原　　　著

Development of Total Artificial Heart

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Introduction

The term "artificial heart" may represent any type of man-made blood pump, intracorporeal or extracorporeal ventricular assist device, or a total heart replacement device. The first total artificial heart (TAH) replacement was performed in 1957 on dog that survived 90 minutes[2]. Since that time extensive investigation has been performed all over the world, and more than 50 different models of artificial hearts have been designed and used in animal experiments.

The initial goal of obtaining a 100-hour survivor, however, was not achieved until 1970[34], and in the past maximum survival time was selected as a common measurement of success. Particular milestones were survivals of ten days[26], two weeks[27], twenty-five days[20], one month[36], three months[37], 122 days[51],145 days[59], and six months[14]. In 1971 the first ten-days survivor was obtained[26]. The first two-weeks survivor was achieved in 1972 using deep hypothermia[27] ; and the first twenty-five-days survivor was attained in 1973[20]. Survival times were dramatically extended in 1974 to thirty and thirty-six days[36] in the early part of the year and seventy-eight and ninety-five days in late 1974[37]. In 1976 a 122-day survivor was achieved by saving the natural outflow valves in Salt Lake City, Utah[51], and a 145-day survivor was obtained with the biolized artificial heart by NOSE's group in Cleveland, Ohio[59]. Since then, many other groups reported longer than 100-days survivors all over the world using different materials, designs and animals[24] (Dr. ATSUMI, goat, 100 days ; Dr. PIERCE, automatic feedback system, 100 days ; Dr. BUCHERL, silicon rubber,

HISTORICAL RECORDS OF　　TOTAL ARTIFICIAL HEART RESEARCH IN UNIVERSITY OF UTAH, SALT LAKE CITY, UTAH

Year:	1967	1968	1969	1970	1971	1972	1973	1974	1975	1976	1977	1978
Record Survival Calves	◄----- less than 100 hours				No Name K-G 7D* (100 hr)	Latina K-G 7D* (1 wk)	Taro K-G 8D* (2 wk)	Crocker J3 DF† (25day)	Tony J3DF† (1mo)	Burk AOPA J3B† J3A† (3mo)(4mo)	Abebe J5B⁻ (6mo)	75% a month survival

		1967	1968	1969	1970	1971	1972	1973	1974	1975	1976	1977	1978
HEART	Material	◄-------- Silastic ----------------------►						◄--------------------- (only for DOE heart)------------					
			◄------- Latex ------►					◄- Dacron fibril -►		◄------ Biomer ---------------			
										◄---- Avcothane 51 elastomer ----			
	Housing					◄---- Kwan-Gett (8cm) -----►						◄--- Jarvik 7	
		◄- Green sack -►	◄---	Kwan-Gett (7cm) -----------►			◄------ Jarvik 3 --►		◄----------Jarvik 5 ------			
								◄--------► DOE**heart --------------------					
	Valve	◄-- Edward (ball)-----------►											
		◄-- Ham-Smith----►		◄--- Three leaflet (outflow)-►								
					◄------ Wada- Cutter ------►								
				◄------ Flap valve (inflow) --►									
											------- Saving natural valve--		
					◄--------------------------------Bjork-Shiley --------------------►								
Driver system		◄-- NASA --►	◄------- Kwan-Gett ----------►			◄-- Kwan-Wong --------►		◄------------- Utah -------------				
								◄---------------- Mechanical ----------------------------					
Assist in surgery				◄-------------------------------------- Heart - Lung Machine -----------------------------								
				◄-- Deep hypothermia --►									
		◄-- Transsternal --►	◄------Midsternal ---------				-(only for DOE)- --►					
								◄-------------------------------Right thoracotomy----------------------					

		1967	1968	1969	1970	1971	1972	1973	1974	1975	1976	1977	1978
POSTOP. CARE	Driving conditions	◄---- 6 PSI(left)& 4 PSI(right)---►				◄---6 PSI& 2 PSI--►		◄- 4PSI 2PSI ►	◄----- 90mmHg(r) 190mmHg(l) ------►			◄- 60mmHg(r) 160mmHg(l)	
		◄---- HR: 60-120 B/M -----►				◄--------90 B/Min.---►		◄---------- 90 B/M ----------- 90 - 120 B/M-----					
						◄-------- Vacuum (7cmH₂0)-----(15cm)------(5cm)--------------------							
	Drugs Other	◄-------- Diuretics --------------------►						◄---------- Exercise on treadmill -------------------					

Figure 1. *K-G= Kwan-Gett type heart,　D= Diameter in cm made from Silicone tur.;　†J-3= Jarvik 3 type haert, DF= Dacron fibrils, B= Biomer, A= Avcothane-51 elastomer;　**DOE= U.S. depertment of energey.

Fig. 1　Historical records of total artificial heart research at the University of Utah, Salt Lake City, Utah, since 1967.

121 days). Finally a six-months survival was achieved in Salt Lake City, Utah using the Jarvik-5 (J5) heart in 1977 and 1978[14,17].

These accomplishments were associated with particular advances in a prosthetic device's desingn and/or material, and its surface and/or surgical or postoperative management procedures and electronics (Fig. 1). The two-weeks survivor was implanted with an 8 cm Kwan-Gett Dacron velourcoated silastic heart implanted via midsternal split with hypothermia[27,52]. The twenty-four-days survivor was achieved with Dacron fibril-coated Silastic JARVIK-3 (J 3) ventricles implanted via a right lateral thoracotomy[49]. The seventy-eight-days and ninety-five-days survivors were obtained with polyurethane, smooth-surfaced J3-type hearts, and Utah heart drivers which were compactly equipped with alarm systems and emergency systems[37]. Thrombus generation within the artificial ventricles was dramatically reduced by changing the design of ventricles from the J3 heart to the J5 heart in 1976. The improved surgical techniques, such as the lateral thoracotomy[49], and saving the natural valves[59], and postoperative care utilizing the idealized monitoring air pressure waveform[15,16] and the automatic control feedback systems[35,58], increased the chances of long-term survival of calves with a TAH[24,17], and extended maximal survival time up to six months[14].
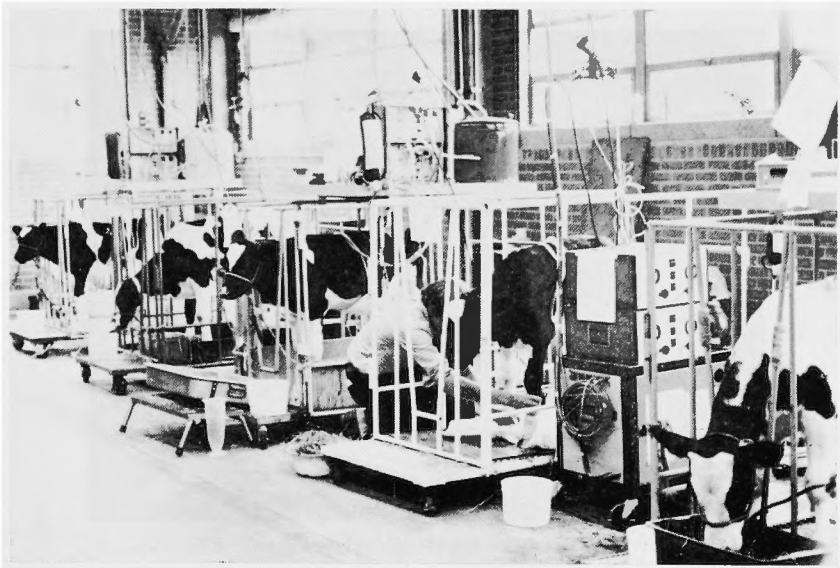
Fig. 2   Calves with a total artificial heart. Recently the healthy survival rate
is over 75% and the longest survival time has been over six months.

However, the goal of obtaining a 75 percent healthy survival rate beyond the early postsperative period (a month) in the animal experiments was not achieved until 1977 (Fig. 2). The complication and early morbidity rates had been higher than 75 percent in all laboratories in the world[24], which was a major limiting factor on the way to human application of the TAH[13]. This paper describes how we were able to increase the healthy survival rate to 75 percent in 1977 through 1978, and discusses major problems to be solved and our present ideas for future human application of the TAH.

Materials and methods

A. *Prosthesis and instrumentation*

We use three different types of TAH's : the pneumatically driven heart, the electromechanically driven heart and the electrohydraulically driven heart[43]. Since only the air-drivn heart can be considered almost ready for clinical application, the author will describe in detail only the air-driven heart in this section, and discuss a little bit about the electromechanically driven and electrohydraulically driven hearts later.

The J5 heart has been implanted in twenty-one calves during the last year since Jun 1977, in this laboratory. Fig. 3 is a picture of the J5 heart. It has two ventricles, which can be attached to each other with velcro. The ventricles can be attached to the artificial atria and to the artificial outflow tracts with quick-connects. Both the artificial atria and outflow tracts are sutured to the natural remnant atria and outflow tracts (PA and Ao). The housings of the J5 ventricles are hemispherical and the blood contact surface of the J5 ventricles has no sharp diaphragm-housing (D-H) junction (Fig. 4), but rather a con-
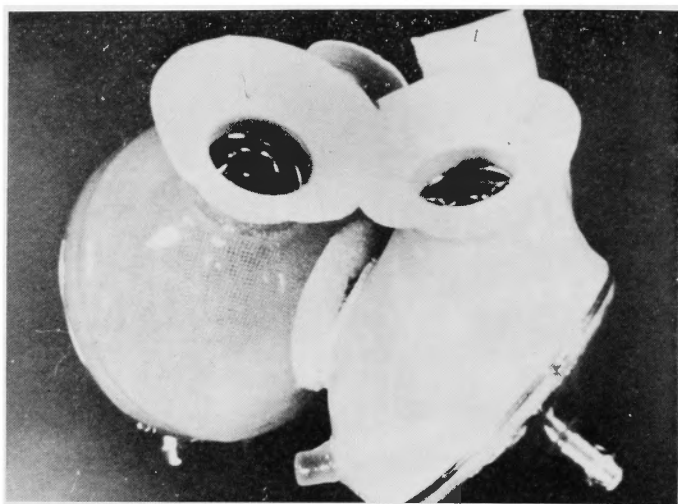
Fig. 3 Jarvik-5 ventricles made of polyurethane. This type of heart has been implanted in more than eighty calves since 1976.
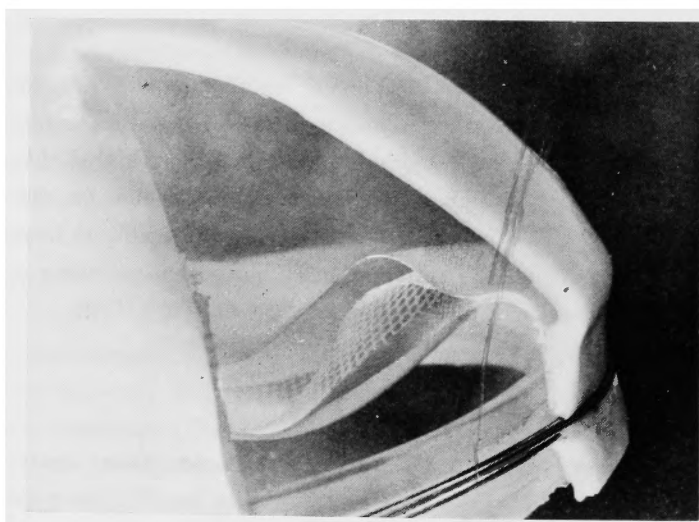

Fig. 4 A cross-section of the Jarvik-5 ventricle demonstrating no sharp diaphragm-housing junction, with thin layers of diaphragm shown.

tinuous smooth intima made of polyurethanes (Biomer[R] and Avcothane-51 elastomer[R]). The bases of the J5 ventricles are made of aluminum and are connected to the air drive lines, which are made of polyvinyl chloride tubing (3/8 inch) and covered with velour on those segments buried subcutaneously, and on the percutaneous junction to avoid or delay infections. In some cases a transcutaneous flange lead system is adapted to the percutaneous junction of the air drive lines. The air drive lines are seven feet long and are connected to the Utah heart driver (details are given later) at the other end. Björk-Shiley valves
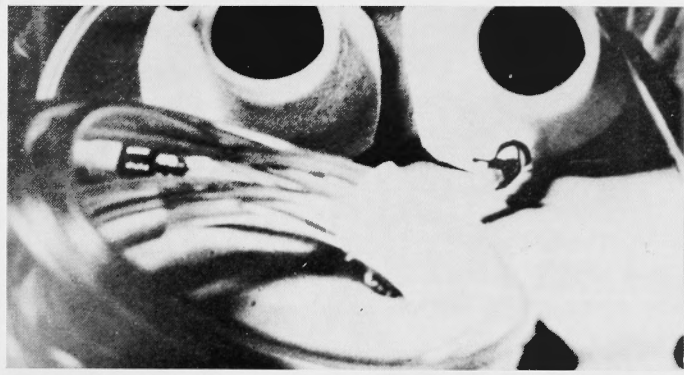
Fig. 5 Atrial cuffs with a pressure line. Recently the atrial cuffs are trimmed to an oval shape on the surgical table.

were used for the inflow valves. For the outflow valves, we used the natural valves, saving the natural PA valve and the natural aortic valve with the outflow myocardium (details later) in twenty cases, and the Björk-Shiley (B-S) valve in one case.

