug-resistant bacterial strains are not available.

Inadequate microbiologic diagnostic capability—also the result of the national and international political climate—works to the advantage of emerging microbes. During the plague outbreak in India, laboratory facilities that could confirm the diagnosis were lacking. In the United States, similar inadequacies in laboratory diagnostic capacity interfere with rapid reporting of common community-acquired infections and their susceptibility to antibiotics. If physicians promptly knew what they were treating, the need for use of an antibiotic as well as the proper kind of antibiotic would be based on data, not guesswork.

The emergence of antibiotic resistance was not factored into strategic planning by public health authorities. If it had been, perhaps conditions could have been in place to handle it, as well as AIDS, tuberculosis, and other emerging pathogens. Insurance against devastating happenings in infectious disease has never been given the attention it deserves. Such insurance would have been helpful, not just in money, but also in expertise to forfend and then cope with the calamity, like insurance for earthquake damage to structure and other unexpected disasters. Should we not consider insuring our future by putting more money and expertise into basic research, into systems for surveillance, and into ways to curtail the spread of a disease once it has emerged?

To meet the demands of increased public health activity and to implement an "insurance policy" for the future, we need to be able to *communicate* the problem to a broad audience that sometimes has little understanding of the science. To some public health officials, recognition that an infectious disease problem exists is sufficient to address the problem. However, to those not trained in the field who may be making important policy decisions, the "public safety" aspect of the problem can be emphasized. Health, like crime and traffic, should become once again a major society issue.

Requests for increasing support for surveillance, education, and research must take into account current political and social priorities and

emphasize direct benefits to the U.S. population; international efforts should involve the collaboration of other countries.

Nongovernment agencies need to be enlisted in this public health effort; thus a larger portion of society will be involved in the fight against the ever-increasing threat of infectious diseases.

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Xenotransplantation: Risks, Clinical Potential, and Future Prospects

The reemergence of xenotransplantation as a therapeutic option for the hundreds of thousands of people dying each year of heart, kidney, lung, and liver failure has raised ethical, social, and scientific questions. End-stage organ failure is one of the most important public health problems facing Americans today. Heart failure, for example, kills four times as many people as does HIV infection and three times as many people as does breast cancer; it is a disease with an increasing incidence, and the cost of taking care of affected patients is 8 to 35 billion dollars each year. The single most effective therapy for it is transplantation. Preventive therapies have had little impact on diseases due to end-stage organ failure and are unlikely to have an impact at least in the next decade. In the meantime, demand for organs, which far outstrips the supply, continues to grow. It has been estimated that approximately 45,000 Americans under age 65 could benefit each year from heart transplantation, yet only 2,000 human hearts are available annually. Patients are more likely to die waiting for a human donor heart than in the first 2 years after transplantation.

Although clearly an experimental procedure, xenotransplantation between closely related species, such as baboons and humans, offers an alternative to allotransplantation as a source of human organ replacement. Alternatives to allograft donors, such as baboon or pig xenografts, require serious investigation if clinical transplantation is ever to meet the current demand and continue the explosive growth pattern it has established over the past quarter century.

Biologic cardiac replacement poses the immunologic problems of rejection and infection associated with transplantation. Increasing clinical experience worldwide has shown that rejection and infection can be managed successfully in most patients who receive human cardiac allografts. Further, the introduction of cyclosporine as the primary immunosuppressive agent for cardiac transplant recipients has resulted in excellent survival rates (85% 1-year survival at most centers) and has decreased illness associated with infection and rejection. Although considerable advances have been made in the field of cardiac xenotransplantation since its first clinical application by Hardy in 1964 (1), it remains uncertain whether xenotransplantation as destination therapy can be successfully applied to humans. However, heart, kidney, and liver xenografts have been able to support human life for an extended period. It is this fact that investigators wish to exploit in clinical bridging studies. By providing temporary heart, kidney, or liver support as a bridge-to-transplantation, these biological devices may allow patients to recover end-organ function and await allograft transplantation in a more stable clinical state, thus improving their chances of survival. Bridging strategies cannot alleviate the human organ donor shortage. However, if one views bridging strategies as a first feasibility test, then cross-species transplantation does offer the possibility of eventual long-term organ replacement. Success in this more ambitious goal would help alleviate the human organ donor shortage.

