EXPERT PANEL REVIEW

OF THE NHLBI

TOTAL ARTIFICIAL HEART (TAH) PROGRAM

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PREFACE

The National Heart, Lung, and Blood Institute asked Vallee L. Willman, M.D. to chair an independent, expert panel review of the Total Artificial Heart Program. The panel was asked to assess the need to continue targeted Institute-directed research to achieve long-term mechanical circulatory support. The panel carefully reviewed the field, discussed the issues, and reported their assessment and recommendations to the Institute. The Institute has accepted the panel's report and is considering the recommendations. The report is published herein and is available to all interested parties.

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EXECUTIVE SUMMARY

In response to the National Heart, Lung, and Blood Institute (NHLBI) Director's charge, the panel appointed to assist in the Institute's review of the Total Artificial Heart (TAH) program reports on its deliberations concerning continued NHLBI support of that program.

It is the panel's considered recommendation that NHLBI funding of the two ongoing TAH programs be continued through the stages of readiness testing, in-vivo animal verification and clinical trials. The level of support is not specified because it will depend on the rate of progress; the level of required verification of safety and effectiveness, as determined in conjunction with the NHLBI staff and regulating agencies; and the extent to which private developers and health care agencies contribute. As the devices move towards clinical application, it is appropriate that contributions by involved private developers be increased, particularly in the realm of hardware and technology. It is most important that in the clinical trial stage health care funding agencies assume responsibility for the components of patient care that are not directly related to the evaluation of devices. It is also of great importance that the NHLBI maintain an oversight role through clinical trials.

This recommendation has several bases. Paramount is the fact that chronic congestive heart failure persists as a major cause of morbidity and mortality. Apart from cardiac allotransplantation, which has limited applicability due to limited donor organ supply, there are no evolving methods of amelioration quantitatively or qualitatively comparable to that of mechanical assistance.

Some current ventricular assist devices (VADs), which derive from the NHLBI mechanical circulatory support program, can provide reliable biventricular support on a temporary basis, while others allow untethered activity during prolonged periods in patients responding to isolated left ventricular assistance. All continue to undergo improvement. They provide confidence in the promise of comparable accomplishments for the TAH. Although several biological, technological and socioeconomic nuances yet exist, it is judged that there are no insoluble problems that nullify the expectation of a clinically effective TAH.

Estimating the number of patients that will potentially benefit from TAHs was as troublesome for this panel as it has been for past review groups. The panel started by considering the number of patients from several background populations expected to benefit from mechanical assistance. It is estimated that currently 1 percent of the 250,000 patients annually undergoing cardiac surgery in the United States receive mechanical device support exclusive of an intra-aortic balloon pump. This support is overwhelmingly temporary with a very small percentage of these 2,500 likely to be appropriate candidates for TAHs. Currently, 20 to 30 percent of patients coming to cardiac transplantation are on mechanical support. The Institute of Medicine (IOM) panel (1991) proposed that there would be 35,000 to 75,000 candidates annually for mechanical

assist devices, assuming a wearable and effective device were available. The current panel, reviewing recent information on refractory heart failure prevalence in relation to age, systolic function, and clinical severity, estimates that 35,000 to 105,000 patients would be candidates for mechanical assistance. Using the approach of estimating from death statistics, the size of the population that would benefit from cardiac transplantation is 50,000 to 100,000. From all of these considerations, the panel judged that it was reasonable to anticipate that 100,000 patients are currently candidates for long-term out-of-hospital mechanical assistance. The percentage of this total group that will require a TAH instead of isolated left ventricular support is not accurately determinable; the panel estimates it to be from 5 to 10 percent, yielding a population of 5,000 to 10,000 annually.

Panel discussion did not disclose any ethical, public policy or quality of life issues that have not been discussed in prior reviews. The panel reemphasized the need for the NHLBI and the Food and Drug Administration (FDA) to jointly work towards eliminating the need for duplication of data acquisition in the process of moving from laboratory to clinical application. The panel also urged the establishment of a mechanical device patient registry and urged payers of health care to assume responsibility for funding appropriate components of care in the clinical trial setting.

The panel considers the contemporary employment of VADs an example of the considerable accomplishments of the NHLBI mechanical circulatory support program. It is not probable that development of assist devices would have occurred without the government support that is now being increasingly assumed by industry as clinically effective devices move towards marketing approval. The panel believes that funding of the TAH should take the same course.

EXPERT PANEL REVIEW OF THE NHLBI TOTAL ARTIFICIAL HEART (TAH) PROGRAM

I. HISTORY OF PROGRAM AND CHARGE TO PANEL

Late in 1996, the NIH awarded two contracts intended to bring two totally implantable orthotopic artificial heart models through the stage of preclinical trials in anticipation that clinical trials would begin in the first decade of the twenty-first century. Implementation of those clinical trials would be the crowning achievement of the NHLBI Artificial Heart Program initiated thirty-five years ago to address the problem of end-stage cardiac disease through the application of new medical and surgical technologies.

Initial efforts in the artificial heart program, spurred by the enthusiasm to apply technology to the practice of science, led to the realization that replacing an essential organ with a mechanical device was an unattainable short-term goal because of the nature and extent of attendant mechanical and biological problems. The revised assessments of time and effort required to achieve the goal of the artificial heart program, along with increased concern as to the ultimate economic, ethical and social implications of this technology resulted in extensive discourse in both the scientific and public domains. The program has undergone many technical and non-technical (legal, ethical, social) evaluations both within and outside the NHLBI. The productivity of the program in elucidation of biological phenomena, development of a variety of effective devices of an assistive rather than replacement nature, and the albeit slow but nonetheless steady progress towards the initial goal, along with the nagging persistence of the problem of end-stage cardiac disease, have inevitably led to recommendations for continued support of a program in mechanical circulatory assistance which has included the TAH design. Detailed reviews of the program have been presented in the 1991 IOM report, *The Artificial Heart* and the NHLBI *Report of the Workshop on the Artificial Heart: Planning for Evolving Technologies* (1994).

Anticipating completion of the statement of work under the current funding, the Director of the NHLBI judged it appropriate as a part of a contemporary assessment of the TAH program objectives to convene this panel. The charge to the panel did not encompass another exhaustive review; it was rather to assess the need to continue targeted research to achieve long-term mechanical support.

The panel addressed their charge by directing attention to the following considerations:

- the continuing role for the TAH in the treatment of end stage cardiac disease, giving consideration to development of other therapeutic or preventive modalities.
- an assessment of the remaining scientific and technological obstacles to attaining a successful TAH.
- review of public policy, quality of life and ethical issues related to the TAH.
- the ongoing roles of government and industry in the continuing support of research, development, clinical testing and application of the TAH and mechanical circulatory support.

- estimation of the need for government support, and if so, duration, method, and level.

The panel first met on July 15, 1998 for a briefing by the NHLBI staff and a status report by the current contractors. Panel members reviewed the most relevant material from recent published literature and from specific program reports. They reconvened on October 30, 1998 to discuss and plan this final report.