The artificial atria (atrial cuff) consists of a polyester felt and a flexible polyurethane quick-connect. During the last year we used two different types of surface on the artificial atria : the rough surface of the polyester felt and a biolized surface of the glycerol-treated porcine dura mater attached on the polyester felt. Both right and left atrial cuffs were trimmed from a round shape (Fig. 3) to an oval shape (Fig. 5) on the surgical table. The artificial outflow tract consists of a polyester-felf or Dacron woven arificial vessel and a flexible polyurethane quick-connect. The polyester-felt vessels were covered with polyure-thane (Avcothane-51 Elastomer[R]). The length of these outflow vessels was 0.5 cm for the right outflow tract and 0.7 cm for the left outflow tract during the last year.

Open catheters for monitoring postoperative hemodynamics when desired were built into both the atrial cuffs and the right outflow tract, and covered with velour on those segments buried subcutaneously the same as the air drive lines. Another end of the seven-feet open catheter was connected to an extracorporeal pressure transducer (Statham[R]). The tip of the open catheter in the artificial grafts was mounted with the polyurethane and fixed to the graft (Fig. 5). The ascending aortic pressure was monitored by the open catheter, which inserted retrogradely via the left coronary artery. Three ECG leads were mounted on the right atrial pressure line under the velour and were fixed to the natural remnant wall of the right atrium on the tips. An electromagnetic flow probe was placed around the main pulmonary artery, when wanted. Recording of blood pressures and flow, and the P-wave, was done with Hewlett Packard[R] multichannel scopes and recorders.

B. *Equipment to Drive the Jarvik-5 Heart*

The Utah heart driver has been used in all cases. It allows setting of driving pressures individually for right and left ventricles, and setting of driving rate and percent systole. It also has two dp/dt valves, which regulate steepness of the pressure raising curve for
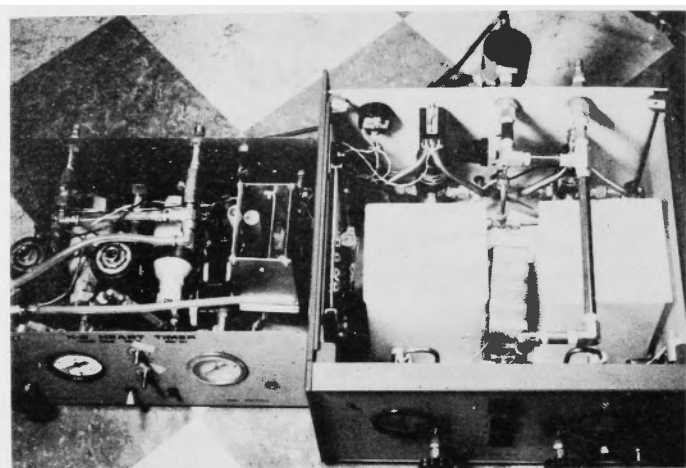
Fig. 6 The Utah heart driver (right) and the Kwan-Gett-Wong
heart driver (left). The Utah heart driver has several
alarm and emergency systems built into a compact console.

each side, and has a synchronization system so that the heart rate can be controlled by electrical impulses that are sent to it. Contrary to most other drive systems that have been developed, the Utah heart driver is an extremely simple system, but also includes several alarm systems and emergency systems in compact form (Fig. 6). Most recently the solenoid electric three-way valves, which produce a high level of noises, were made nearly silent by changing its pilot valve. During diastole, negative ventricular pressure was provided by a house vacuum system used with low water level regulators in almost all cases. In one case a small rotor vacuum system, which is portable and has a low noise level, was adopted for over two months. Two units of the Utah heart driver have been used for the calf, with one for emergency use.

C. *Experimental Animals*

Calves weighing 70 to 110 kg (average 86 kg) were used. Acceptable animals, after two to three weeks of observation in the farm, are brought into the laboratory three to four days before surgery and examined for their preoperative physical conditions. Particulary, pulmonary function studies were performed regularly. Reduced functional residual capacity of the lung was an important factor indicative of insufficient pulmonary function. Some of the animals could not undergo surgery because of high fever spikes or functional residual capacity less than 4,200 cc. These animals are utilized for control studies after careful observation for a certain period of time.

D. *Anesthesia and Surgical Preparation*

After blood samples are collected for regular chemical and hematological studies (preoperative control), the animal is anesthetized by introduction of 2 mg atropine and pentathol (5 mg/kg), and is intubated with a cuffed intratracheal tube. Total anesthesia is maintained with only 0.5 to 1.0% Fluothane. PEEP (5 cm) is maintained during total

extracorporeal perfusion. Tidal volume under respirator is 1,600 to 1,800 ml and inspiratory pressure is kept under 25 mmHg with long inspiratory periods. Ventilation rates vary from 13 to 18/min. Recently drugs such as muscle relaxants (Anectin, curare, etc.) and a kind of muscle relaxant (Ketamine) have been eliminated to avoid their prolonged effects in calves with hypothermia. The dosage of Fluothane was also minimized. No anesthesia is utlized after the half-way point of extracorporeal perfusion, in many cases. The anesthetized animal is placed on a rubber mat on a surgery table in left lateral recumbancy. The right lateral thorax and right upper third of the neck are clipped free of hair and prepared for surgery. The right rear leg is secured and the area over the medial aspect of the left stifle joint is prepared for catheterization of the saphenous artery and vein.

E. *Surgical Procedure*

A skin incision is made over the fifth rid (previously the fourth) extending from the right edge of midsternum to close to the vertebral attachment. The incision is continued through the cutaneous trunci muscle and through the serratus ventralis, the costal attachment of the pectoral muscles and the periosteum of the fifth rib. At this time a skin cover sheet is attached to both sides of the chest incision to protect from contamination of the chest cavity by the skin during the operation. The periosteum of the fifth rib is elevated and the fifth rib is transsected at approximately 1 cm from the vertebral attachment and at the costochondral junction. After the anesthetized animal is checked by monitoring femoral artery pressure and central venous pressure, the subcostal periostium incision is made and extended as long as possible, to get a wide surgical field.

The right phrenic nerve and the parietal pleura are dissected free of the inferior vena cava, 2 to 3 cm posterior to the pericardial sac, and an umbilical tape tourniquet is placed loosely around the inferior vena cava. The superior vena cava also is loosely tourniqueted anterior to the azygous vein, making sure that the phrenic nerve is freed. The azygous vein is separately tourniqueted in a similar manner.

The right lateral wall of the pericardial sac is removed, taking care not to enter the left hemithorax. The intermediate lobe of the right lung, which is encased in a pleural pouch is opened for drainage into the right hemithorax immediately posterior to the pericardial sac.

The aortic root is tourniqueted by a double umbilical tape through the small dissection of the main pulmonary artery from the ascending aorta. The subcutaneous tunnels for the air drive lines and the monitoring pressure lines are made by lifting the skin and cutaneous trunci muscle over the eighth and tenth ribs. Skin incisions for the air drive lines are made at places 8 cm to 10 cm ventral to the midline of the back. After unheparinized blood (approximately 60 ml) is collected for preclotting the outflow grafts and the atrial cuffs, 5 mg/kg of heparin is given.

A bubble oxygenator is primed with 500 ml of rheomacrodex, one liter of bovine blood, and two liters of Ringer's lactate solution. A pH of 7.4 is attained by addition of sodium bicarbonate (40 to 80 mEq). The arterial return catheter is retrogradely placed
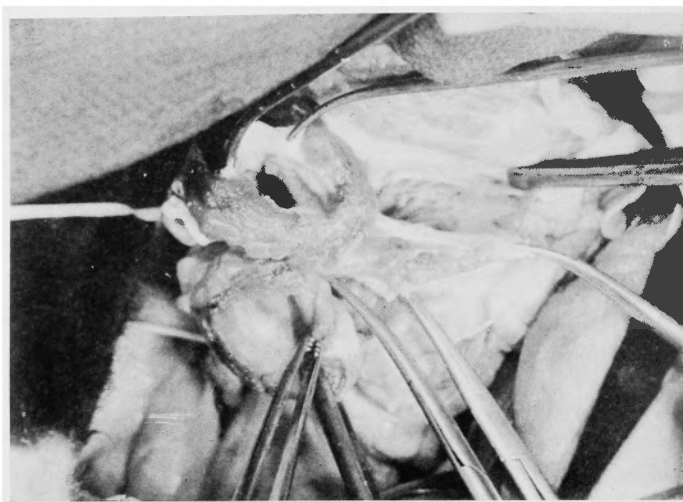
Fig. 7 A surgical procedure for saving the natural outflow valves for a total artificial heart. A pulmonary artery root is almost separated from an aorta. Excessive ventricular myocardium and the anterior leaflet of the mitral valve are trimmed to proper sizes. Pulmonary artery, aorta and right atria are seen in this view.

into the right carotid artery. Two venous withdrawal lines are inserted into the superior vena cava via the right external jugular vein, and into the inferior vena cava at the level of the liver via atriotomy of the right auricular appendage. After partial bypass is maintained for five minutes with an extracorporeal perfusion flow at 0.5 l/min, tourniquets are tightened on the azygous vein, superior vena cava and inferior vena cava (total bypass). Under total bypass the hemiazygous vein is tied with a 3-0 silk under the heart, out of the pericardial sac, and the ascending aorta is clamped with the double umbilical tourniquet. During total bypass mild (32°C) hypothermia is used.

Almost all of the ventricular myocardium is excised, leaving the inflow valve leaflets at the atrio-ventricular junctions and 2 cm of the myocardium, comprising the ventricular outflow tracts, from the semilunar cusps, in situ. Both coronary arteries are separated from the fatty tissues at the atrio-ventricular groove and are prepared for ligation and/or cannulation of the aortic pressure line later. The great coronary vein is also separated from the fatty tissues at the atrioventricular groove and was ligated with a double suture of 3-0 silk, circumscribing the ostia of the coronary sinus. Then the myocardium of the outflow tracts is further trimmed close to 0.7 cm underneath the semilunar cusps, and both the tricuspid valve leaflets and the posterior leaflets of the mitral valve are removed from the atrio-ventricular rings, leaving a 0.5 cm base of the leaflets (Fig. 7).

When the TAH had four B-S valves, in one case, the pulmonary artery was excised at the attachment of the valve leaflets and the aorta was excised similarly just distal to the coronary artery ostia. In all other cases the natural aortic and pulmonary valves were

saved in situ. The roots of these great arteries were separated until near the bifurcation of the common carotid artery. The left anterior descending (LAD) coronary artery is reflected from the ventricle toward its origin. The pulmonary valve remained in the PA by transsecting the right ventricular outflow tract at infundibular level through the middle of the superventricular crest. The proximal right and left coronary arteries guide the dissection separating the roots of the great vessels. This dissection is simplified by working from the distally well-defined aortic and PA vessels between the valvular rings into the ventricular septal myocardium (Fig. 7). When a small hole is made on the aorta or the PA (two cases), the hole was repaired by a few mattress sutures of 4-0 silk with two small pledgets outside.

The excess myocardium and epicardial fat is trimmed from the PA, leaving sufficient tissue (0.7 cm) for anastomosis of the artificial vascular graft with a felt-supported everting mattress suture of 3-0 Prolene. The myocardium of the left outflow tract and the anterior leaflet of the mitral valves are trimmed to 0.7 cm underneath the aortic valve. The ventricular septal myocardium also was trimmed to 0.3 to 0.5 cm, close to the atrio-ventricular junction. The anterior leaflet of the mitral valve is trimmed to a straight line at the same level as the myocardium of the left ventricular outflow tract. A short aortic vascular graft with flexible quick-connects is inverted and placed into the aorta. Both right and left atrial cuffs with flexible quick-connects are also inverted and placed into the right and left atria. Edges of both left and right atrial cuffs and the aortic graft are put together and sutured to the remnent ventricular myocardium and the mitral leaflet with 2-0 and 3-0 Prolene. A mattress suture of 2-0 Prolene is placed encompassing the aortic graft with the left and right atrial cuffs and the intervening septal myocardium. The straight edge of the left atrial cuff is sutured to the mitral leaflet and the aortic graft with a single running suture of 3-0 Prolene, and the rest of the aortic graft is sutured to the remnant ventricular myocardium with running mattress sutures which include a long Dacron felt pledget on the free wall of the left outflow tract. The suture line on the left outflow tract is 1 mm behind the aortic valve leaflets. A running mattress suture is used where the two atrial cuffs are in contact with the septum. A single running suture made around the periphery completed anastomosis on the rest of both atrial cuffs. PA graft anastomosis is completed, similar to the Ao graft. The rewarming of the animal is initiated when we start to sew the atrial cuffs.

The left coronary artery is ligated (with or without a chronically indwelling catheter) which yields an excellent pressure monitoring and sampling portal, at the near-original orifice. The right coronary artery is ligated similarly just distally to the original orifice. After all the cuffs and grafts are everted, a plug is snapped into the quick-connects and blood is injected into the PA, aorta and atrial cuffs, to check for hemostasis of all anastomosis. Small bleedings are repaired with 4-0 silks and small felt pledgets, if necessary. Integrity of the natural aortic valve is insured by releasing the aortic tourniquet and viewing the leaflets. Voluminous bronchial artery flow of a calf permits a similar inspection on the PA

valve leaflets.