Nonhuman primate organ donors have been favored by those wishing to minimize the genetic disparity between donors and human recipients. Chimpanzees, although most compatible with standard selection criteria (e.g., compatibility of size and blood types), are unavailable as an acceptable source of clinical xenotransplantation. Another choice is the baboon, which is not endangered, has an anatomy and physiology similar to those of humans, and grows to a weight of approximately 70 pounds. Baboon size would limit the clinical application of xenotransplantation with baboon organs to pediatric patients and small adults. Small body size, the infrequency of blood group O (universal donor) animals, and the limited number of colony-bred animals are distinct disadvantages to the baboon as a donor.

Extended graft survival is possible, but ABO blood group compatibility is mandatory before xenotransplantation (2). The distribution of ABO blood groups found in baboons indicates that approximately one third are group A, one-third group B, and one-third group AB. Universal donor group O, however, is exceedingly rare. In Americans of Western European descent, the relative frequency of blood types is approximately 45% group A, 8% group B, 4% group AB, and 43% group O (2).

Although available in large numbers, wild baboons are not suitable from an infectious disease perspective. Most experts have suggested that colony-bred animals represent a more suitable donor pool. However, these animals number only in the hundreds and are, therefore, only likely to

partially meet the epidemiologic demands of the pediatric population with end-stage organ failure.

Xenotransplantation between baboons and humans raises the issue of xenozoonoses (3,4). The organisms of greatest concern are the herpesviruses and retroviruses, which can be screened for and eliminated from the donor pool. Others include *Toxoplasma gondii*, *Mycobacterium tuberculosis*, and encephalomyocarditis virus. Less likely to be found in animals raised in captivity in the United States are the filoviruses (Marburg and Ebola), monkeypox, and Simian hemorrhagic fever virus. Organisms that are unlikely to be transmitted with an organ transplant (but should be screened for) include lymphocytic choriomeningitis virus, gastrointestinal parasites, and GI bacterial pathogens.

The risk for xenozoonoses is likely to be restricted to the xenogeneic tissue recipient. Nevertheless, one must consider and anticipate the potential for xenozoonotic transmission through the human population, constituting a public health concern. The risk for recognized zoonotic pathogens can be reduced, if not eliminated, by controlling the donor animal vendor source and the individual donor animal by employing described screening tests and strict sterile procedures during organ harvesting and donor autopsy for tissue and blood. The risk for unrecognized pathogens is present but ill defined.

Surveillance for the transmission of known or unknown pathogens among health care workers must be conducted by monitoring for unexpected or unexplained adverse health events. It is difficult to monitor for the unknown; therefore, surveillance should include notifying the principal investigator's office of any unexplained illness in exposed health care workers, as well as telephone interviews of these personnel every 6 months by the principal investigator's office.

Concurrent with scientific advances in xenotransplantation have been the necessary ethical debates concerning the appropriateness of this endeavor (5). Disputes regarding animal experimentation notwithstanding, the ethical issues raised by many of these debates are strikingly similar to those put forth 25 years ago in reference to the (then new) field of human heart transplantation. Indeed, the timeless nature of these queries itself attests to their essence, for such ethical concerns are appropriate in the appraisal of *any* new therapeutic procedure in medicine.

Can one ever hope to determine if or when the clinical application of xenotransplantation is justified? The assessment of any experimental therapy, as Fox and Swazey (6) have suggested, should encourage the investigator to address three critical questions: 1) in the laboratory, what defines "success" sufficient to warrant advancement to the clinical arena? 2) under what clinical conditions should this advancement proceed? and 3) in the clinical arena, what defines "success" sufficient to warrant further evaluation (6)? Providing answers to this threefold inquiry requires a reliance upon defined "success," itself an appraisal of judgment that can only confidently be made in retrospect.