II. STATE OF THE ART

Ventricular Assist Devices

The initial goals of circulatory support were to rescue patients with cardiogenic shock and reverse myocardial injury in the acute phase. For the most part, this technology was applied to patients having undergone cardiac surgery who either could not be weaned from cardiopulmonary bypass or developed shock in the postoperative intensive care unit. A number of devices have been employed for several years so that meaningful data have accumulated concerning the utility of these technologies. Listed in Figure 1 are the available devices at the time of this report (September, 1999).

Ventricular Assist Devices (VADs) in Use as of September 1999 (Figure 1)

Type of Device	IABP	ECMO	Centrifugal pumps	Abiomed	Thoratec	Novacor	HeartMate
FDA Approved Indications	Recovery or Bridge	N/A	N/A	Recovery	Recovery or Bridge	Bridge (investigational)	Bridge (electric-investigational)
Position	Intra-aortic	External	External	External	External	Internal	Internal
Ventricular Support	Partial Left	Complete Cardio-pulmonary	Left, Right, or Both	Left, Right, or Both	Left, Right or Both	Left only	Left only
Patient size	Small-Large	Small-Large	Small-Large	Small-Large	Medium-Large	Large	Large
Average Duration	Short	Short	Short	Interrmediate	Intermediate to Long	Long	Long
Power Source	Pneumatic	Electric	Electric	Pneumatic	Pneumatic	Electric	Electric or Pneumatic
Cannulation Site	Peripheral Arterial	Peripheral Arterial and Venus	Arterial	Arterial	Arterial or Ventricular	Ventricular	Ventricular
Native Ventricle	Remains	Remains	Remains	Remains	Remains	Remains	Remains
Anti-coagulation	Not necessary	Yes	Yes	Yes	Yes	Yes	No
Patient Ambulation	No	No	No	No	Yes w/assistance	Yes	Yes
Patient Discharge	No	No	No	No	No	Yes	Yes (electric)

Except for centrifugal pumps, all these devices are approved by the FDA for the applications indicated. The more complex devices are suitable for longer-term support while others, such as the Abiomed system, are clearly designated for post-cardiotomy support only. While all of these devices are currently available on the market or through FDA trials, most centers in the United States utilize only one or two of them because of the obvious expense in maintaining multiple devices.

It is currently estimated that about one percent of the 250,000 patients annually undergoing cardiac surgery in the United States receive some type of VAD support. Estimates of post-cardiotomy intra-aortic balloon pump (IABP) use are as high as 12 percent in some centers and the survival rates of patients supported with balloon pumps after cardiac surgery range from 20 to 50 percent. From these data, one might deduce that there is a greater need for ventricular assist devices in post-cardiotomy patients than is currently being met. The most commonly used post-cardiotomy devices are the Bio-Medicus centrifugal pump and the Abiomed VAD. Extracorporeal membrane oxygenation (ECMO) systems have gained some popularity in recent years but have limited effectiveness in the post-cardiotomy period due to the need for anticoagulation and the risk of bleeding.

A major factor in post-cardiotomy support is the presence of right ventricular failure and the need for bi-ventricular devices. This need can be met by ECMO, centrifugal VADs, and the Abiomed and Thoratec VADs. The incidence of bi-ventricular support in post-cardiotomy patients often exceeds 50 percent. However, in individual series, the use of a single left ventricular assist device has had much more success than bi-ventricular devices. Less commonly, there has been successful application of right VADs using IABP for left-sided support.

The success of post-cardiotomy VAD support is related to several factors including the time interval of device application, the presence of an acute peri-operative myocardial infarction, the presence of massive bleeding, and the development of renal failure. While the primary goal of application of assist devices in most of these patients is recovery of ventricular function, some of the devices can be used to bridge patients to transplantation if recovery does not occur. For example, the Thoratec VAD has been used successfully to bridge post-cardiotomy patients to transplantation if there was insufficient myocardial recovery.

While the overall survival rate for patients undergoing post-cardiotomy support is a disappointing 25 to 30 percent, these patients would almost certainly have died if not supported. Therefore, it is important that development continue for devices that can be applied expeditiously in the operating room and that can supply bi-ventricular support, ideally, without anticoagulation. It is also important to develop methods of determining which ventricles are likely to recover so that more specific applications of these devices may be made, particularly in patients who are not candidates for cardiac transplantation. Determination of irreversible failure of both ventricles would provide rationale for replacing the heart in post-cardiotomy patients with a TAH either as a bridge or alternative to cardiac transplantation.

The observation of the reversibility of operative ischemic injury led to the application of mechanical cardiac assist in selected instances of cardiac shock associated with myocardial infarction. Successes have been noted but the frequency of application is low; slightly more than one hundred have been reported.

The more common application of ventricular assist is in candidates for cardiac transplantation who are at risk of sustaining impaired organ function as a result of low cardiac output. Now, with the availability of implanted, electrically powered VADs with a wearable battery power source, patients formerly hospitalized on inotropic and other intensive medical therapy can be

discharged to home awaiting transplantation. The observed efficacy and safety has warranted the establishment of a randomized clinical trial comparing long-term course and outcome of patients with such implanted devices to those on a medical regimen in a population with New York Heart Association (NYHA) functional Class IV cardiac failure who are not candidates for transplantation. (REMATCH trial)

These longer-term and elective applications of assist device technologies employ one of a variety of pulsatile devices that are either extracorporeal or implanted, powered pneumatically or electrically, and tethered to a console or to a wearable electrical harness. Recently there has been considerable effort directed to the development of axial flow devices which are considerably smaller than the pulsatile devices, implantable either in intra- or extra-cardiac positions and driven by a wearable electrical source. One such device is reported to be at the stage of clinical use.

The following is a partial listing of the most commonly employed long term (weeks to months) devices for ventricular support, all of which were developed under the auspices of the NHLBI (Figure 1):

- Abiomed extracorporeal, pneumatically driven, pulsatile, left, right, or biventricular, introduced in 1988, is FDA approved for in-hospital use for low output syndrome.

- Thoratec extracorporeal, pneumatically driven, pulsatile, left, right, or biventricular is approved for in-hospital use for post-cardiotomy low output and as a bridge to transplantation.

- TCI (Heartmate) implantable, pulsatile pneumatically driven, is approved for in-hospital use as a bridge to transplantation. The electrically powered totally implanted configuration with a wearable power source, trans-cutaneous power lead and vent, is approved for in-hospital as well as out-of-hospital use for bridging to transplantation and is currently used under an IDE in the randomized REMATCH trial.

- Novacor implantable electric, pulsatile, left ventricular, wearable power source, trans-cutaneous power lead and vent, is approved for in-hospital and out-of-hospital use for bridge to transplantation.

Although neither the United States nor the world experience of VAD use has been accurately tallied, it is currently estimated to be above 6000 patients. Information from the four principal domestic VAD providers indicates that VADs are used in approximately 2000 patients yearly. Slightly more than 4000 have been employed as a bridge to transplantation. The incidence of VAD use has steadily increased so that currently it involves 20 to 30 percent of patients coming to transplantation. The periods of use in individual patients extend to over three years in two, two years in nine and over a year in ninety-five. Patient functional capacity on a VAD is judged to be comparable to that of NYHA functional Class III (in some instances Class II) patients. Some patients are employed. Some attend school. The dramatic unloading of the left ventricle with the mechanical assist devices has been associated with histologic, biochemical, and functional myocardial improvement. The native heart has demonstrated adequate function

following device removal in 75 cases, but there is no systematic long-term follow-up of these patients, some of whom have developed later deterioration. In NYHA Class IV patients with critical hypoperfusion and progressive organ dysfunction, there is evidence that the improved organ function following VAD application improves the outcome of transplantation. One multi-institutional non-randomized study of transplant candidates compared those receiving VADs and those receiving medical therapy. Of the 75 receiving a VAD, 91 percent of those transplanted survived 1 year compared to 67 percent of those treated medically.