The left ventricular drive line is passed out of the chest at the level of the costochondral junction of the seventh intercostal space, and through the previously made subcutaneous tunnel, and is attached to the heart driver. The left atrial and aortic quick-connects are snapped onto the left ventricle and air in the ventricle is completely removed through the venting port. When the left ventricle is totally primed with blood, the aortic tourniquet is released and the driver is started at 40 beats/min and with 100 to 110 mmHg of driving pressure. This slow rate is maintained until the right ventricle is attached to the right atrium and the PA, to avoid left atrial overload from the return of bronchial artery perfusion. The right ventricular drive line is passed through the sixth intercostal space and the subcutaneous tunnel, and is connected to the heart driver. The right atrial and PA quick-connects are fastened to the right ventricle, which is primed by releasing tourniquets on the inferior vena cava. When totally primed with blood the right ventricle is pumped at 40 beats/min. Hemostasis of all the anastomosis are examined again and repared, if necessary. Both artificial ventricles are put in their own places inside the chest and their positions are corrected to avoid any kinking, obstruction and collapse on the inflow and outflow tracts, especially on the ascending aorta behind the right ventricle. After both ventricles are examined again for latent air bubbles, and taken out, the tourniquets on the superior vena cava and azygous vein are released, and the two venous withdrawal cannulae in both vena cavae are slowly occluded.

The heart rate is gradually increased up to 80 to 90 beats/min. The driving pressures are increased to 150 mmHg on the left and to 50 mmHg on the right. The percent systole ratio is selected at 30 to 33 percent. Blood in the extracorporeal perfusion system is gradually returned to the body until both mean atrial pressures are between 7 to 10 mmHg. At this time the monitoring air drive line pressure waveforms (details are later) are very carefully examined to be optimal on both sides, and the heart driving pressures are adjusted to the optimum at the range of 145 to 160 mmHg for the left, and 45 to 60 mmHg for the right ventricle. If we find any abnormalities on the mean atrial pressures, the femoral arterial pressure waveform, the monitoring air drive line pressure waveform, and the driving parameters, we re-examine the positions of both ventricles and hemstasis of all the anastomosis and correct them if necessary. No vacuum is initiated to the heart drivers during the diastolic phase until the chest incision is closed and vacuum applied on the chest drains. The protamin sulfate (7.5 mg/kg) is given intravenously following withdrawal of the venous cannula and arterial return cannula. Activated clotting time (ACT) is adjusted to normal preoperative values.

One or two chest drainage tubes are placed at the bottom of the chest cavity and another drainage tube is placed at the roof of the chest cavity, which is very useful to avoid postoperative pneumo- and hemothorax in a calf. Purse-string sutures are placed around all the percutaneous lines and the chest is closed in the usual fashion. The calf is placed in the cart. Vacuum is applied to the chest drains and to the heart drivers,

and recovery procedures are initiated.

F. *Postoperative care immediatety after surgery*

Normothermia (38.5°C) is restored with an electric blanket or hot water bags, if necessary. The heart driving parameters are frequently checked to confirm optimal air driving pressure waveform on both sides, Usually the systolic ratio is increased from 32 to 38% after vacuum is adapted during the diastolic phase. Blood or fluids are administered when needed, to keep both atrial pressures between 7 to 10 mmHg. Driving pressures are maintained in the range of 145 to 165 mmHg for the left and 45 to 65 mmHg for the right, with 80 to 90 beats/min heart rate and 35 to 40% systolic ratio. When it is necessary to change these driving parameters, we presume that something is abnormal with the driver, the heart or the animal. In three of twenty cases, we found excessive blood loss in the chest wich required abnormal driving parameters, and reopened the chest to stop bleeding.

The chest drains are frequently stripped until hemorrhage ceases, and are removed within 24 to 48 hours. Assisted respiration is given with the respirator until the animal wakes up well from the anesthesia. Recently, however, we have been able to extubate the trachial tube in an hour after surgery on almost all the calves. Antibiotics (penicillin and streptomycin) are given routinely for 3 to 5 days immediately after surgery. The animals are allowed free feeding if they have an appetite, and are able to stand. After the animals become stable (usually within six hours after surgery) they are moved with the portable heart driver in the house elevator to the animal barn, which is located 100 meters from the surgery room.

G. *Postoperative management for a long-term experiment*

Our postoperative management for a long-term experiment is started immediately after the animals are moved to the animal barn. We divide the calves into two groups according to the purpose of the experiment: the long-term survival calves and the research calves. The research calves include several types of experiments, which require many pressure lines and flow measuring equipments ; hemodynamic studies at rest and during exercise, pulmonary function studies at rest and during exercise, drug studies at rest and during exercise, and studies of the influence of alternate ventricular pumping and of ventricular pumping synchronized with the P-wave on postoperative hemodynamics, etc. The long-term survival calves have a pressure line on either the right atrium or the left atrium, or most recently no pressure lines at all. Seven cases, however, were long-term experimental calves, three of them had only ECG monitoring leads on the right atrium, which did not cause any complications.

1. *Animal Care*

The calves have some slight difficulty upon first standing, and often need to be helped to stand up during the first twenty-four hours. Nevertheless, the calves are allowed to stand up as they want. The selected optimal driving parameters are not changed until the growth of the animals requires higher cardiac outputs, or some significant abnormalities are found in their hemodynamic status. When the growth of the animals requires higher

IDEAL DRIVING PARAMETERS

	After surgery	50 Days	100 Days	150 Days	Sirius at 160 days
HR (BPM)	90	90–100	105	110–120	110
% Systole	35	35–40	35–40	35–40	35
LDP (mmHg)	155	160(170)	160(170)	160(170)	170
RDP (mmHg)	60	60(70)	60(70)	60(70)	70

Fig. 8　Ideal driving parameters. These parameters are used with the Jarvik-5 ventricles which have a 165 ml stroke volume. A calf named Sirius had a driving condition of 110 beats/min, 35 percent systole, 170 mm Hg LDP and 70 mm Hg RDP at the 160th postoperative day.

cardiac outputs, the heart rates and the driving pressures are increased according to previously determined best driving parameters (Fig. 8). When some significant abnormalities are found, the clinical diagnosis is made clear, and then the driving parameters are adjusted to compensate for the anomalies. Further treatment, including a second surgery or even selective termination, is then instituted.

2. *Chemical and Hematological Studies*

Blood samples (50 ml for each time) for the routine chemical and hematological studies such as WBC, RBC, Ht, Hb, plasma Hb, FDT, platelet count, BUN, TP, albumin, PPT, and liver function tests (GOT, GPT, LDH) etc. are taken regularly three times a week during the first two weeks, and once a week after the second weed until the end of the experiment. Some of those chemical or hematological studies are performed selectively when needed for clinical diagnosis. No blood transfusions are given for compensating those blood samples.

3. *Special Studies on Research Calves*

The previously scheduled research studies as described above, are performed on the research calves intensively during the first two months when pressure lines are still open. The research calves are transferred to the long-term calf group after the pressure lines are occluded. The pressure lines are cut off near the transcutaneous junction and are clamped.

H. *Autopsy*

Complete autopsies were performed at the termination of all twenty experiments. Gross findings were recorded and correlated to observation during the course of the examination. All of the twenty animals were given 2 mg/kg heparin, and 5 mg/kg pentothal after recording the final clinical diagnosis, and the final driving conditions of the artificial heart, and then were terminated after final ventricular pumping for two minutes. Final blood samples were taken before administration of the heparin and pentothal, and the mean circulatory blood pressures were measured 3 minutes after termination. Each of the animals are suspended by its back, and inspected inside its chest, by taking out two or three ribs on both sides. After the additional ribs were taken out the position of the artificial heart and kinking or obstruction of both inflow and outflow tracts were examined

very carefully, and both artificial ventricles were excised. Samples for bacterial culture were taken when needed. After fresh blood was washed out of the ventricles very carefully with normal saline, the inside surface of both the atria and the artificial heart were inspected for the thrombus formation, pannus formation, neointima ingrowth and neotissue growth, etc. One ventricle (right or left) was sent for mock circulation tests, and the other ventricle was sent to the polymer surface testing lab for microscopic examination of the surface. Tissue samples from all of the important organs including lungs, kidneys, liver, and the brain and spinal cord when the animal had any neurological abnormalities while alive, were sent for microscopic examination. During the last year tissue samples of the skin around the drive lines and of both right and left remnant atrial myocardium (including septum) were sent for microscopic examination. All of those samples were stored with formalin solution in the autopsy library, and were used for further examinations.

I. *Reoperation*

Six reopertive surgeries were performed in four cases during the last year. Four of them were to stop postoperative bleeding, and three of the four were performed on one animal within twenty-four hours of the TAH implantation. This animal survived for eighty-two days. Two of the reoparative surgeries were performed for the correction of left inflow stenosis caused by pannus formation, and of right outflow stenosis caused by mechanical failure of the artificial outflow valve. Both of them were performed under total extracorporeal perfusion. In one case, which had right outflow stenosis, right thoracotomy was performed on the same day as the main surgery. After the artificial heart was exposed, the right ventricle was disconnected from the PA quick connect and the Bjork-Shiley valve was replaced with a new Bjork-Shiley valve. In another case, which survived for ninety-six days, the left thoracotomy was performed on the sixty-seventh postoperative day. There was no adhesion in the left chest cavity and the left atrium could be exposed without any difficulties. Cannulation for the total extracorporeal perfusion was done via the left carotid artery and jugular vein, retrogradely. No aortic clamp was required because there was no regurgitation across the natural aortic valve. The pannus formation was successfully cleaned up around the left inflow tract with the open method via the left atriotomy.

Results

Five calves out of twenty (25%) died within the first two postoperative weeks (Fig. 9). Two of those five calves died from pulmonary failure. The two calves received over 35 mm Hg ventilatory pressures, causing pulmonary interstitial emphysema during surgery and postoperatively, although lungs of cattle, especially calves, are very sensitive to such high ventilation positive pressures, and we usually use low ventilation pressure, less than 20 mm Hg, using high tidal volumes with low air flow. One calf died from severe hemolysis caused by a miss-matched blood transfusion. This calf was given two liters of blood, in order to compensate for postoperative bleeding, and the blood samples for its hematologic

OUTCOME OF SURGERY & POSTOPERATIVE CARE FOR THE TOTAL ARTIFICIAL HEART IMPLANTATION

Exp.	No.	Name of Calves	Type (Heart)	Survival	Primary cause of death	Immediate	Complication
TH 77	C12	UNCHI	J5 A 5	86.4	*Neoplasm (Outflow)	Hemolysis	Thromb. embolism
	C13	ROCKEY	J5 B 14	47.8	Broken diaphragm	Air embolism	
	C14	SIRIUS	J5 A 6	183.6	Excessive growth	Accid. paralysis	Sepsis, Pul. fail.
	C15	LONE STAR	J5 B 15	30.4	Broken diaphragm	Pul. embolism	
	C16	TOM	J5 A 7	5.0	Pul. care failure	Pul. emphysema	
	C17	WINSTON	J5 B 16	12.5	Miss matching blood	Hemolysis	
	C18	SNOOPY	J5 A 8	12.4	Low heparin dosage	Throm. formation	Pseudo-pannus
	C19	RALTH	J5 A 9	49.8	*Neoplasm (Outflow)	Throm. embolism	Pul. hypertension
	C20	GODWIN	J5 B 17	64.3	*Neoplasm (Outflow)	Throm. embolism	Pannus
TH 78	C 1	SHERLOCK	J5 B 18	48.3	*Neoplasm (Outflow)	Throm. embolism	Renal hypertens.
	C 2	WATSON	J5 A 10	2.5	Cong. pul. malform.	Pul. emphysema	Pul. care failure
	C 3	CLAUDIUS	J5 A 11	162.4	Pannus (Left inflow)	Low card. output	Lat. broken diaph.
	C 4	THEODORE	J7 A 1	96.7	Infection (Endocard.)	Infected thromb.	Pseudo-pannus
	C 5	BOBBY	J5 A 12	60.2	*Neoplasm (Outflow)	Throm. embolism	Hemolysis
	C 6	SPOCK	J5 B 20	81.9	Infection (Sepsis)	Sepsis	Pannus
	C 7	CURLY JOE	J5 A 13	151+	On going		
	C 8	NONAME	J5 A 14	0.3	Surg. Failure (VSD)	Postop. bleeding	
	C 9	CASPER	J5 A 15	48.2	*Neoplasm & Pannus	Low card. output	Infection
	C10	ALEXANDER	J5 B 21	80+	On going		
	C11	ROMULAS	J5 B 22	45+	On going		

Total experiments ; 20 cases, Average survival time ; 63.09days (83.02 days without early death) Over one-month survival ; 75%, Over two-month survival ; 45-50%, The longest survival ; 183.6 days

Fig. 9 Outcome of chronic experiments during the last year. The primary causes of death are summarized with immediate causes of death and complications in the last twenty cases. (*Neoplasm meanes thromboblastic proliferation).

studies, which was unusual. Calves have more than forty-six different blood types, and a well-matching blood in an in vitro test causes severe, unexplained hemolysis in this calf's body. Another calf died from fresh thrombus formation in the ventricles, especially around the artificial inflow valves. In this case, 0.5 mg/kg heparin was mistakenly given instesad of the usual dose of 5 mg/kg heparin, during the total heart lung machine bypass. The fifth calf died from untreatable bleeding immediately after surgery. This calf had an unexpected congenital heart disease (ventricular septal defect). We were unable to repair it with a Dacron felt patch and to save the right outflow myocardial edge with natural aortic valve. The repair of this ventricular septal defect was thought successful. However, a huge amount of postoperative bleeding occurred through the patch. Twenty-four liters of blood were given, but could not save the calf.