Because human heart transplantation is now considered by most justifiable for the treatment of end-stage heart disease, I would first like to review the history of cardiac allotransplantation in light of its ability to address the above threefold inquiry. I will also discuss the history of cardiac xenotransplantation with reference to scientific advances made in the field throughout the past quarter century. Finally, in light of these analyses, I hope to illustrate the role of baboon heart xenotransplantation as an alternative to allotransplantation for permanent cardiac replacement in the treatment of end-stage heart disease.

After the first human cardiac allograft procedure performed by Barnard in 1967 (7) the field of cardiac transplantation witnessed a surge in both enthusiasm and attempted trials, which was followed by a marked drop in procedures throughout the 1970s because of poor survival rates. During the initial peak, 21 human heart allotransplants were performed in the 6-month interval between December 1967 and June 1968 (with a cumulative 1-year survival of 22%), and 105 cardiac allotransplantations were performed in 1968 alone (8-10). However, these early clinical trials were marred by numerous failures, as 65% of persons undergoing the procedure before June 1970 died within 3 months of transplantation (6).

Few centers continued animal research and human procedures during the so-called black years of cardiac transplantation. The initial explosion in clinical trials accordingly elicited numerous responses suggesting that too much was being attempted too soon.

Some would propose that this was the price of eventual "success," and that further experimental studies at the time could not have avoided early

losses. And yet, there has been, and may always be, a tacit recognition by medical innovators that the ultimate experiment must be performed in humans, for no animal model can truly reflect the human condition. Proponents of allotransplantation at the time of the first heart transplantation cited the more than 60-year history of experimental cardiac transplantation, beginning with Carrel's original work in 1905. Although most of this work began in the 1930s, subsequent investigations regarding the experimental transplantation of mammalian hearts showed that cardiac transplantation was technically feasible and suggested the possibility of clinically relevant survival rates. During the decade before Barnard's first clinical application, cardiac allograft survival had been shown to exceed 250 days (mean 103 days) in adult dogs treated with an immunosuppressive regimen that included azathioprine and methylprednisone used intermittently. The mean survival in untreated dogs used as controls was 7 days (11).

Since that time, with further expansion of knowledge in virtually all areas of clinical cardiac transplantation, 1-year survival has increased from 67% in 1976, to approximately 85% reported currently at most hospital centers (3). Human recipients have survived for as long as 20 years after transplantation, and the 10-year posttransplant survival rate is now approximately 45% (12). While these figures depict a clear improvement in raw survival, cardiac transplantation is still not a cure for end-stage heart disease. Recipients must take immunosuppressive medication for life and be monitored for infection, rejection, and graft arteriopathy. However, these results are impressive considering that the recipient population today is considerably sicker than earlier allograft candidates. In light of these findings, few would deny cardiac allotransplantation its present claim to "success." To further understand the evolution of this achievement, however, we may now look back upon the early years of cardiac allotransplantation and try to address the proposed threefold inquiry.

First, for Barnard and co-workers what can we presume as "success" warranting advancement to the clinical arena? They performed the first human adult cardiac allotransplantation when the maximum survival in immunosuppressed adult dogs had been 250 days (average survival 103 days) (11) and suggested that "against the background of this research . . . the time arrived when a cardiac transplant could be contemplated with hope of success" (7). Indeed, in their report of this case, they further described the scientific basis of their clinical advancement by explaining that "this achievement did not come as a surprise to the medical world. Steady progress toward this goal had been made by immunologists, biochemists, surgeons, and specialists in other branches of medical science all over the world during the past decades to ensure that this, the ultimate in cardiac surgery, would be a success" (7). Although we may, in retrospect, consider them justified in their declaration, in fact, at that time the endeavor was highly controversial and came as a surprise to much of the medical world.

Second, under what conditions did they proceed with this clinical trial? Given the "hope of success," Barnard and colleagues selected a patient "considered to have heart disease of such severity that no method of therapy short of cardiac transplantation could succeed" (7). The patient, a 54-year-old man, had remained in intractable congestive heart failure (following multiple myocardial infarctions) despite all medical management (13).