Complications have been frequent. The most common has been bleeding related to anticoagulation and perturbations of the coagulation system. Choices of anticoagulation regimens and pump chamber surfaces have been found to influence both bleeding and thromboembolism. Infection has been troublesome and believed to be related to trans-cutaneous lines and to the compromised immune competence in severely ill patients. A review of more than 2000 patients from 73 centers reported clinically important infections in 25 percent of cases.

Thromboembolism, a frequent event in very early designs of VADs, has been strikingly reduced as a result of improvements in pump design. In a contemporary multicenter study, the thromboembolic event rate was reported to be 0.01 per patient per month. Data were available from 223 patients for a total support time of 53 patient-months.

The increasing use of VADs along with their increasing efficacy and decreasing complication rates is encouraging evidence for the successful development of a clinically effective TAH.

Total Artificial Heart

The first successful experimental animal implantation of a total artificial heart somewhat over forty years ago sustained the recipient for ninety minutes. This experiment encouraged the view that total replacement of the heart was an achievable goal. Persistent efforts in the ensuing years have provided steady progress toward that goal.

The first human TAH implantation in 1969 was in a patient who could not be weaned from cardiopulmonary bypass following cardiac operation. The intent was to sustain life while awaiting a donor heart. Transplantation was accomplished but the patient died thirty two hours later of sepsis and multiple organ failure. The second human TAH implantation (1981) was also in a post-cardiotomy patient employed as a bridge to transplantation. This patient died eight days following transplantation due to sepsis and multiple organ failure.

In 1982, at the University of Utah, the first of five patients had TAH implantation as definitive treatment of acute decompensation of chronic Class IV heart failure. Survival in these five patients ranged from112 to 620 days; complications were numerous and eventually fatal. Continued application of TAH as definitive treatment required further device refinements.

In 1985, at the University of Arizona, a modified and improved pneumatic TAH was tested as a bridge to transplantation. The application of a TAH in this setting has gained limited international acceptance. In 1992, the world experience of TAH implantation was reviewed. Between 1969 and 1991, eleven TAH models, all pneumatic and thus requiring trans-cutaneous

lines for connections to monitoring and drive systems, were implanted in 221 patients. The procedures were performed at 39 centers, 20 in North America, and 19 outside North America. Limited data on 15 patients treated at centers in Eastern Europe reduced the patients available for evaluation to 207 when studied in 1992. Device dysfunction occurred in seven (3 percent), most at the time of implantation and required device replacement. One patient died as a result of device malfunction. Of the 207 patients, 135 (65 percent) subsequently underwent orthotopic cardiac transplantation. Seventy three of these died following transplantation, 26 of sepsis, and 14 of donor heart rejection. Multiple organ failure, neurological events and a variety of other causes constituted the cause of death in 33. Of the entire group of 207, 32 percent (66) died while on the device. Sepsis was the cause of death in 33 percent (22 of 66) and multiple organ failure in 32 percent (21 of 66). The neurologic complication rate was 5 percent for stroke and 4 percent for transient ischemic attack. The Symbion Jarvik device had the best overall performances of the eleven TAH variations.

Since 1993, surgeons at the University of Arizona have been the principal investigators in a trial of the pneumatic Cardio West TAH (formerly known as the Symbion Jarvik-70) conducted under an Investigational Device Exemption (IDE) from the FDA. The intent of this device is as a bridge to transplantation. Of the114 patients worldwide that have received this device as a bridge, 24 have been at the University of Arizona and permit the most complete analysis. Of these 24 patients, the mean duration of device use has been 53 days ranging from 3 days to 186 days with one patient on the device for 42 days at the time of this report. Nineteen have been transplanted (79 percent of the total, 83 percent of those not currently on device support). All nineteen transplanted patients are surviving. Twenty of the total group of 24 (83 percent) are alive and 4 (17 percent) have died. One death occurred on the 124 th post-implant day due to device failure. A second death occurred at 22 days following device implantation in a patient who could not be weaned following coronary revascularization. The patient died of sepsis that dated to the time of implantation, when there was a positive culture of gram negative bacteria from the mediastinum. The third death was at 3 days post-implantation from multiple organ failure present at the time of implant and not reversed. The fourth death resulted from a problem with a central venous line that migrated across the right-sided inflow valve, freezing the disk in a closed position.

During the total 1274 patient days at the University of Arizona, there have been 4 episodes of bleeding, all occurring during the first post-implantation week. The most frequent complication has been infection, with a total of 40 instances: 13 upper respiratory, 7 urinary, 6 drive line, 5 related to decubitus ulcers, 2 mediastinal (both in the patient dying of sepsis), 2 gastrointestinal, 1 bronchial, 1 digital (of the great toe), 1 oral, 1 vaginal, and 1 at a cut-down site.

There have been 13 neurologic events; 7 TIAs, 2 strokes, 1 anoxic encephalopathy, 1 retinal hemorrhage, 1 syncope, and 1 seizure. Clinical manifestations of the strokes have resolved.

Evidence is thus accumulating to indicate steadily improving outcomes and efficacy of the TAH in providing a bridge to transplantation for patients that would not otherwise be satisfactorily managed.

III. STATE OF DEVELOPMENT OF DEVICES CURRENTLY SUPPORTED BY NHLBI CONTRACTS

The NHLBI has been supporting ventricular assist systems for more than 22 years and total heart replacement systems for 11 years through the contracting mechanism. Currently, 8 contracts exist which will terminate in September 2000; two contracts in total heart replacement, six in ventricular assist systems.

Total Artificial Heart Contracts

Two contractors are in the final stages of their research and development activities to demonstrate reliability and performance of TAH designs that evolved over a several year period. The design goal is for 5 years of failure-free performance. In vitro studies are conducted with the TAH in a mock circulatory loop with the goal of running 8 systems for 2 years without failure. Animal studies are conducted in calves to achieve 24 animal-months of failure-free operation. The NHLBI monitors these activities with the advice of a Data Review Board. The experiments performed under strictly supervised protocols are intended to qualify systems for clinical studies, and both contractors are in the process of preliminary discussions with the FDA with the aim of seeking an IDE within the next 2 years.

1. Pennsylvania State University

This program has a history dating to 1970. In 1976 there was limited patient application of a pneumatically driven device that evolved into the current Thoratec model. The program at Penn State, in conjunction with 3M/Sarnes Health Care, reoriented the device to one that is electrically driven with right and left sac-type blood pumps that are alternately compressed by a pusher plate. An intrinsic mechanism compensates for the right and left flow imbalances. The device is totally implantable. It is powered by inductive coupling of electrical energy across the intact skin. At the time of the beginning of the current contract period, 90-day pilot durability studies had been conducted and there were some design alterations yet to be made. During the current contract period, the design has been frozen and extensive in vitro studies have been conducted.