All of the remaining fifteen cases (75%) survived for over a month. Nine (45%) of the fifteen survived for over two months, and four cases (20%) survived for over three months. Three of these calves are still going, with excellent health, at 151 days, 80 days and 45 days. The longest survival time was 183.6 days in those cases. Average survival time is 63 days (on-going), including the five calves that died during the first two weeks. The average survival time without early death is 83 days (on-going). Fig. 9 shows the primary causes of death and the secondary causes of death in those 15 cases.

A broken diaphragm (13%) in the artificial ventrcle was one of the major causes of death, until the diaphragm of the Jarvik-5 heart was redesigned (September 1977). After the new diaphragm was built, using four layers instead of three, the major causes of death were shifted to the pannus formation on the inflow tract (22%) and the neoplasm (proliferative fibrosis) on the outflow tracts (40%). Infection (endocarditis, sepsis) was another major cause (13%) and a damaged diaphragmatic surface became a latent cause of death. The pannus (Fig. 10) originates as an extention of the neointima on the rough surface of the polyester atrial cuff and was found in all of the 15 cases that survived for over a month. Some of the pannus formations caused severe obstruction of the inflow tract. Biolized material (dura mater) also had pannus formation. Neotissue growth (Fig. 11) on the left outflow tract originates from the remnant outflow myocardium which is degenerated and replaced with fibrosis during the first month. Some parts of the fibrosis proliferate and produce nodal tumors inside the left outflow tract, causing subaortic stenosis. Of this neotissue, 67% was infected on the surface. Neotissue growth appeared very rapidly after the first month in 47% of the cases. Neotissue was never found in the right outflow tract (PA).

A cracked diaphragm was found on one side or both sides in five cases. Blood infiltrated the layers of the diaphragm and made them brittle, causing reduction of the cardiac output. Excessive growth of the animal was another primary cause of death (7%). The calf grew quickly and doubled its body weight during the first postoperative months, so that it required higher cardiac output than the artificial heart could supply. The calf Sirius (183-day survival) slipped on the slippery rubber mat and died from complete paralysis of the
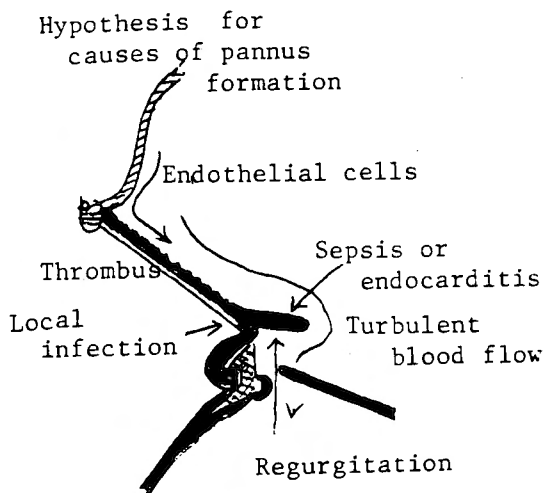
Hypothesis for
causes of pannus
formation

Endothelial cells

Thrombus

Sepsis or
endocarditis

Local
infection

Turbulent
blood flow

Regurgitation

Fig. 10　A pannus formation in the inflow tract.
There are several hypotheses for causes
of pannus formation.

Degeneration
of myocardium

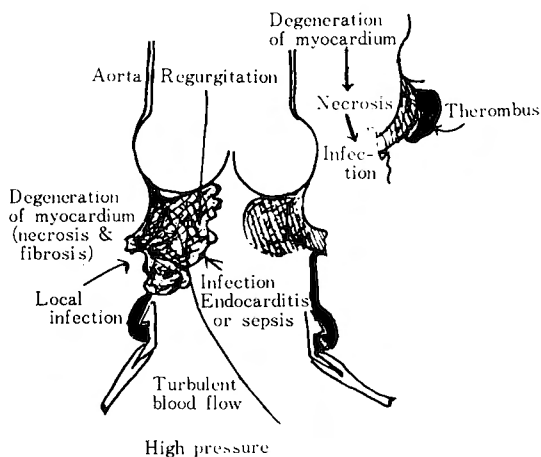Aorta　Regurgitation

Necrosis

Therombus

Infec-
tion

Degeneration
of myocardium
(necrosis &
fibrosis)

Infection
Endocarditis
or sepsis

Local
infection

Turbulent
blood flow

High pressure

Fig .11　Thromboblastic proliferation in the left outflow
tract with a total artificial heart. There are
several causes of a neoplasm growth.

lower body. At that time, when it sustained a damaged spinal cord, its body weight was
178 kg (75 kg at the time of surgery). There were no accidental deaths duringthe last year,
such as a power failure, driving machine failure, or drive line disconnection, as previously
has occurred.

There were several complications or secondary causes (Fig. 9) of death : hemolysis, air
embolism, hypovolemia, cardiac insufficiency, septic shock, thromboembolism with renal and
pulmonary complications. Those secondary diseases or complications made clinical diagnosis

difficult at the time of termination, and confused the data from blood chemistry and hematology.   Recently, early elective termination is always considered.

The outcome of reoperative surgery was excellent. All of the four cases were able to survive their immediate problems.   Their average postreoperative survival time was 56.5 days. However, reoperative surgery increased the incidence of infection. Two (50%) died from infection.   In one case (25%) infection was the primary cause of death.   In another case we could not control the endocarditis with reoperative surgery.
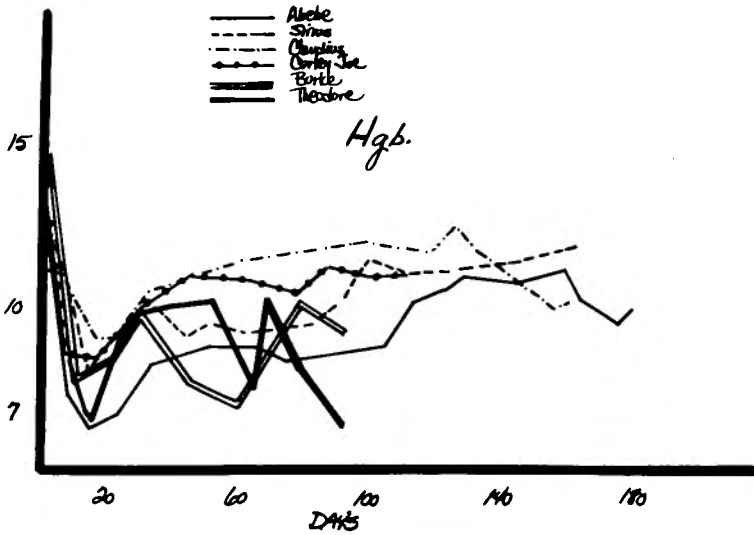
Fig. 12A

Total hemoglobin.
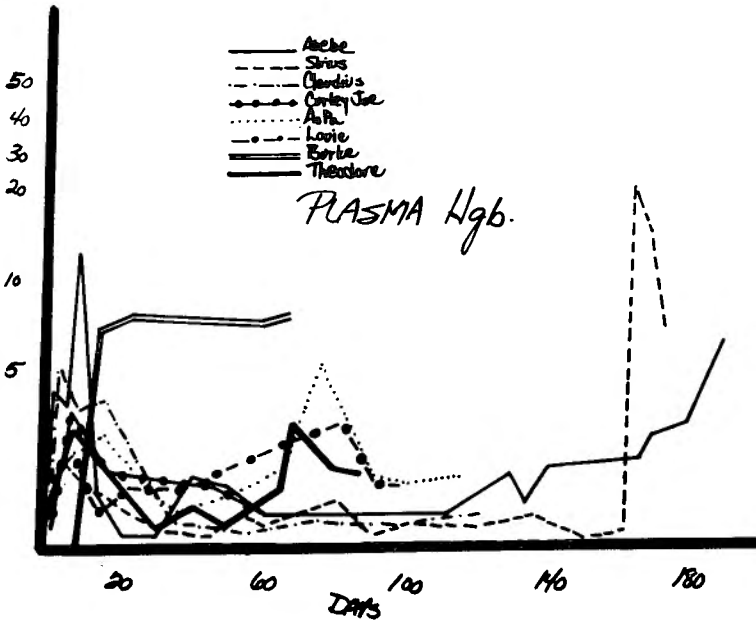
Fig. 12B

Plasma hemoglobin.
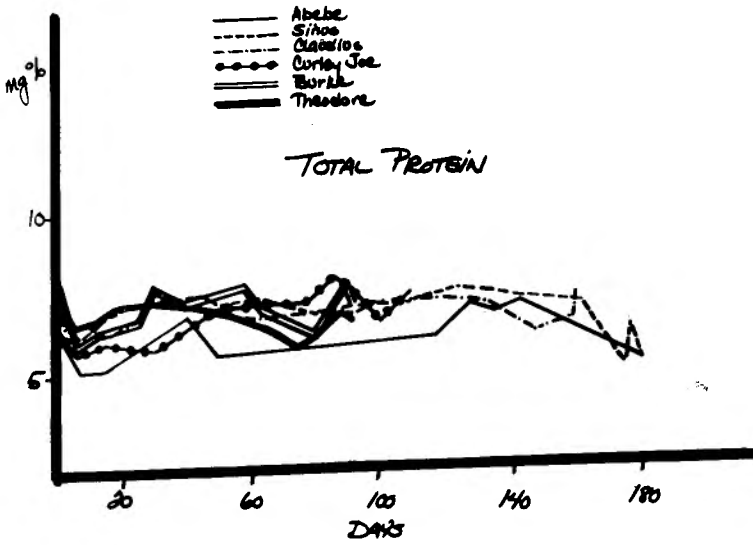
Fig. 12C
Total protein.
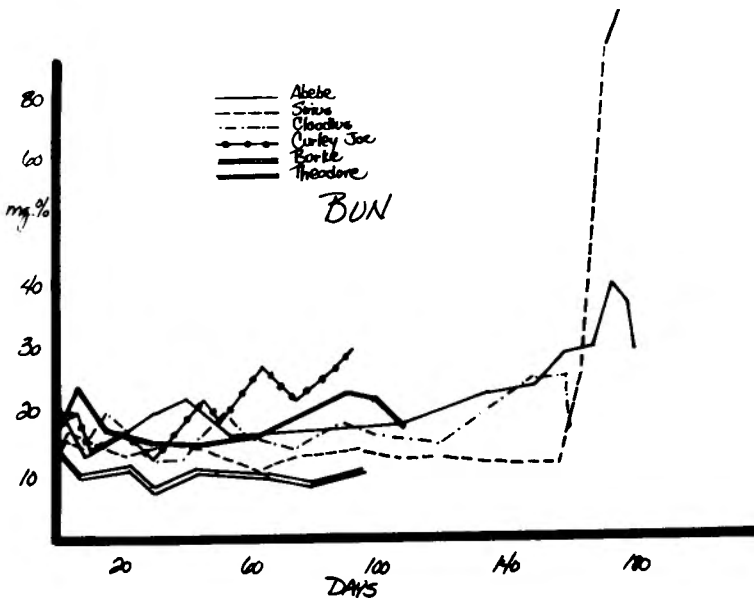
Fig. 12D
BUN

Discussion

The outcome of chronic animal experiments during the last year was so excellent (Fig. 12) that human application of the total artificial heart is now thought to be almost ready[32]. These accomplishments were associated with particular advances in the prosthetic device's desing and material, and its surface (fabrication), electronics in the heart driver and monitoring system, and surgical or postoperative management procedures.
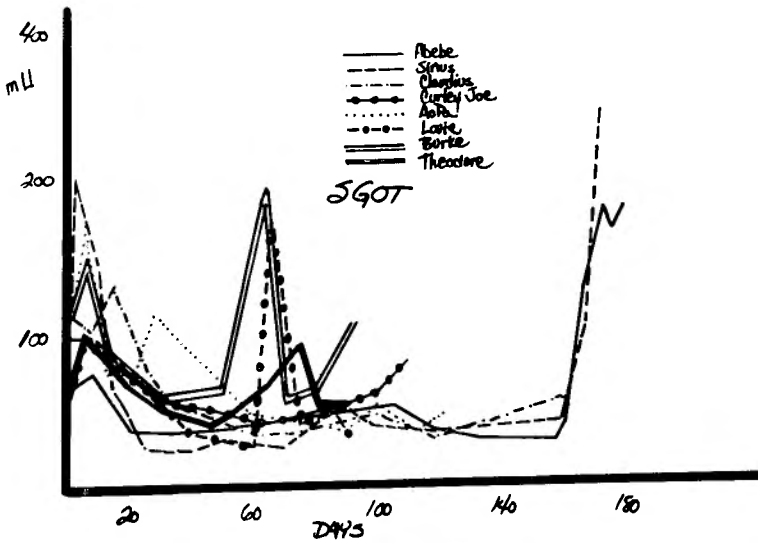
Fig. 12E
Serum SGOT.
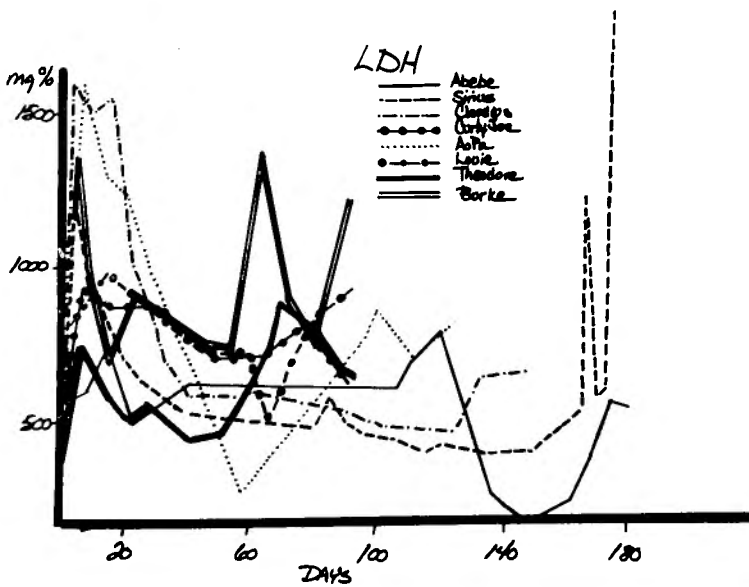
Fig. 12F
Serum LDH.