Finally, in this clinical arena, what defined for Barnard and colleagues "success" warranting further investigation? A concurrent editorial in the *South African Medical Journal* may provide some insight into their thinking: "The claim 'successful' can be used even at this early stage because to-date it is a feat which makes medical history, no matter how short the further survival of the patient might be (4). "Success," by such an analysis, was thus not targeted posttransplant survival time, but rather *any* posttransplant survival time (given the ground-breaking nature of the endeavor). Further editorials regarding the ethics of cardiac transplantation viewed the procedure as a legitimate experiment but not a treatment (15), while in 1968, the American College of Cardiology suggested (with regard to the "success" of allotransplantation) that results varied: ". . . the spectrum of success ranges from short-term restoration of circulation to complete physical recovery" (16).

Indeed, "success" did vary along a spectrum of results. Barnard and colleagues' first allotransplant recipient lived for 18 days and ultimately died of pneumonia. However, their second recipient, 1 month later, survived more than 19 months before dying of chronic rejection (17). Their third

patient also lived more than 20 months after allotransplantation and ultimately died of carcinoma of the stomach without signs of acute or chronic rejection (18). One can only speculate how different the world reception to allotransplantation would have been had the latter two patients represented the first and second recipients of cardiac allotransplants. Would these survival data be considered "success," or would they still pale in comparison with the theoretical goal of obtaining a graft that could function normally indefinitely?

Clinical cross-species transplantation dates to the early twentieth century, with kidney xenografts from rabbit, pig, goat, non-human primate and lamb donors (19). After these early failures, the scientific literature was largely devoid of reports of clinical xenotransplantation for nearly 40 years. In 1963, Reemtsma and colleagues described six human recipients of chimpanzee kidneys, the longest survivor of whom died of causes unrelated to rejection 9 months after xenotransplantation (20).

The first cardiac xenotransplantation, performed by Hardy in 1964, also represented the first attempt at cardiac transplantation in humans, predating Barnard's report by nearly 4 years (1). Since 1964, when Hardy and colleagues at the University of Mississippi performed the world's first heart xenotransplant using a chimpanzee as a donor, there have been eight documented attempts at clinical heart xenotransplantation. Five of these donors were nonhuman primates (2 baboons, 3 chimpanzees) and three were domesticated farm animals (1 sheep, 2 pigs) (21-25). The longest survivor was a newborn infant with hypoplastic left heart syndrome. "Baby Fae" was the recipient of an ABO-blood group mismatched baboon heart that functioned for 20 days (26). However, by the time the first human neonatal cardiac xenotransplantation was performed by Bailey in 1984 (the so-called "Baby Fae" case), there had been only limited experimental experience with prolonged graft survival in the newborn xenotransplant recipient. Studies presented by Bailey and co-workers shortly before the Baby Fae case described a mean survival time of 72 days in newborn lamb-to-goat xenotransplants, with one survivor living to 165 days (27).

This advancement of xenotransplantation into the clinical forum was met with resistance in the medical community because of a perception that research with acceptable survival "success" had not been achieved experimentally. As Losman in an editorial regarding the Baby Fae experience stated, "It appears that this baboon-to-infant transplantation did not rest on such a [scientific] basis [as did Barnard's earlier operation in 1967] "(28).

During the past 3 years, investigators at the University of Pittsburgh reported two cases in which they transplanted a baboon liver into a human recipient, obtaining a 70-day survival in their first reported case, and a 26-day survival in the second (29; J.J. Fung, pers. comm.) The investigators' overwhelming effort to prevent rejection led them to use a harsh immunosuppressive regimen that permitted multiple life-threatening infections. Rejection was not the major clinical obstacle they encountered; therefore, they recommended a more directed and less arduous immunosuppressive regimen for future patients.

More alarming have been the attempts to apply xenotransplantation of distantly related species to the clinical arena. In 1968, both Cooley and Ross transplanted sheep and pig hearts, respectively, into dying human recipients (30,31). Both grafts failed upon reperfusion, presumably because of hyperacute rejection.