In the period from November 1993 to November 1996, a developmental version of the device was implanted in twenty animals. The duration of support varied from 2 days to 160 days (mean 36). Device problems were the reasons for termination in eight instances and prompted changes in device design or fabrication in seven. Respiratory complications were responsible for termination in five and contributed in three. Sepsis was the primary cause of death in three; one of these was associated with respiratory insufficiency. There were two thromboembolic strokes, one associated with sepsis as the cause of death.

From November 1996, the design has been frozen and through November 1998, prototype devices were implanted in six animals. One failed due to a surgical problem with fitting. One failed at seven days with sepsis and multiple organ failure. Two were discontinued the day of implantation due to device dysfunction; another at 34 days for poor pump performance in the presence of bleeding. One functioned for 88 days without event and was explanted according to protocol at that time.

2. Abiomed, Inc.

The Abiomed program began in 1988. In the decade since initiation, multiple variations of design and materials have matured to the reliability testing phase. The device, in its final design, is totally implantable. It has an electrohydraulic energy system placed between blood pumps, which fill and empty alternately. An intrinsic mechanism adjusts left-sided volume to compensate for the discrepancy between right and left output requirements. Energy is provided by trans-cutaneous transmission.

During the period between November 1993 and November 1998, fifty-seven animal studies have been undertaken. Twenty-two of these did not involve the totally implanted unit. The thirty-five studies employing the complete system between February 1996 and November 1998 have been in the current contract period. Considering the entire group, 36 of the 57 studies lasted less than ten days. The termination cause was overwhelmingly animal-related (26 of the 36). Device problems accounted for 10 of the 36. In contrast, in those 21 studies extending more than ten days (ranging 11 to 108 days), device problems caused termination of 14 (14 of 21); animal causes accounted for 6. One animal was electively terminated at 61 days. Many of the device problems have led to changes in device design or fabrication. The investigators have concluded that animal problems are manifest in the first three weeks, beyond which survival is governed more by the device.

Both the TAH contractors have completed an analysis of the design and manufacturing problems that have caused system failures. Corrective action plans were developed and reviewed by an independent, non-federal Data Review Board. This board approved the plans and the contractors are implementing the design, manufacturing, and quality control procedures that needed corrective action. New systems will be manufactured and reliability tests will be restarted in the fall quarter of 1999.

Innovative Ventricular Assist Systems Contracts

Six contracts were awarded in 1996 for 5-year research and development efforts to design and test ventricular assist systems that have the potential to provide significantly improved performance with reduced size and high efficiency, over currently available systems. These systems are intended for long term use, i.e., exceeding 5 years.

1. Nimbus, Inc.

In conjunction with the University of Pittsburgh, an axial flow pump is being developed and tested. It has ceramic bearings and is lubricated by the plasma. It will be able to deliver either pulsatile or non-pulsatile blood flow. The design is complete and animal experiments ongoing for more than a year demonstrate thrombus-free operation. Computer simulation studies are continuing at Pittsburgh to improve algorithms for controlling motor speed. Preparations have begun for a pre-IDE submission to the FDA.

2. Cleveland Clinic Foundation

In collaboration with the Ohio State University, a centrifugal pump with blood lubricated bearings delivering non-pulsatile blood flow has been developed. It is driven by a specially designed motor that should be highly efficient and small in size. Short duration animal implants are being conducted to evaluate thrombus formation.

3. Transicoil Inc.

In collaboration with the Texas Heart Institute, a rotary blood pump is being developed and tested. The pump is placed within the left ventricle through the apex. The bearings are lubricated by blood. It delivers either pulsatile or non-pulsatile blood flow. Many animal experiments have been conducted and design changes continue to be made on the basis of these experiments. Several month studies in animals have demonstrated thrombus-free operation.

4. Abiomed, Inc.

Collaborating with the Columbia Presbyterian Medical Center, N.Y., a pump is being developed which is a hybrid of biologic augmentation and mechanical assistance in such a way as to eliminate blood contact with artificial surfaces, thus avoiding any thromboembolic effects. An innovative mechanism is being developed that wraps around the left ventricle and is energized to assist in the contraction of the heart. Animal experiments are ongoing demonstrating minimal myocardial damage.

5. Whalen Biomedical, Inc.

In collaboration with the University of Utah, a muscle powered heart assist system not requiring an external power source is proposed. Skeletal muscle, trained to behave similar to cardiac muscle, is wrapped around the heart and provides mechanical assistance. Animal studies indicate that good performance is obtained without damaging the myocardium.

6. Pennsylvania State University

The group has developed an improved electromechanical ventricular assist system with long life bearings and an adaptive control technique to deliver pulsatile blood flow. This device is an extension and improvement over a design that has been in use for many years.

IV. NEED OF TREATMENT FOR END STAGE CARDIAC FAILURE

The scope of the population for whom permanent mechanical circulatory support might be considered has been estimated by the IOM study (1991) and the NHLBI workshop (1994). Based largely on prevalence of heart failure diagnosis per decade of life and the population density by age, the IOM panel proposed that by 2020 there would be between 35,000 to 75,000 candidates yearly, dependent on such factors as the efficacy of the device, third party sponsorship and age considerations. This estimate assumed a wearable device would become available in 1997. Heart failure with relatively preserved ejection fraction, which accounts for over half of heart failure in

patients over 65, is associated with better cardiac output and prognosis and thus rarely serves as an indication for mechanical support, although symptoms, hospitalizations, and resource utilization are often similar to those in patients with low ejection fractions. An unknown number of patients will be excluded due to major comorbidities: for this reason this panels estimates that many of the patients over 80 years of age would be excluded. Assuming that most of the 1 million hospitalizations related to heart failure occur in patients with NYHA Class III and IV heart failure, and that there is a 40 percent rate of rehospitalization within the next year, one can estimate that there will be 350,000 patients under 80 years old with limiting symptoms and low ejection fraction. A comparable estimate of 250,000 has been made for the prevalence of advanced heart failure, defined as the presence of left ventricular ejection fraction <30 percent with persistent or recurrent symptoms limiting daily life (Class III and IV) despite use of currently available medications (*Report of the Task Force on Research in Heart Failure*, 1994 NHLBI). Many of these patients would be expected to respond to institution of currently available aggressive therapies for advanced heart failure, after which the population with persistent Class III to IV symptoms would be diminished.