A. *Materials and design for the pump device*

When the most suitable materials are selected, from which the blood pump is fabricated, among the presently available materials, we have to consider all blood or tissue compatibility from the biological point of view, and of availability, workability, usability, (and) durability of the materials from the mechanical point of view[6-39]. There are many different materials 📖 used : Latex, Silastics (including Dacron velourcoated Silastic, Dacron fibril-coated Silastic[20], smooth surface Silastic[6]), polyvinyl chloride[4,21], biolized rubber[47], and polyurethanes[36,52,42,5] (Fig. 2). Currently, in our animal experiments, polyurethanes seem to offer the best
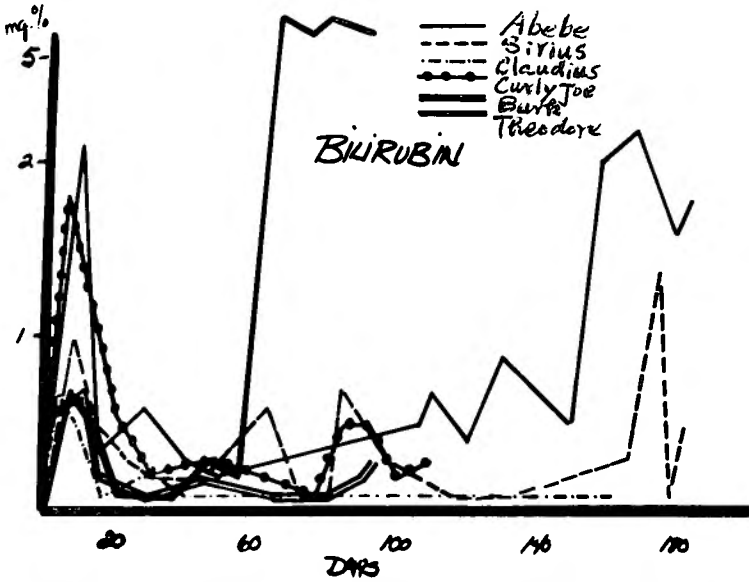
Fig. 12G

Bilirubin.
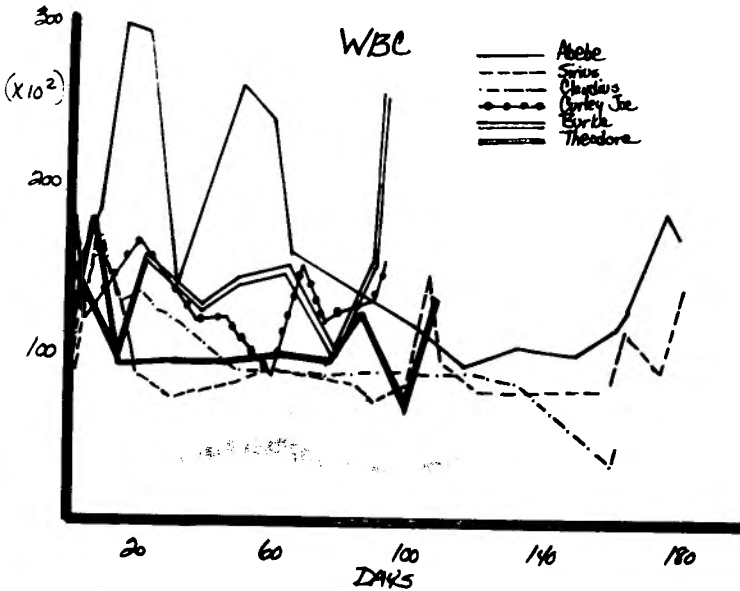
Fig. 12H

White blood cell count.

Fig. 12 Hematological and chemical studies in several calves with a total artificial heart that survived for over three months. One calf (Burk) was achieved in 1974, two calves (Aopa and Louie) in 1976, a calf (Abebe) in 1977, and four more calves were achieved during 1978. The healthy calves with total artificial hearts have demonstrated normal values of all hematological and chemical studies.
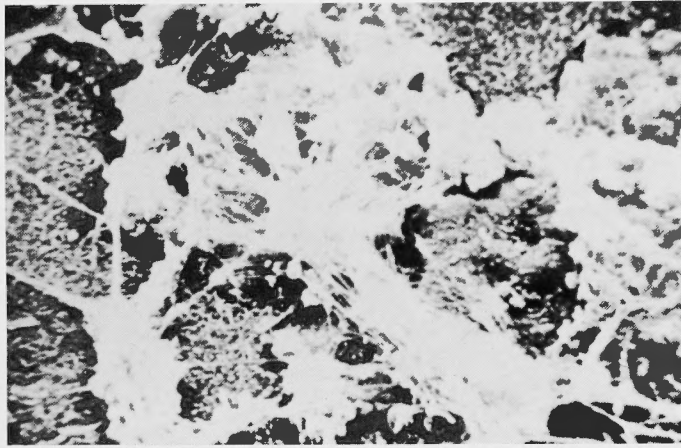
Fig. 13 A microscopic view (400X) of the blood-contacting surface
of polyurethane in the artificial heart after six months of
implantation.

combination of biocompatibility with mechanical properties. We choose two types of polyure-
thane—Biomer and Avcothane-51 Elastomer. The purpose in using them is that fabrication
of the ventricles is easy, their blood-contacting surface is very smooth, and they appear to
be nonthrombogenic. Utilization of the polyurethanes in the artificial heart extended
significantly the longest survival time, from twenty-five days up to three months, in this
laboratory in 1974. This accomplishment was not only due to blood compatiblilty of the
polyurethane surface, but also due to the flexibility of the polyurethane diaphragm. Since
that time we have implanted more than 150 polyurethane hearts in animals.

There were only minor differences seen between the Biomer heart and the Avcothane
heart until short durability of the diaphragm became a major problem in obtaining long-
term survials. Fig. 13 shows thrombus formation and calcium deposits on and in the poly-
urethane blood-contact surface. Macroscopically, almost no thrombus formation was found
in experiments lasting as long as six months. Microscopically there is a small amount of
thrombus formation and calcium deposits seen in the same areas as the thrombus formation.
There are no significant differences between the Biomer and Avcothane hearts in blood
chemistry and hematology studies of fifteen cases (Fig. 12).

During the last year nine Biomer hearts and eleven Avcothane hearts have been
implanted in the J5 configuration, which has three or four separate thin layers in the
diaphragm. Of the 20 cases, seven Biomer (78%) and eight Avcothane (73%) survived
surgery for over a month. Only three cases (43%) with the Biomer heart and six cases
(75%) with the Avcothane heart survived for over two months. The average survival times
of those three cases and six cases were 68 days and 118 days respectively. Those differences
were definitely related to the breaking of the diaphragm. Two cases with the Biomer hearts
died from a broken diaphragm, and four cases had a latent broken diaphram in either the
left or right ventricle, or both (Fig. 9). In contrast, no Avcothane cases died from broken

Fig. 14 A microscopic view (40X) of the mesh-side surface of a polyurethane diaphragm after six months of pumping. There are many cracks on the polyurethane surface.

diaphragms and three cases had a latent broken diaphragm. These differences are due to the design of diaphragms in the J5 ventricles. The multiple layers of a diaphragm in the J5 ventricles rub each other when the diaphragm moves back and forth. Fig. 14 shows the mesh-side surface of the blood-contacting membrane in the old J5 ventricles. There are cracks on the polyrethane membrane where the fibers of mesh cloth rub. These cracks led to the broken diaphrams of the J5 ventricles. The Avcothane membrane is a little more slippery than the Biomer membrane. The problems with the Biomer heart could be solved by a new design of the diaphragm.

To design an artificial heart to replace the natural heart, we have to study carefully the volume and shape of the natural heart[6]. Shortness of space and lack of flexibility in connecting sites are the first two difficult factors we have to confront and solve in the development of an intracorporeal (implantable) blood pump. Also we have to study the intraventricular hemodynamices including the blood flow pattern and hemostasis in the ventricles. It is important to avoid, if possible, any areas of turbulent flow or of stasis[21,1,19] There are many types of artificial hearts used (Fig. 1), including sack types and diaphragm types. Recently in this laboratory the J3 and J5 ventricles are used. These ventricles are the diaphragm-type, and the J3 ventricles have a D-H junction with a strong angle. In contrast, the J5 ventricles have no sharp D-H junction and turbulent flows of blood are eliminated in these ventricles[25].

Since 1974, 67 of the J3 ventricles and 83 of the J5 ventricles have been implanted in calves. Figure 15 shows progress in the survival rate with the J3 and J5 ventricles. Those significant accomplishments were achieved by advances in the surgical and postoperative management (detailed later), but also in the changing design of the J5 ventricles[30]. Fig. 16 shows significant differences between the J3 and J5 ventricles in platelet aggregation
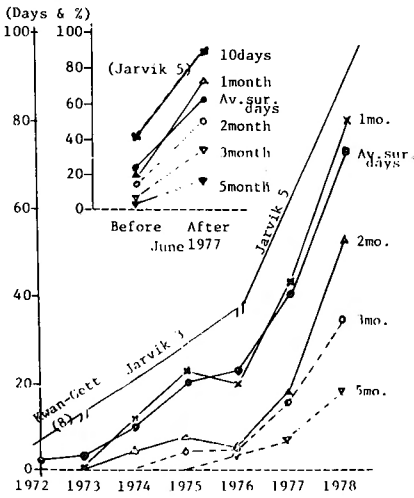
Fig. 15 Progress in survival rates and time : ten days, one month, two months, three months and five months. Survival rates and average survival times with the total artificial heart have been dramatically extended during the last several years.
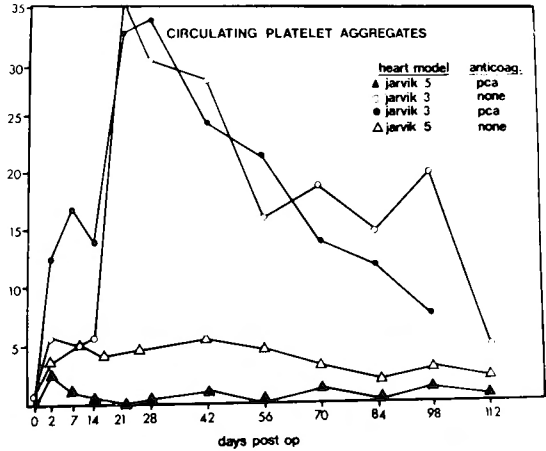
Fig. 16 Circulating platelet aggregates. The alternated design of the Jarvik-5 ventricle has dramatically reduced the thrombogenicity of the artificial heart, even without anticoagulants.

tests. In this figure, there were five cases with J3 ventricles and with anticoagulants (Warfarin, Aspirin and Persantine[R]), two cases with ventricles without anticoagulants, four cases with J5 ventricles and anticoagulants, two cases with J5 ventricles without anticoagulants, summarized with mean values.

B. *Fabrication of the pump device*

There are many different methods to make artificial pump devices from various materials[2,47,5,3,33], and also several methods to make the pump devices from polyurethanes[28,40]. To get a good pump we have to consider what kind of blood contact surface in a ventricle we want : smooth surfaces, semi-smooth surfaces or rough surfaces[31,48]. When we used Dacron fibril-coated Silastic on the diaphragm of the J3 ventricles in 1973, we thought that a rough surface was better than a smooth surface, because we expected that biologic cells covered over the surface of the foreign materials very smoothly. However, it was not true. Neointima built on the surface of the foreign materials continued to grow up until the diaphragm became too hard to be moved by our heart driver[36,37]. In our experience, the semi-smooth surfaces also have been prone to thrombus formation. Hemostatic areas on the semi-smooth blood-contacting surface are thought to be the source of thrombus formation. We are now using smooth surfaces on the blood contacting surface in artificial heart pump devices.
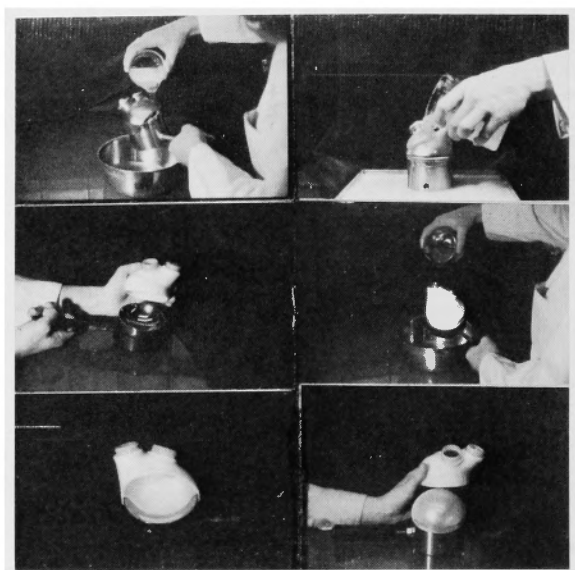
Fig. 17 Fabrication processes of the Jarvik-5 ventricle. An air drying method is used, using several smooth-surface, stainless steel molds.