More recently, Czaplicki and co-workers in 1992 described a case in which they attempted the xenotransplantation of a pig heart into a human recipient with Marfan's syndrome (32). By their report, no evidence of hyperacute rejection was present at the time of death nearly 24 hours after xenotransplantation. Their protocol used an unusual immunosuppressive regimen in which both donor and recipient received, in addition to conventional immunosuppression, both thymic tissue extracts and fetal calf sera. This regimen also included the extracorporeal perfusion of two pig hearts with the recipient's blood in an attempt to remove human anti-pig antibodies before the orthotopic transplantation of the functional pig heart (33). As astonishing as this case may be in its extension to the clinical arena of a technique not yet shown to be effective in the experimental laboratory, it is not unique. Also in 1992, Makowka and colleagues transplanted a pig liver into a 26-year-old woman dying of acute liver failure from autoimmune hepatitis (pers. comm.). Despite the fact that, at present, it appears unlikely that sufficient "success" has been achieved in the laboratory regarding xenotransplantation between distantly related species to warrant

advancement to the clinical arena, these investigators were able to obtain approval from their hospital's ethics committee and institutional review board to proceed with the clinical trial. Most experts in the field of xenotransplantation share the opinion that pig-to-human organ transplantation remains at least 3 to 5 years from clinical trials.

Considerable advances in the field of cardiac xenotransplantation have subsequently emerged worldwide since Hardy's first clinical attempt in 1964, with a better understanding of the xenorejection process and a more sophisticated insight into mechanisms for its control. Extended graft survival has been achieved in a number of different experimental models, including a greater than tenfold graft survival in non-human primates treated with conventional cyclosporine-based immunosuppression (34,35) a more than thirtyfold increase in survival over controls described by Celli and colleagues in a rodent model (36), and survival beyond 1 year reported by Kawauchi and colleagues in a non-human primate model (37). These findings support the potential for achieving clinically relevant graft survival in humans.

The question is whether we have reached a stage in laboratory experimentation to justify further attempts at advancing cardiac xenotransplantation to the clinical arena. If we view the current status of experimental accomplishments in xenotransplantation with the same scrutiny as that of allotransplantation at the time of Barnard's endeavor, we are left with similar conclusions; first, comparable graft survival time has been achieved in animal models of xenotransplantation as was evident for allotransplantation before 1967. Second, with our current understanding of cardiac allotransplantation has also come a greater awareness of its limitations. Thus, the conditions for the advancement of xenotransplantation arguably could be fulfilled by a patient with end-stage heart disease who is a candidate for allotransplantation, but for whom a donor cannot be identified in time. Finally, the clinical "success" of xenotransplantation might also be considered (as was the case for allotransplantation) *any* graft survival, and the goal of xenotransplantation to strive for extended graft survival.

However, political and scientific sensibilities today clearly differ from those of the 1960s, and so the critical assessment of xenotransplantation must be more rigorous than our previous discussion. Indeed, the above comparison was put forth largely to underscore the more humble origins of the (now) successful therapy (allotransplantation) to which xenotransplantation is currently compared.

What then defines "success" in the laboratory warranting advancement from the laboratory to the operating room? Having demonstrated dramatic prolongation of cardiac xenograft survival through experiments in rodent and non-human primate models (27,34-37), which model most closely approximates the human condition (and thus which therapy will be most successful in avoiding clinical rejection) remains to be established. Therefore, it is reasonable to suggest both that we have reached a formidable limitation for precisely predicting the applicability of experimental laboratory evidence and that answers may only be sought from experiment in humans. This concept was realized by the American Medical Association with regard to allotransplantation, in reference to which it released an official statement acknowledging this notion in 1969 (38).