Currently available therapies for patients with advanced heart failure include angiotensin converting enzyme (ACE) inhibitors at target doses based on major trials or as tolerated, diuretics to relieve congestion resulting from fluid retention, and digoxin to improve functional status and reduce hospitalization. Recent randomized clinical trials show a survival benefit of beta-adrenergic blocking agents in addition to ACE inhibitors, diuretics and digoxin in Class II and III heart failure patients. Also, a recent randomized clinical trial demonstrates a survival benefit of spironolactone in addition to ACE inhibitors in patients with severe heart failure. However, beta-adrenergic blocking agents are currently contra-indicated for patients with Class IV symptoms or recent clinical instability, in whom these agents can precipitate dangerous decompensation. Such patients often require individualization of therapy, which can include combinations of ACE inhibitors, nitrates, hydralazine, angiotensin-receptor antagonists, and additional diuretic agents such as spironolactone, which may have other beneficial effects. There is current debate regarding the value of hemodynamic monitoring to re-design therapy when severe hemodynamic decompensation is persistent or recurrent. Trials of inotropic agents have uniformly been shown to increase mortality. Clinics have arisen to provide intermittent or continuous outpatient infusions of the same drugs, in the absence of data indicating efficacy or safety. Although there are differences in the details of medical therapy provided, there is broad consensus that a critical component of advanced heart failure management is enrollment into a program providing education, activity prescription, and regular telephone contact.

It is difficult to estimate the population of patients with low ejection fractions who would fail to respond to the best available heart failure management. The most thorough trials of such therapy suggest 10 to 30 percent of patients may have “refractory heart failure” for a total population of 35,000 to 105,000 in the United States. These numbers, however, depend on the referral population and apply largely to potential transplant candidates, who are younger and have fewer comorbidities than the typical patient in whom permanent circulatory support would be employed. A different approach derives from the number of deaths attributed annually to causes which could have been prevented by transplantation, i.e., approximately 50,000 for patients under 65, with a doubling for every 5-year age increase (Evans). It is not possible to determine how many of these deaths could have been predicted in time to be averted by mechanical support

devices. Considering the disparate assumptions, these estimates are remarkably concordant and establish a working order of magnitude of 100,000 current candidates for long term mechanical assist.

The prevalence of refractory heart failure with low ejection fraction cannot be equated to the population in whom mechanical assist devices could be implanted. There is no information on how the comorbidities that render patients ineligible for transplantation impact device placement. Little is known about the rates at which heart failure patients move through diagnosis and deterioration prior to irremediable organ system failure. Such rates of flux would determine the steady state pool of mechanical support candidates, which could be smaller than the current estimates. Rates of flux into this population could in the future be diminished by increasing use of therapies, which may limit progression from mild heart failure to advanced heart failure. On the other hand, improved abilities to identify individuals susceptible to sudden death or the development of therapies to decrease sudden death in patients before and during deterioration may increase entry into this population. Once the quality of life has become intolerable, development of drugs offering symptomatic improvement while diminishing survival might appeal to some patients who would otherwise consider mechanical support.

V. THERAPIES FOR END STAGE HEART FAILURE THAT IMPACT ON NEED FOR TAH

Allotransplantation

Cardiac transplantation has established its effectiveness for the treatment of end-stage heart failure. The 85 percent immediate survivors, 65 percent five-year survivors and 40 percent ten-year survivors generally have good functional capacity. Currently, transplantation is strikingly limited by the supply of donor hearts, which number approximately 2500 yearly in the U.S. There is no optimistic vision for increase in donor organs in the near term.

Surgical Procedures

Surgical procedures currently offered or under clinical investigation are unlikely to substantially diminish the population of patients suffering refractory heart failure with low ejection fraction. Left ventriculectomy has not led to meaningful clinical improvement in the majority of patients and has been abandoned in some centers. In the absence of clear benefit, cardiomyoplasty is no longer under active clinical investigation. After routine options for revascularization have been exhausted, adjunctive therapy with growth factors or transmyocardial laser boring may be offered in investigational protocols, but these to date have excluded patients with severe left ventricular dysfunction. Mitral valve repair or replacement for regurgitation secondary to heart failure has been encouraging in small numbers of patients, but has not yet been applied in larger heart failure populations.

Xenotransplantation

It can be envisioned that the utility of biological replacement could be strikingly enhanced by the use of non-human hearts. Although clearly feasible from a technical perspective, xenotransplantation of the heart faces three significant hurdles. The first is the immunological

response of the host against the graft. Recent years have brought new information regarding the molecular basis of this immune response and the development of new therapeutic strategies including the application of genetic engineering of large animals for dealing with these immunological responses. Still, complete control of the rejection process has not been achieved. Permanent cardiac replacement through xenotransplantation cannot be anticipated, even on an experimental basis, in the next several years. If genetically engineered animals were to be used, widespread application would require further years for production of appropriate stock. The second hurdle is the possibility that the animal heart, particularly the porcine heart, would function inadequately when transplanted into a human. Few data are available to address this question. Yet recent studies have suggested that for at least a period of days to weeks, the porcine heart can in fact provide reasonable physiological function in nonhuman primates. Were the physiology of the xenotransplanted heart proven to be limiting, further manipulations, perhaps including genetic engineering, might be applied. The third hurdle is the possibility of transferring infectious organisms from the source animal to the recipients and from the recipients then more broadly in society. There are currently efforts in a number of laboratories in the United States and abroad focused on identifying organisms that might pose a risk severe enough to make xenotransplantation a public hazard. Currently these efforts focus on an endogenous retrovirus of the pig. Evidence of an agent being transferred to humans has yet to be found.

Despite these rather daunting hurdles, there is guarded enthusiasm that xenotransplantation will eventually be applied for cardiac replacement. It is most likely that the early application will be as a temporary measure such as a bridge to homotransplantation. This application might impinge on the need for temporary mechanical support but not on the need for long-term mechanical assistance or replacement. It is seen as an important step to verify current knowledge regarding the immunology, physiology, and infectious disease questions, and in identifying other unforeseen problems.

The two technologies of xenotransplantation and the TAH are not necessarily mutually exclusive. If xenotransplantation were to be applied widely, it is probable that a certain fraction would fail immunologically. An alternative to transplantation might then be needed for a significant number of patients given the empirical observation that immunological failure or rejection of any transplant increases the risk of subsequent rejection of a transplant.

In the light of all of these considerations, it is unlikely that xenotransplantation will achieve widespread application in less than five to seven years and should not be seen as alternative to the TAH.

Cellular Transplantation

The past decade has brought significant advances toward the application of cellular transplantation in the treatment of cardiac disease. The overall approach generally taken is to inject myoblasts derived from cardiac or skeletal muscle into affected myocardium. The transplanted myoblasts mature and then take on the function of cardiac myocytes augmenting myocardial function. Functional effects have been seen in small animals and there is no reason to think that this technology could not eventually be applied in the clinical setting. The extent to which this type of therapy can augment cardiac function under optimal conditions is not known.

Nor is it clear whether this type of therapy could be broadly applied for the treatment of cardiac failure. One limitation may be the ability of myoblasts to implant in damaged tissue. Another uncertainty is the extent to which cellular transplantation can effectively treat diffusely damaged myocardium.

If myoblast transplantation holds promise, a significant question would be the source of myoblasts which could be used for augmentation of myocardial function. Under ideal circumstances the cells would be taken from the individual to be treated. It is uncertain whether such cells could be isolated from skeletal muscle of older individuals. On the other hand, it may be possible to generate differentiated muscle cells from a variety of mesenchymal or other stem cells. There is the possibility that human or animal cells could be used; the immunological hurdles to cellular xenotransplantation appear to be lower than those of whole organ transplants.