To get a very smooth blood-contact surface, we utilize a method of air-drying the surface of polyurethanes on a very smooth, stainless-steel mold. Other methods, including injection molds[29], direct-contact metal molds[28], low-melting temperature Epolene molds[29,31], etc. may cause problems related to the solvent evaporating rate of the polyurethanes after the polyurethane membranes start to dry. When the solvent from the polyurethane fluid evaporates from the polyurethane membrane, the molecular construction of the polyurethane is changed by various solvent evaporation rates. Although we don't know yet what kind of solvent evaporation rates prepares the best kind of smooth surface for the polyurethanes (Biomer and Avcothane), the air-dried method gives us at least a constant smooth surface on the polyurethane membranes.

Fig. 17 shows how we make the air-dried surface in the artificial ventricles. The J5 ventricles are built with no sharp D-H junction and a continuous blood-contacting intima inside the ventricles, by using smooth-surfaced metal molds. There are three layers of polyurethanes in a diaphragm. When the blood-contacting layer of the diaphragm is built, another layer of polyurethane covers the inside surface of the housing to get an air-dried surface. A thin Dacron mesh and a powder lubricant layer of graphite are placed in between these three layers, because the Dacron mesh functions as a volume limiter and the lubricant of graphite protects the thin blood-contacting membrane from breaking.

C. *Artiflcial atrium and arterial vessels*

In the past the artificial heart was inserted in one piece[3] and surgical implantation was very difficult. Currently we use quick connect systems between artificial ventricles and

both artificial atria and arterial vessels, which are sutured to remnant atria and great vessels (Ao and PA) separately before their connection.

The artificial atria and arterial vessels are made of polyester felt and woven graft (Fig. 3) respectively, or are made of biolized materials (dura mater, pericardium), coated polyester or silicone rubber. A serious problem has been a continuous growth of neointima from the remnant natural vessels to the artificial vessel, forming a "pannus"[23,50]. If one choose a smooth surface on the artificial vessels the neointima floats in the blood stream and disturbs blood flow. In contrast, a rough surfaced artificial vessel develops a neointimal ingrowth on the rough surface.
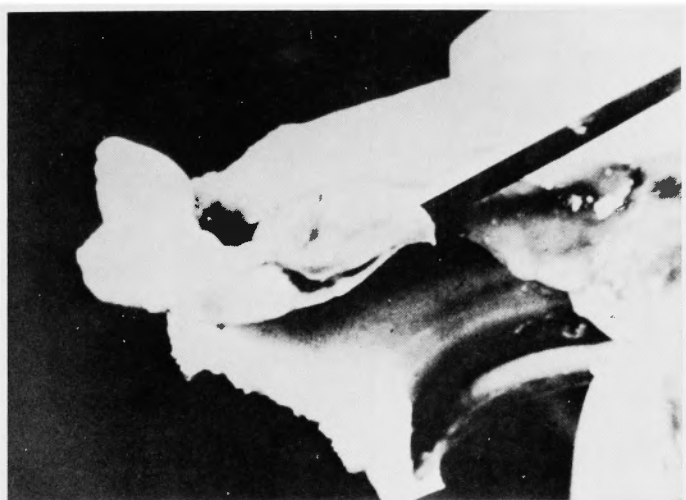
Fig. 18 A floating pannus on the smooth surface of an artificial atrium. The smooth surface was made of silicone rubber.
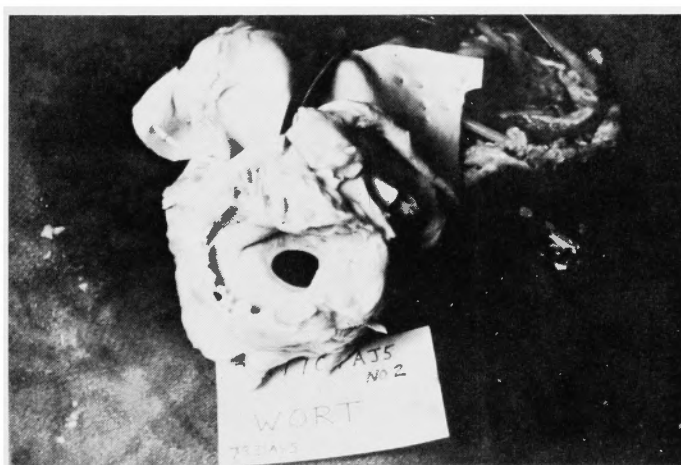
Fig. 19 Smooth neointima on the rough surface of the atrial polyester felt cuff. A suture line and a tip of a pressure line also are covered with a smooth neointima.

Thrombus formation on rough surface
from remnant atria
Pannus ← Neointima
on rough surface
Infection
Abnormal blood flow
Turbulant
Regergitation
Others
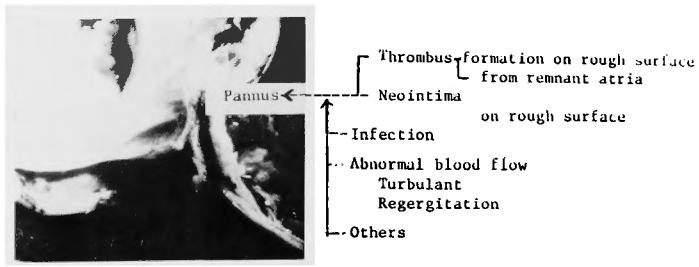
Fig. 20   A cross-section of pannus. The pannus originates at the neointima on the rough surface of the atrial cuff, at the edge of the polyester felt.
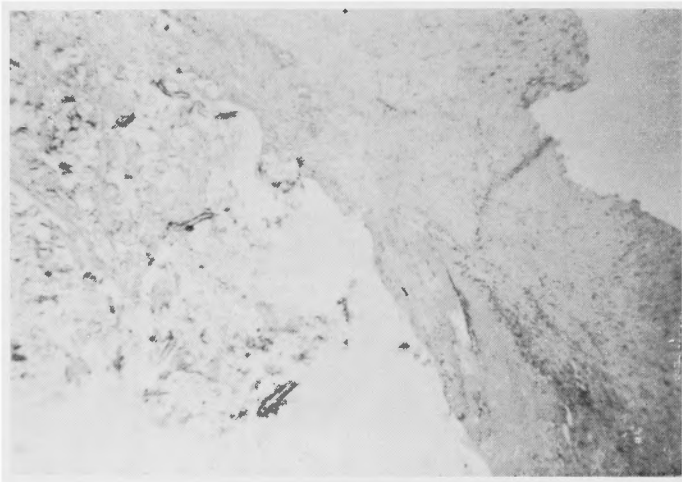

Fig. 21 A

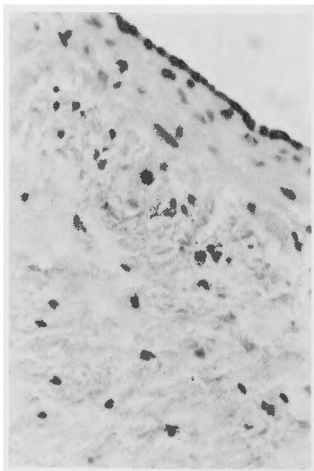A pannus formation at the edge of the polyester felt.

Fig. 21B

Neointima. There is a layer of endothelial cells.

Fig. 21   Microscopic views (40X and 400X) of the pannus and neointima on the rough surface of the atrial cuff.
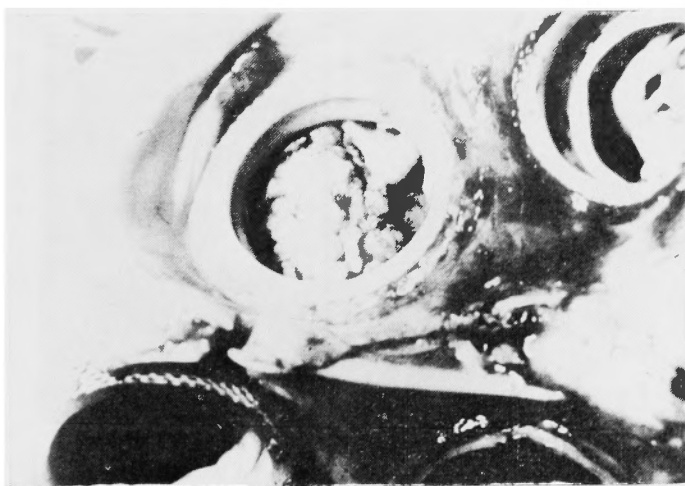
Fig. 22 *Neoplasm in the left outflow tract. The surface of this
neoplasm was infected and formed a cauliflower shape.
A pannus in the left inflow tract is seen also in this
picture. (*Neoplasm means thromboblastic proliferation)

Fig. 18 shows the pannus floating in the blood stream from the suture line on the
atrial cuff, which has a smooth surface (Silastic).   Fig. 19 shows the beautiful neointima
ingrowth on the rough surface of the polyester atrial cuff. Utilization of the rough surface
was very successful to get a smooth surface of neointima on the artificial atria, until a calf
with a TAH survived for over at least a month.

Fig. 20 shows the pannus formation in the inflow tract of the artificial ventricle, from
the edge of the rough surface on the artificial polyester atrium, two months postoperative.
Most recently, when average survival time exceeded two months, this kind of pannus
formation became a major cause of death in this laboratory. Fig. 21 shows a microscopic
picture of the pannus. The main histological finding was fibrosis.

This kind of pannus formation is never seen in the outflow tract, even if we use
polyester woven graft with a rough surface. A different type of neotissue growth[50] has
been found in the outflow tract (aorta) ; nodular neotissue growth (Fig. 22). It originates
at the outflow myocardium, which was saved in situ, in order to save the natural outflow
valve[59], and sometimes is associated with infection on its surface. Postoperatively at two to
three weeks all of the myocardiums had degenerated and been replaced with fibrosis, and
the nodular growth of neotissue (fibrosis) appeared in 43% of the cases. Fig. 23 and 24
show a cross-section and a histological finding of the neotissue.

We are not sure yet, but there are several possibilities considered to be the main
causes of the neotissue growth : infection (endocarditis, local infection around the quick-
connect), turbulent blood flow or jetting blood flow[53], and high pressure etc., as well as
degeneration of the myocardium and replacement with fibrosis. The nodular neotissue
growth was found only at the myocardial part of the outflow tract and was never found at
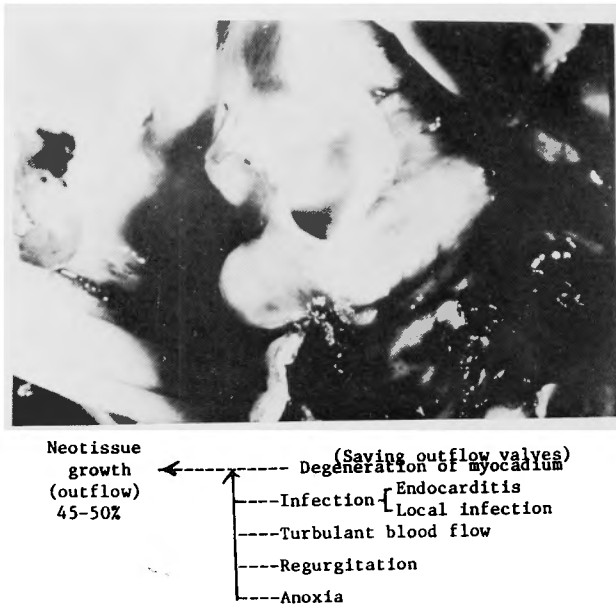
```
Neotissue            (Saving outflow valves)
  growth   <-----+----- Degeneration of myocadium
 (outflow)        |                  ┌Endocarditis
  45-50%          +----Infection----┤
                  |                  └Local infection
                  +----Turbulant blood flow
                  +----Regurgitation
                  └----Anoxia
```

Fig. 23   A cross-section view of the left outflow tract with neoplasms.
The neoplasms in this picture had a relatively smooth
surface, although the surface was infected.
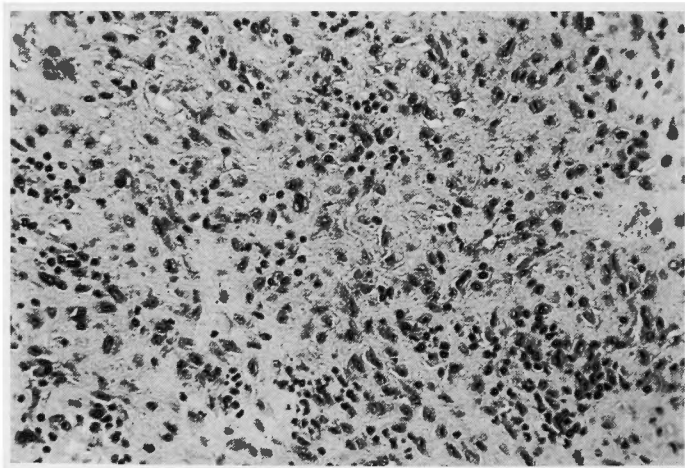
Fig. 24   A microscopic view (400X) of neoplasm in the left outflow
tract. There are many inflammatory cells in fibrosis.

the area of the mitral anterior leaflet.   And in the cases in which the outflow myocardium
and outflow valves were not saved, no neotissue growth was found.   Thus, degeneration of
the myocardium might be an essential factor.   Also high pressure or abnormal blood flows
with high pressure might be one of the essential factors because none had the neotissue
growth in the right outflow tract. Infection also may be a factor. There are always inflam-
matory reactions in the fibrosis.