Concerns most commonly voiced with respect to the clinical application of xenotransplantation, however, pertain to a larger ethical controversy regarding human experimentation. Reemtsma, in a related comment concerning the Baby Fae case, suggested the following: "There is a widespread misperception that medical treatments and surgical procedures are easily classified as either experimental or accepted. In fact, all treatments have an element of experimentation, and new surgical procedures are based on extrapolations from prior work. . . . When does a surgeon decide to apply a new operation to a patient? . . . the decision is based on balancing, on the one hand, the experimental evidence suggesting that the procedure may succeed, and, on the other, the clinical urgency. . . (39).

Under what conditions will the clinical advancement of xenotransplantation proceed? For those initial patients in whom clinical xenotransplantation will first be applied, clinical urgency, in the complete absence of other suitable alternatives, undoubtedly will represent the motivating factor to proceed. Who will comprise this initial cohort? As Caplan has pointed out: "There would appear to exist a pool of terminally ill persons, both children and adults for whom no therapeutic alternatives exist or are likely to exist in the near

future. . . . It would [thus] appear ethically defensible to allow research involving xenografting in human subjects to proceed in those areas where no reasonable alternative to therapy exists (40). In this context, innumerable reservations have been voiced regarding the ethics of proposing alternative experimental therapies to such patients for whom therapy has either failed or is non-existent. However, with regard to clinical experimentation under these circumstances, one must also recall (as Shimkin has suggested): "To do nothing, or to prevent others from doing anything, is itself a type of experiment, for the prevention of experimentation is tantamount to the assumption of responsibility for an experiment different from the one proposed" (41).

What is the goal of the clinical application of xenotransplantation? The need for donor organs irrefutably outweighs the resources available, and mechanical devices and xenotransplantation have emerged as the two most promising alternatives to allograft cardiac replacement. Mechanical left ventricular assist devices (LVADs) have witnessed relative success as "bridges" in carefully selected patients with heart failure. (A "bridge" is a temporary method of life support designed to carry a patient indefinitely until a human heart can be found and transplanted. It is not a "destination" therapy.)

Criteria for LVADs exclude patients with biventricular failure, and (because of the relatively large size of the device) patients with a total body surface area less than 1.5 square meters (~120 lb). Thus, many women and virtually all children are not candidates for mechanical left ventricular assistance. As has been the case for Food and Drug Administration protocols using LVADs, proposed investigations involving biologic assist devices (xenografts), have sought to evaluate a short-term alternative to allotransplantation in patients for whom a donor heart is not immediately available, and death is imminent. Only candidates who meet criteria for heart transplantation, but do not meet criteria for LVAD insertion, would be considered for a heart xenobridge. Similar clinical scenarios have been proposed for other solid organ transplants. Since they were first introduced by Cooley in 1969, temporary mechanical circulatory support devices have become critically useful tools in the therapeutic armamentarium available to patients awaiting transplantation (42). Nevertheless, at present, the widespread application of mechanical circulatory support is limited both by patient selection criteria and by the temporary nature of the device. For excluded patients, as well as many adult male candidates. For excluded patients, cardiac xenotransplantation may be the only reasonable alternative to cardiac allograft replacement.

Investigations in clinical xenotransplantation have been accused of using "the guise of [being a] bridge-to-transplantation" to appear acceptable to Institutional Research/Ethical Boards (5). However, the use of xenografts (or mechanical devices) solely as bridges to allotransplantation will not increase the donor pool, and, therefore, successful permanent xenotransplantation must itself be seen as the target for future clinical investigations. The goal of these studies is thus not to engage, as Hastillo and Hess (5) would suggest, in the "premature use of unproven procedures in fellow humans," but rather to impact positively on the current shortage of human donor organs (6). In 1996, the clinical picture is no less bleak and the conclusions no less valid. The question that remains is not how but rather *when* xenotransplantation should advance to the clinical arena. Most of the uncertainties surrounding its advancement will only be answered by its undertaking.

In the foreseeable future, clinical xenotransplantation may achieve its targeted goal of extended graft survival. As was the case during the early years of allotransplantation, clinical xenotransplantation must persevere under the consideration of and often in spite of scrutiny by its most demanding critics, for while "success has a hundred fathers, failure is an orphan" (43).

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