Organogenesis and Tissue Engineering

Recent advances in cell and developmental biology and in the isolation of stem cells has encouraged the view that certain tissues and even organs might one day be produced "artificially". The application of this technology varies widely in difficulty. While the development and application of such tissues as skin and cartilage can be anticipated in the next several years, application for replacement of organs with a complex structure such as the heart would seem to be only a distant prospect.

VI. ROLE OF TAH IN TREATMENT OF END STAGE HEART FAILURE

Although the rather consistent estimates are that at least 50,000 and perhaps as many as 100,000 patients yearly might benefit from mechanical cardiac assistance, there has been no consistent estimate as to how many might be in need of a TAH. There is no evidence that imminently available technologies will dramatically decrease the need for mechanical assistance, or TAH in particular. However, as more mechanical support devices have become available, it is still uncertain how the correct device should be selected for each patient. The initial impression derived from post-cardiotomy experience was that biventricular support would be required for a majority of patients, reported by some centers to exceed 50 percent. More recent experience indicates a lower need for biventricular support in chronic heart failure, which may reflect in part differences in chronic heart failure and acute post-cardiotomy shock, and also the benefit of wider use of nitric oxide to reduce pulmonary vascular resistance. The current need for biventricular support when mechanical assist devices are used in chronic heart failure is estimated to be 10 to 20 percent, with a slightly higher proportion of patients post-cardiotomy and post-infarction who will be best served by replacement with a TAH.

Despite the prevalence of biventricular failure in patients with chronic heart failure, some, at least in the short term, now demonstrate resolution of severe heart failure symptoms with left ventricular support alone. The long-term persistence of this improvement is not yet established. It is not known how many patients are considered ineligible for isolated left ventricular support due to predominant right ventricular compromise, intrinsic valve disease, small left ventricular cavity size, complex congenital anatomy and other factors. There is also insufficient information regarding the long-term success of LVAD placement in patients with ongoing ischemia or

arrhythmias, although there are reports of progression of these conditions limiting the efficacy of the LVAD.

Long-term LVAD support is also frequently associated with severe systemic hypertension that could possibly be related to the nature of the isolated left-sided unloading.

Although it is not possible to determine at this time exactly how often total heart replacement would be required annually in the approximately 100,000 patients currently demonstrating refractory symptoms of heart failure with low ejection fractions, 5 to 10 percent (or 5,000 to 10,000 patients) would represent a conservative estimate. As discussed above, less is known about the population fluxes that would contribute to the steady state population of potential recipients once the TAH became available.

VII. REMAINING OBSTACLES TO ATTAINING GOAL OF CLINICALLY USEFUL TAH

Many of the obstacles remaining to successful implementation of the TAH are similar to those experienced with VADs. While considerable strides have been made in design of the TAH, two main obstacles to clinical success stem from the continued thrombogenic nature of the materials employed in the devices, coupled with design limitations that continue to require percutaneous lines. However, the newer devices are being designed without the need for a percutaneous lines. The surface thrombogenicity necessitates systemic antithrombotic therapy with the attendant risk of hemorrhage. Major remaining clinical complications with the TAH include infection, hemorrhage, end organ failure, thromboembolism and device dysfunction. Major causes of death with current TAH designs include sepsis, multi-organ failure, neurological death most likely due to thromboembolism, hemorrhage and problems with device fit. There is a delicate balance between hemorrhagic sequelae and thromboembolism that can be modulated by the antithrombotic therapeutic regimen, which remains to be optimized for most devices.

Thromboembolism

Thromboembolism in VAD and TAH recipients is thought to result from biomaterial surface-induced thrombus formation with systemic embolization. Considerable progress has been made in the development of materials with improved blood compatibility, but no materials developed to date are completely blood compatible and surface-induced thrombosis remains a real concern. Some devices employ a textured surface, which at first appears counter-intuitive. However, while the roughness of such surfaces encourages fibrin deposition and platelet adhesion, the development of an adherent pseudointima so formed may be less prone to embolization than thrombi forming on smooth surfaces. Indeed, the use of these textured surfaces has decreased thromboembolism from approximately 20 percent of patients (range 8 to 35 percent) to 0.01 events per patient-month (2.7 percent). However, optimism regarding the improvement in thromboembolism should be tempered by the fact that thromboembolism may be underestimated when only clinically evident events are recorded. The true thromboembolic rate may be higher as techniques such as transcranial Doppler detect microemboli in 34 to 67 percent of patients. Other features of device design that may encourage thromboembolism include non-physiologic hemodynamics and the increased heat caused by the device operation.

Macroscopic thrombi are commonly seen in VAD/TAH devices at explantation, but this has recently been improved by changes in device design. Clinically evident thrombosis in VAD/TAH recipients is most often cerebral thrombosis (20 to 47 percent), but is rarely fatal and the neurological symptoms are often transient. Non-cerebral emboli are seen in a much lower percentage of patients (approximately 9 percent). These are most often seen in the spleen and kidney and are usually subclinical. In one study, the occurrence of thromboembolism did not correlate with the duration of support or the adequacy of anticoagulation. However, platelet function was not monitored.

Antithrombotic therapy is considered essential to prevent thromboembolism with many of the current TAH/VAD designs. However, there is little agreement on anticoagulation protocols. A notable exception is seen with VADs utilizing textured surfaces, where antiplatelet therapy alone has been used with success. While use of antithrombotic therapy is generally employed, there is a great variability between centers in the use of antiplatelet vs. anticoagulant drugs, variability in implementation protocols and drug timing, and variability in whether hemostatic monitoring is used. There are few objective, prospective trials of antithrombotic therapy in this population on which to make recommendations. Part of the reason for the lack of clinical trials is the continually changing device designs, the relatively small numbers of devices implanted per center, and variability in the clinical use of anticoagulant therapy between centers.

Many of the newer device designs utilizing textured surfaces do not require the use of long-term anticoagulant therapy, but utilize antiplatelet therapy alone. In the TAH/VAD designs that do require some form of long-term anticoagulation, even though antithrombotic therapeutic regimens vary, heparin or dextran sulfate often is used in the early postoperative period once chest tube drainage decreases to acceptable levels, with cross-over to coumadin once the patient can ingest oral medication. Antiplatelet medications, such as aspirin, dipyridamole, clopidogrel or ticlopidine, are sometimes used, with occasional centers utilizing pentoxifylline. Many of these anticoagulant and antiplatelet medications are given empirically. Coumadin therapy is usually monitored by the PT/INR, with a suggested therapeutic range of 2.5 – 3.5, which was derived empirically. Antiplatelet therapy is rarely monitored by objective techniques.

One prospective study of a centrifugal VAD compared standard heparin therapy to a multi-drug antithrombotic regimen (La Pitie Protocol) with functional monitoring of hemostatic inhibition. The investigators found a marked decrease in bleeding (from 81 to 9 percent) with the multi-drug regimen without a concomitant increase in thromboembolic events. Other studies also suggest that monitoring of coagulation and platelet function may decrease bleeding risk. Due to the delicate balance between bleeding and thromboembolism with both antithrombotic therapy and variability in baseline hemostatic integrity, there may be a benefit in adapting antithrombotic therapy to individual patients.