Conclusively, those pannus formation in the inflow tracts and neotissue growth in the outflow tracts are a kind of refuse reaction of living body tisssue ageinst the foreingn materials, and are major problems at this time in the animal experiments of the TAH and should be solved.

D. *Remnant atria*

Until the present time, it has not been sure if long-term prognosis of the remnant atria is good or not, without a blood supply from the coronary arteries, but portions of the natural atria are being saved in situ. The prognosis of the remnant atria has been
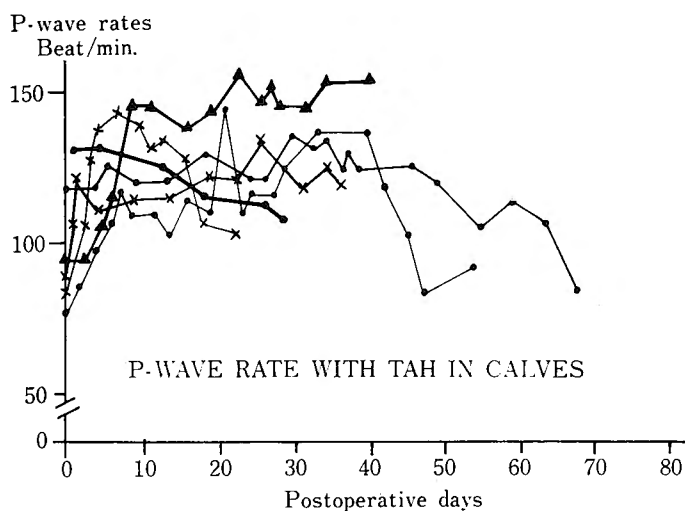
Fig. 25A The postoperative P-wave rates with the total artificial heart. Function of the sinus mode remains after ligation of the coronary arteries.
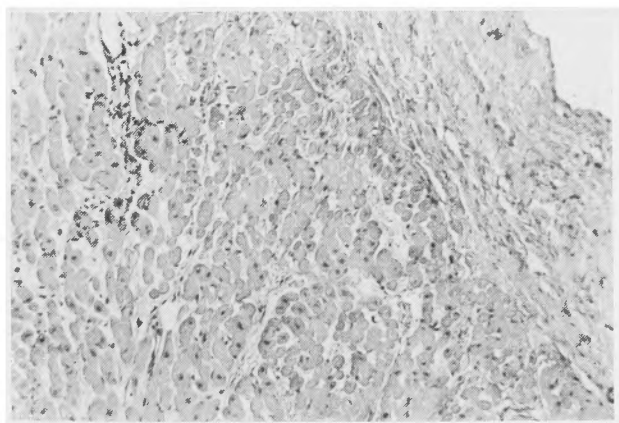
Fig. 25B The remnant atrial myocardium (400X). There is necrosis, fibrosis and inflammatory cells in the relatively healthy myocardium.

examined, with histopathological examination[23]. and function studies including monitoring of the P-wave[15,16] and atrial pressure wave, for up to six months. There were some grades of degeneration in the remnant atrial myocardium, but the monitoring of the P-wave and atrial pressure wave have indicated that functions of the remnant atria remains for at least six months. None has had a rupture of the natural atria, and some of the cases which had high mean atrial pressures during the experiment had hypertropy of the atrial myocardium. Fig. 25A shows the postoperative P-wave rates in several cases. Fig. 25B shows one of the histopathological pictures of the atrial myocardium.

E.　*Valves in or out of the pumping devices*

For an artificial heart pumping device an inflow and outflow valve systems are needed. The B-S valve is now being used for an inflow valve, and the B-S valve or natural valve for the outflow valve[18,51], although several kinds of valves have been used in the past, including the Edward ball valve, a flap valve made of Silastic, a three-leaflet valve made of polyurethane, the Wada-Cutter valve, tissue valves, etc. (Fig. 1). When the most suitable artificial valves are selected for a pumping device, the available space for valve stents between the postition of the inflow valve and the diaphragm has to be considered, and the possibility of thrombus formation or calcium deposits on or around the valve, and also high stress on the artificial valve during the closing or opening phase with high dp/dt of the intraventricular systolic pressure in the artificial heart[18]. The size of the valve orifice also is an important factor, especially in the case of the inflow valve.

The B-S disc valve has a low profile which fits nicely inserted into the inflow position of the J5 ventricle, and enough low flow resistance allowing the cardiac output that a 100 to 150 kg calf needs, and has been used since 1971 for the inflow valve. However, when a calf grows over 180 kg, and requires higher than 16 l/min of cardiac output, the B-S valve cannot respond well, even with the largest commercially available size (No. 29).
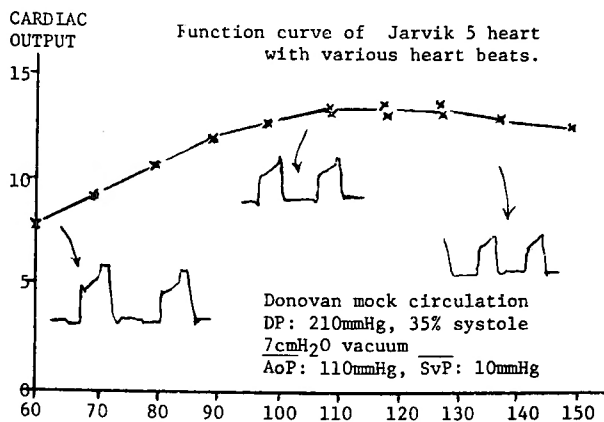

Fig. 26　Function curve of the Jarvik-5 ventricle. Cardiac outputs were measured with various heart beats in the mock circulation system. The maximum cardiac output (13.6 1/min) was obtained with 120 to 130 beats/min.
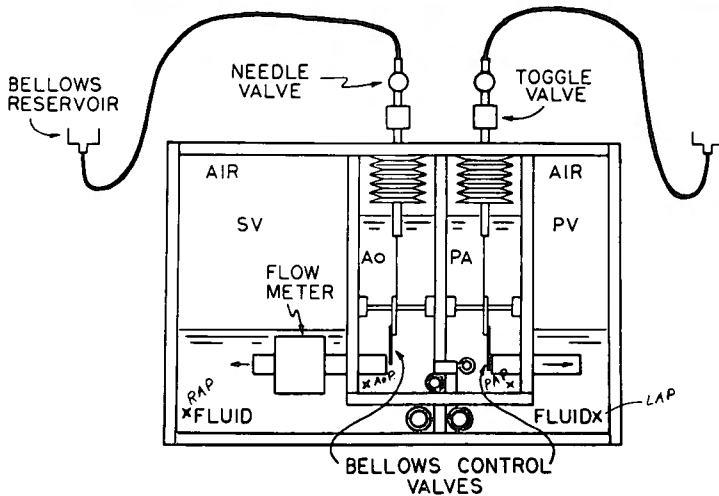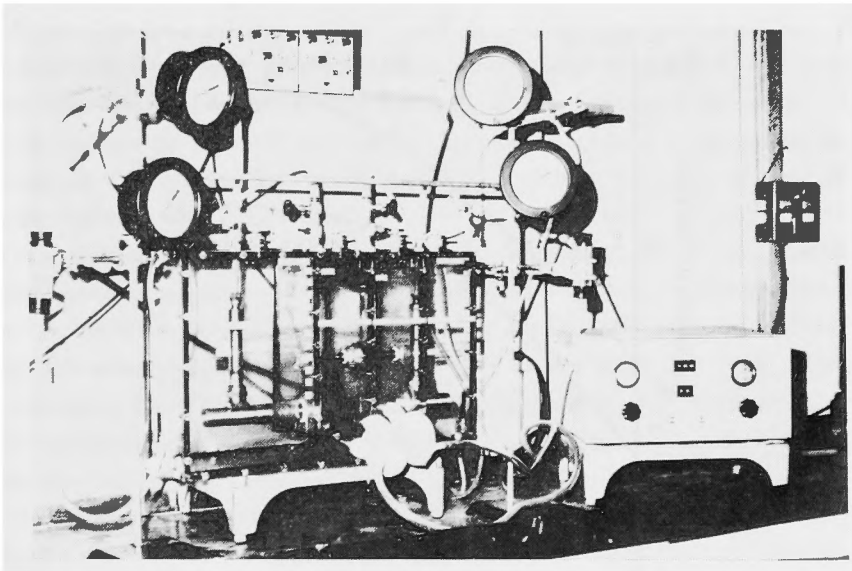
Fig. 27 The Donovan double-sided mock circulation system. This system, which simulates the circulatory system of the calf, has been used to evaluate the pre- and postoperative functions of many different artificial hearts, since 1972.

Fig. 26 shows the cardiac outputs of the J5 ventricle, which has 165 ml of maximum stroke volume and two B-S valves, with various heart rates in the mock circulation (Fig. 27) (Donovan mock circulation system[12]). In this study the maximum cardiac output with the Jarvik-5 ventricles obtained with 120 to 130 beats/min. was 13.6 l/min.

Tissue valves might be the best inflow valve in human patients[38]. However, in calves thrombus formation following calcification on the leaflets appears very quickly, often three weeks postoperatively, and good function of the tissue valve is lost. Dr. NOSE's group has
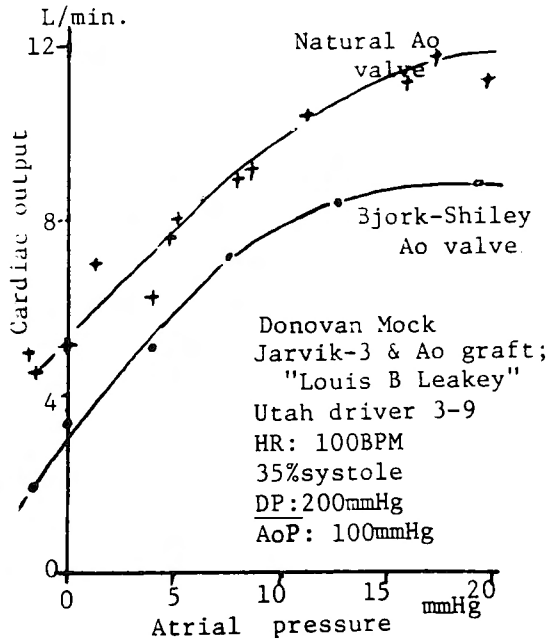
Fig. 28 Function of the natural outflow valve compared with that of the B-S valve. This test was performed 100 days after the TAH experiment.

reported good function of the dura mater valve[45] in a long-term surviving calf (145 days). The dura mater valve may be better than others, but tissue valves are not being used in this laboratory in calf experiments, at this time.

To get the best valve for the artificial heart, natural outflow valves have been saved in situ since 1975 in this laboratory[51]. The natural valves function well, even after six months of the experimental period and there are no calcium deposits on the leaflets at all. Fig. 28 shows the postexperimental function test of the natural valve, which was exised from the six-month survival calf, in the mock circulation system, compared with the function of the B-S valve. The function of the natural aortic valve was significantly superior to the function of the B-S valve.

F. *Equipment to drive pumping device*

To drive the blood pumping device, several types of driving control systems or energy converters[46] have been designed and developed since 1957 : a pneumatic driving system, an electromechanical driving system[55,17], an electromagnetic driving system[7], an electrohydraulic driving system[17,57], an hydraulic driving system[56], an electro-thermo-converter[60], and an atomic energy thermoconverter[54,8]. Among these driving systems or energy converters, the pneumatic driving system is the most common driving system in the animal experiments.

The Utah heart driver (Fig. 6) is the simplest and most reliable pneumatic driving system, including alarm systems and emergency systems. It was redesigned and developed

from the Kwan-Gett-type driving system[27] and the Wong-type driving system, in 1974. Since that time, the Utah heart driver has been used in more than 150 animal experments. The reliable lifetime of the Utah driver has been proven for over 1,250 days. Also, the Utah heart driver can be repaired very easily. It features modular construction, so that in case of failure of the electronics, which has not occurred, an entire printed IC circuit board can be replaced with a new one.

There are several alarm systems built in the Utah heart driver : an electric power failure alarm system, a pneumatic power failure alarm system, a vacuum failure alarm system, and an air-driven pressure monitoring alarm system. Those alarm systems give us individually different signals within 30 seconds after any failure occurs, and automatically switch to emergency supply systems. The air driving pressure monitoring alarm system is the most unique system. It starts to work in both cases when the air driving pressure drops below previously set limits, or when air driving pressure exceeds previously set limits. Other alarm systems are very simple but have saved many calves from accidental power failures.

The emergency systems which are connected to the alarm systems include an extra compressed air tank and emergency batteries. We alway hold another Utah heart driver for emergency use beside the main heart driver. Any calf sitter can switch the heart driver very easily and quickly. Those emergency systems have saved many calves.