Thromboembolism may also occur for reasons apart from the device itself. In patients receiving a univentricular VAD, persistent atrial fibrillation and thrombosis in the native ventricle due to poor contractile function may occur. Another potentially devastating, but rare cause of thrombosis in VAD/TAH recipients who are receiving heparin therapy is paradoxical thrombosis due to Heparin Induced Thrombocytopenia and Thrombosis (HITT). HITT is caused by an immunologic response to heparin complexed with platelet factor 4 and is manifested by

progressive thrombocytopenia while on heparin. In some patients HITT is associated with potentially lethal arterial or venous thrombosis. HITT has been reported in occasional VAD recipients and may necessitate cessation of heparin therapy. Alternative antithrombotic therapies include dextran with expedited conversion to oral anticoagulants, the heparinoid danaparoid, and a recombinant hirudin, lepirudin. Both danaparoid and lepirudin may be problematic during cardio-pulmonary bypass (CPB) if the patient is eventually transplanted because danaparoid cannot be monitored by activated clotting time (ACT) nor reversed by protamine sulfate and protocols for lepirudin use during CPB have not been established.

Hemorrhage

Perioperative hemorrhage occurs in about one third of patients receiving the TAH and remains a significant clinical problem. Bleeding is usually observed in the perioperative period or in the early postoperative period. Up to 50 percent of patients with VADs require reoperation for bleeding, although the operative use of the fibrinolytic inhibitor aprotinin may decrease both postoperative blood loss and the need for blood product transfusion.

The causes of hemorrhage in TAH recipients are protean and are associated with preoperative coagulopathies due to hepatic dysfunction or poor nutritional status, cardiopulmonary bypass (CPB)-induced thrombocytopenia or platelet dysfunction, and prolonged antibiotic therapy. This may be accentuated by the necessity of using antithrombotic therapy in some device recipients due to activation of both the coagulation cascade and platelets following exposure to the artificial surfaces of the device together with turbulent blood flow. In general, bleeding may be more of a clinical problem in patients who receive the TAH emergently following failed cardiac surgery with extended CPB or those supported for prolonged periods with extracorporeal membrane oxygenation. Conversely, the risk of bleeding is lower following shorter surgical implantation procedures. Bleeding may also be a significant problem during device explantation due to extensive adhesions.

Hemorrhage remains a significant cause of death in recipients of both VADs and TAHs. However, even if hemorrhage is not life threatening, it often necessitates blood transfusion. The transfused erythrocytes may be more prone to hemolysis by the device, and the increased hemolysis can lead to renal failure. The transfused granulocytes can also lead to alloimmunization, which may be a clinical problem during subsequent heart transplantation.

Infection

Infection remains a major cause of death and morbidity in TAH/VAD recipients. Infection is seen in 25 to 48 percent of VAD recipients and approximately 37 percent of TAH recipients. Infection during VAD implantation has been associated with a decreased probability of survival when used as a bridge to transplantation. Successful treatment of the infection may prolong the time to transplantation but does not appear to preclude it.

In a recent clinical study of the TAH, infections were most commonly noted approximately seven days post implantation, but infectious complications can be observed weeks to months after implantation. Most infectious complications are related to the device and often the use of

percutaneous drive lines has been implicated. Few clinical data are available from totally implanted devices, but the anticipation is that elimination of the trans-cutaneous connection with the totally implantable TAH will eliminate ascending infections. Drive-line related infections have included local infections as well as bacteremia and fungemia. Other device-related infections included abdominal pocket infections, colonization of surface-induced thrombi, and direct bacterial colonization of the device lining materials. The principal pathogens associated with device infection have been Staphylococcus aureus, Staphylococcus epidermidis, Coagulase-negative staphylococci, Enterococcus faecalis, Enterococcus faecium, Serratia marcescens, and Candida species.

Device recipients also may be susceptible to nosocomial infection due to long hospital stays, prolonged immobilization, and multiple intravascular catheters. In this regard, pneumonia and urinary tract infections have been reported. Recipients that receive a VAD after a failed cardiac transplant may be especially susceptible to infection due to their immunosuppressed state.

Prevention of infection in TAH recipients may, of necessity, be multifactorial. Elimination of trans-cutaneous lines promises to decrease ascending infections. Decreased thromboembolism may decrease infection by preventing thrombi, which can be a source for bacterial colonization. Changes in patient management may also be useful to decrease infections and may include gut sterilization, avoidance of central and arterial lines, and use of oral prophylactic antibiotic therapy. Some preliminary evidence, demonstrating reductions in CD4+T helper lymphocyte counts in recipients, potentially implicates device surfaces as a factor in altering immune competence. This finding is of uncertain clinical significance, but warrants validation and further investigation.

Multiple Organ Failure

Multi-organ failure has been reported to be the most common cause of death in a clinical TAH study, where it was observed in 10 of 12 patients who died (83 percent). Multiple organ failure is most likely due to the selection of patients receiving a TAH. Most instances of multi-organ failure are thought to be due to poor perfusion and early end organ dysfunction prior to implantation in patients in cardiogenic shock for whom the TAH was a last resort. This clinical obstacle should be lessened with improved patient selection and employment of the TAH before end organ dysfunction ensues.

Device Malfunction

Device malfunction is now relatively uncommon but is seen in approximately 4 percent of patients. The type of malfunction varies with the design of the device but is most often due to controller malfunctions. Occasional device failures have been due to valve dysfunction, drive line kinking and connector failure with loosening of the outflow conduit. TAH data from animal studies suggest that blood sac calcification may be a limiting factor to survival, but this may be a feature of using the rapidly growing calf as an animal model.

Correct fit of the device in the patient's thoracic and abdominal cavities is an important consideration in preventing device malfunction. Fit complications can be manifested by

compression of the inferior vena cava or pulmonary veins. Most current devices are designed for patients with a body surface area > 1.5 m^2 . In addition to measurement of body surface area, it has been suggested that the anterior-posterior dimension of the thoracic cavity may also be a useful indicator of device fit. Further improvements in device size may allow employment of TAH devices in smaller women and in children.

Other Obstacles

Infrequent complications of TAH/VAD implantation include hemolysis, anemia, chronic hypertension, and early satiety. Hemolysis, a common problem with centrifugal ventricular assist pumps, is infrequent in current TAH designs.

VIII. ECONOMIC, QUALITY OF LIFE, AND PUBLIC POLICY CONSIDERATIONS OF INTRODUCING TAH

Economic and policy considerations related to the TAH were reviewed in detail in the Institute of Medicine Report and in the NHLBI 1994 review of the TAH. Both of these reports provide an outstanding discussion of ethical and policy issues related to the development of the TAH. Given the limited scope of this review, these issues are not discussed in detail again. However, it was the conclusion of the panel that the excellent discussions and insight in these two previous reports be reconfirmed in this review.

Several specific issues were discussed during the panel meetings, which complement the previous work. Given the potential for implementation of the TAH technologies within the next decade, data need to be developed for several specific policy decisions that will have to be made by the Health Care Financing Administration (HCFA), by the Department of Health and Human Services (DHHS), and by private insurers. As with previous reports, these concerns fall into the domains of access, technology assessment, patient decision making and quality of life. Each of these will be discussed briefly.

In terms of access, it is expected that HCFA, through the Medicare program will be one of the major payers for the TAH. Current expectations are that the device itself will cost an estimated $75,000. Costs for implantation of the device, as well as subsequent follow-up medical care, are not known with certainty at the current time, but may add an additional $50,000 to $150,000 to the first year cost of this treatment. The absolute magnitude of these expenditures as well as the potential size of the population that may be impacted by this technology suggests that HCFA begin to consider how coverage decisions would be made, what type of treatment guidelines might be implemented or provided, and how access to the technology can be assured for the broad range of Medicare beneficiaries. The ability to develop specific clinical criteria to help identify those most likely to benefit from this technology is absolutely crucial. The increasing indications for and employment of implanted wearable out-of-hospital ventricular assist devices should be a stimulus to develop a comprehensive registry for cardiac assist devices that would track risks, efficacy and costs. This information is an essential first step in developing policy in this area.

One major contributor to the cost of the technology is the potential liability of the device manufacturer as well as suppliers developing specific components for TAH technologies. One important issue to explore is whether limited liability relief for these manufacturers could result in cost savings to HCFA. The program staff at the NHLBI are to be commended for their efforts to consider the cost of the device in the development of the technology. Further, the NHLBI has specifically fostered an environment where multiple companies are involved in the development of these technologies to try to foster competition in order to control the costs of the technology in the marketplace. However, specific issues related to technology transfer and the price of the TAH for individual consumers, or the Medicare program, should be explored further in light of the recent public concern about the market price of cancer drugs originally developed through the National Cancer Institute.

The second major issue is the role of technology assessment in helping to inform public policy related to the decision of whether or not to provide coverage for the TAH under standard benefit packages. The IOM report, as well as the 1994 NHLBI review, commented on the use of cost effectiveness analysis or cost utility analysis as an appropriate tool for informing these decisions. This panel did not review these considerations in detail but, instead, acknowledged that it was the responsibility of the payers to make decisions about coverage or benefit programs, and was not within the current mandate of the NHLBI to consider payment issues when deciding whether or not to pursue the development of a specific technology. However, given the increasing financial pressures on the Medicare program, there might be a need to consider the implications of this policy at a higher level of the DHHS.

The third issue discussed was patient acceptance of the technology. Here the panel felt that there was a tremendous wealth of experience that has been gained in recent years in terms of understanding the use of implantable cardiac devices in patients through both the left ventricular assist device, and the implantable cardiac defibrillator. Specific issues that will need to be clarified for individual patients considering the use of the TAH are the potential life style implications of the technology and the potential for terminating the use of the technology. Given the development of sophisticated patient decision making tools using video or computer technologies, and given the complicated consent process that would be envisioned for this technology, it is recommended that the NHLBI directly support research in these areas.

The final item for the discussion for this section of the report is the quality of life assessment of the TAH. Here, the issues are functional ability of individual patients who received the device, the potential for catastrophic failure of the device and the impact of this knowledge on patients. Research exploring quality of life for patients with mechanical devices has begun with the left VAD; however, a much more comprehensive assessment of quality of life will be required to fully understand the impact of these technologies on individual patients.

IX. ROLE OF GOVERNMENT IN FURTHER RESEARCH AND DEVELOPMENT

The commitment of NHLBI funds to the artificial heart program has always evoked the consideration as to whether it fit under the rubric of research or development, and, if the latter, whether it is an appropriate allocation for finite NHLBI resources. The deliberations of this panel did not result in a consensus resolution of these questions. The panel appreciated that an

investment has been made in TAH technologies and that the products of the effort have been considerable quite apart from the progress that has been made towards production of a clinically useful long-term implantable device. The contemporary state of VADs is informative as an example of the benefit of this research program. VADs are now being employed extensively, although in most instances under investigational protocols.

All of these devices have achieved their present potential as a result of NHLBI support. Arguably, they would not have progressed to the current state without that support. Now, as feasibility of the VAD concept is established and commercialization is imminent, it is judged appropriate that investigators and private firms identify non-federal support for the continued development and commercialization of these technologies. However, the federal government still has an important role in ensuring access to this publicly funded technology by negotiating technology transfer agreements that ensure a reasonable price for consumers while providing an appropriate return for technology development companies.

The panel uniformly endorses public support to bring the TAH to a comparable state of development. Once the proof of the concept of the TAH has been established, public support would seem appropriate only for innovations or new approaches that receive peer review support and provide sufficient expectations for public good to merit public investment. Federal efforts to ensure broad access to the TAH are required as well as for the VAD.

X. RECOMMENDATIONS

The panel recommends that the two TAH programs be supported through the stages of readiness testing, in-vivo animal verification and clinical trials.

The panel concludes that, as in previous reviews, a large population exists that could benefit from mechanical replacement of the heart. Recent increased application of ventricular assist suggests that this modality will be adequate for a portion of over 100,000 annual candidates but will not be applicable to 5 percent to10 percent that would be well served by a TAH. There are no other emerging therapies that can fill this need. The clinical experience with the use of VADs along with the progress made in TAH development supports the proposition that a clinically effective TAH is an achievable objective.

A specific level of funding is not determined but is judged to be comparable to the current level with the conviction that the current private subsidization should increase as commercialization approaches. The panel ardently believes that at the clinical trial level, health care funding agencies, public and private should shoulder their responsibility in funding those costs that directly relate to the treatment of the illnesses of the patients involved. The panel urges that the protocol for in-vivo animal verification be compatible with a protocol that would satisfy the FDA for issuance of an IDE for clinical trials. The panel also urges the establishment of a national obligatory registry, with oversight by NHLBI, for the collection of data from patients with VADs and TAHs so as to provide a means of assessing the physiologic, economic and social implications of this technology.

Reviewing this program on the eve of its potential transition to the clinical trial setting has highlighted the importance of questions raised in earlier reviews of the Total Artificial Heart Program. NHLBI has specifically acknowledged the importance of these considerations in reviewing the TAH over the last several decades. However, the NHLBI has not implemented a research agenda to begin to answer some of these specific questions raised in these reviews. It is the recommendation of this panel that if further funding for the TAH Program is approved, that funding for the research agenda addressing access to care, patient acceptance, and quality of life for recipients of the TAH be implemented concurrently. Further, it is recommended that this research agenda, especially the policy and patient's acceptance components, be implemented before clinical development in humans is initiated.

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ABBREVIATIONS

ACE	Angiotensin-converting enzyme inhibitor
ACT	Activated clotting time
CPB	Cardio-pulmonary bypass
DHHS	Department of Health and Human Services
ECMO	Extracorporeal membrane oxygenation system
FDA	Food and Drug Administration
HCFA	Health Care Financing Administration
HITT	Heparin induced thrombocytopenia and thrombosis
IABP	Intra-aortic balloon pump
IDE	Investigational device exemption
IOM	Institute of Medicine
LVAD	Left ventricular assist device
NHLBI	National Heart, Lung, and Blood Institute
NYHA	New York Heart Association
REMATCH	Randomized Evaluation of Mechanical Assistance for Treatment of Congestive Heart Failure
TAH	Total artificial heart
TIA	Transient ischemic attack
VAD(s)	Ventricular assist device(s)