The air drive lines which connect blood pump devices in the chest to the extracorporeal
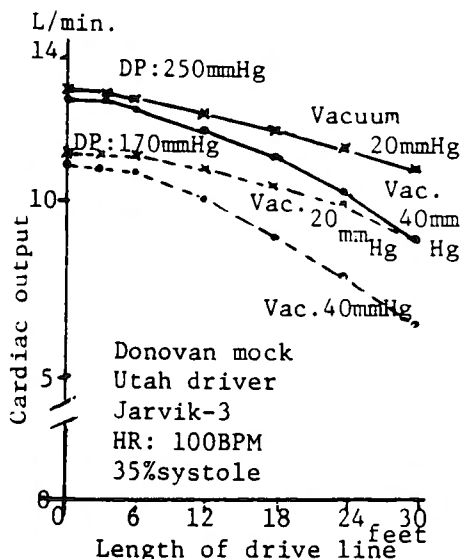

Fig. 29 Effect of long drive lines. The additional length of the drive line decreases the cardiac output. Increasing the positive and negative driving pressures increases the cardiac output in the mock circulation testing.
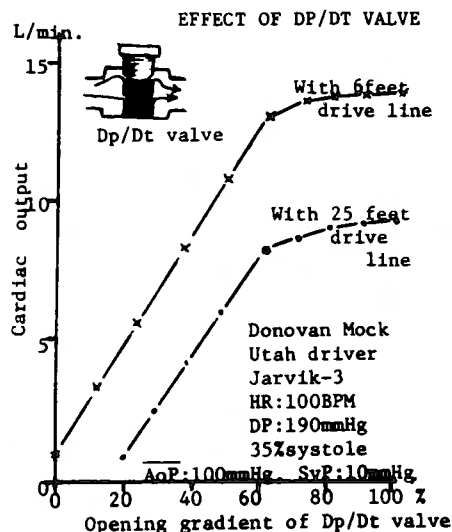
Fig. 30 Effect of the dP/dT valve built into the Utah heart driver. An 80 to 100 percent opening gradient of the dP/dT valve is uually used in animal experiments.

driving system are 9.5 mm OD in size and 2 meters in length. We have not used smaller or longer drive lines because of excessive air pressure drops with high resistance. There are dP/dT valves built in the positive pressure air drive lines which are located before the three-way stop valves, which change airways in both systolic and diastolic phases. Those dP/dT valves reduce only the dP/dT of positive pressures during the systolic phase, but not the dP/dT of the diminishing pressure during the diastolic phase, and protect the artificial valves in the heart and the natural arterial walls from breaking or high stress. Fig. 29 and 30 show effects of a long driving tube and the dP/dT valves. According to this data the effects of seven-foot drive lines and the dP/dT valve on cardiac output of TAH are better than that with only long drive lines, for control of air pressure raise and drop. High vacuum indicated during diastolic phase cannot compensate for the effects of long drive lines in the in vivo experiments, although high vacuum seems to compensate well in the in vitro experiments.

G. *Surgical implantation*

The techniques for surgical implantation of the artificial heart has progressed in parallel with the technology and design of the prosthesis[14]. At the beginning of the artificial heart research, a trans-sternal split was used, opening the sixth intercostal space on the right side across the sternum to the left space. This was obviously not the optimum approach, but the complexity, design and size of the prosthesis required maximum exposure of the atria and great vessels. The Dacron fibrilcoated silicone rubber 8 cm Kwan-Gett ventricles were much smaller than the previous hearts and were implanted by midsternal split in 1972. This was also not a good approach. The anatomical positioning of the calf on a table drastically alters the cardiac output. In three calves (70 kg) placed on a table awake, the cardiac output was 5.6 l/min in lateral recumbancy and 4.9 l/min in dorsal recumbancy. The values for the anesthetized calf were 5.0 and 4.0 l/min respectively. Subsequently a right lateral thoracotomy was adopted in this laboratory in 1973. This approach is applicable only when the prostheses fit well in the chest. Recently many other investigators have used either the right or left thoracotomy, replacing the natural heart of an animal with a TAH.

The right thoracotomy has been used for implantation of the J3 and J5 hearts with or without saving the natural outflow valves. The basic techniques of the present surgical procedures were developed in 1975 through 1977. The improved surgical techniques of the right lateral thoracotomy have been described in detail in the Methods section. Some recent improvements in surgical procedure which have led to a healthy survival rate of more than 75%, were the optimal adjusting of both ventricular positions to avoid kinking or obstruction of both inflow and outflow tracts, and gently placing of the artificial hearts in the chest. A deeper insight into the anatomy of coronary arteries helped to decrease the postoperative bleeding in most of our cases, to less than 400 cc. Excessive bleeding often caused postoperative pulmonary insufficiency and was often caused by the back flow from the Thebesian vessels in the atria. Placing an extra chest drainage tube at the upper side

DRIVING PARAMETERS IN PAST

Year	HR(BPM)	LDP mmHg	RDP mmHg	% Systole	Vacuum(cm)	Types of Heart
1971	90	300	150	33	10	Kwan-Gett (7)
1972	90	150	80	33	10-15	Kwan-Gett (8)
1975	90-100	210	120	33	15	Jarvik 3
1976	90-100	190	90	38	5	Jarvik 5
1977 present	90	145-165	45-65	35-40	5	Jaryik 5+outflow natural valves

Fig. 31 Various driving conditions used in the past.

of the lung has reduced the incidence of postoperative pneumo- and hemothoraxes and made the postoperative management simpler. The author believe now that the TAH is more reliable than the natural heart during at least the early stages of the postoperative course, and has never changed the idealized driving parameters, but looked for any surgical failures and corrected them, if necessary.

H. *Postoperative care*

The postoperative management is now extremely simple, especially since the last year. Circulating blood volume is adjusted carefully, monitoring right atrial pressure between 7 to 10 mmHg. Usually, extubation of the trachial tube is done within an hour or two postoperative, and the animals stand up within five hours. Previously, the postoperative management was so complicated that intensive care was necessary for at least an additional 24 hours, and sometimes for a week. The driving parameters of the heart driver were frequently adjusted to the optimum by watching the monitoring air-driving pressure waveforms. Reopening the chest almost always killed the animals. Preventive antibiotic therapies were always required to avoid severe infection, and anticoagulant therapies were necessary to avoid early thrombus formation. Most recently, two calves without antibiotics and anticoagulants survived for over five months (162 days and 150 days ongoing).

Long-term postoperative management is now extremely simple. During the last year we were able to dependably produce long-term survivors. Four out of eight over three-month survivors and ten out of eighteen over two-month survivors have been obtained during the last year. From these experiences, we have dicided idealized driving parameters (Fig. 8) which have been used for each postoperative period, and postoperative management has been simplified. Previously, various driving parameters were used as shown in Fig. 31. Very high driving pressures used to be used, which could easily lead to severe pulmonary edema or latent pulmonary edema. Most recently, low driving pressures less than 190 mmHg (usually around 155 mmHg) for the left ventricle and less than 80 mmHg (usually 60 mmHg) for the right ventricle are used. Those low pressure requirements have been achieved by the advances in materials and design of the diaphragm.

Diagnosis of the hemodynamic anomalies such as high atrial pressures, prolonged filling time of the blood in the ventricles, shortened effective ejection time, low aortic pressure, and high resistance of outflow tracts caused by the obstruction of the inflow and/or outflow
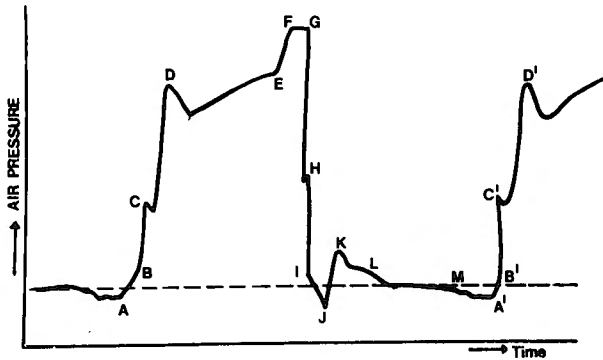
Fig. 32 Idealized air drive-line pressure waveform. Thirteen segments are now well explained in a full cycle of a heart beat, according the experimental results with the NASA telemetry systems. "A" indicates the end of the diastolic phase, "B" indicates the closing inflow valve, "C" the opening of the outflow valve, "D" is the beginning of the aortic blood flow, "E" is the end of the effective ejection time, "F" and "G" segments are the plateau of the setting drive pressure, and "H" indicates the closing of the outflow valve. "I" is the opening of the inflow valve, "J" and "K" are unknown, but overshots on negative pressure at the beginning of the diastolic phase, "L" is seen sometimes when blood from the atrium to the ventricle moves more slowly than the diaphragm does, and "M" indicates the end of the effective filling period.
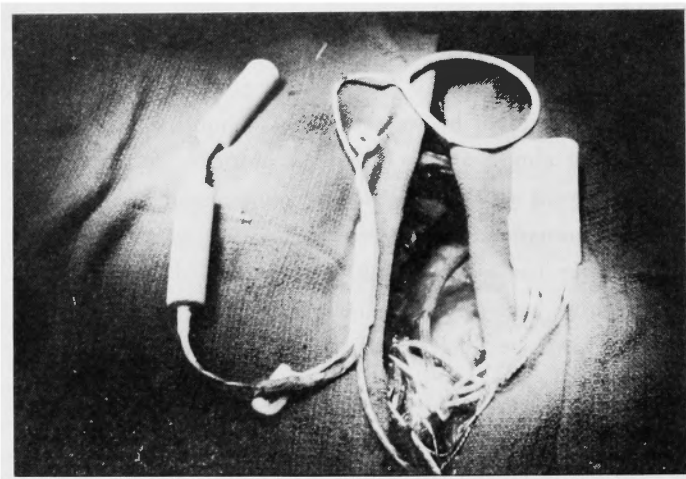

Fig. 33 An implantable NASA telemetry system. This system transmits three pressures, an ECG and a blood flow.

tract and broken diaphragms, which have been major causes of death in calves with a TAH, has been accomplished by studying the monitoring air drive pressure waveforms[15]. Fig. 32 shows an idealized monitoring air drive pressure waveform. This idea was originated by the studies of Dr. COLEMAN et al[22] in 1969 and was studied further by using the NASA telemetry system (Fig. 33) in 1976[16]. Fig. 34 shows the comparison studies of air driving pressure weves with the telemetered aortic, intraventricular and atrial pressures.
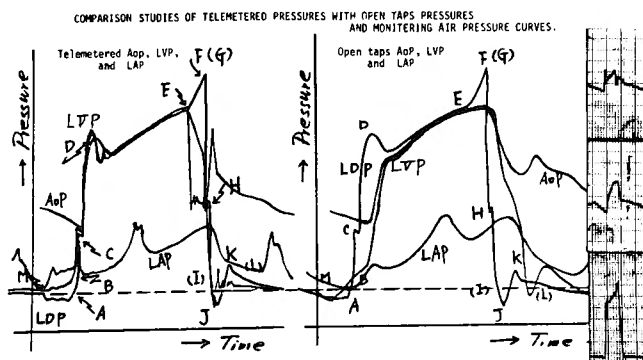
Fig. 34 Comparison studies of telemetered pressures with open pressure taps and monitoring air pressure curves. The telemetered pressures and the monitoring air pressures do not have delay, but the open tap pressures have delay and dumped curves.
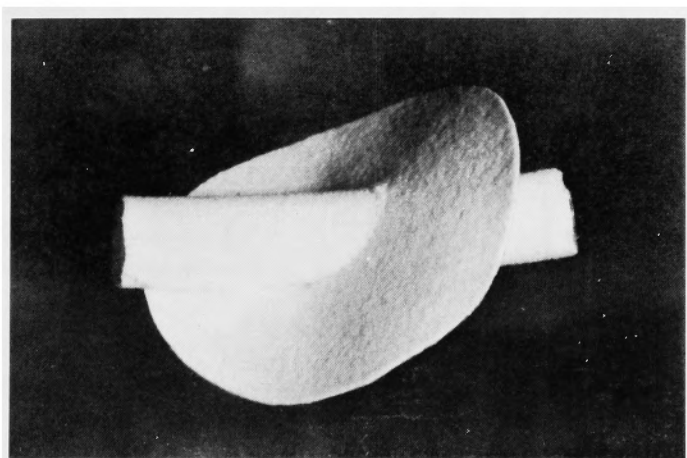

Fig. 35 A transcutaneous flange lead system. The flange protects the drive line from breaking of tissue ingrowth.

Thirteen segments on the air drive pressure waveform can be elucidated, as shown in Fig. 32. Since these studies were completed in 1977, the idealized monitoring air drive line pressure waveform has been utilized in the regular postoperative management.

Infection around the drive lines was minimized by utilizing a Dacron velour cover on the drive lines and a specially designed transcutaneous lead system (Fig. 35)[22]. There are still some degrees of infection around the drive lines in few cases. Nevertheless, extension of the infection into the chest cavity has been eliminated. Less infection made surgical reoperation in calves possible, and successful.

I. *Future human application of the total artificial heart*

Although a time for human application of the TAH cannot be predicted, our final goal is clinical use of the TAH. The first attemp at human application with a TAH was investigated by Dr. COOLEY et al in 1969[11]. It was not quite successful, and was followed by

heart transplantation on the third day postoperative. At this time no one knows when human application will be achieved. A number of questions and problems still remain to be answered or solved before the artificial heart becomes a clinical reality. There are several major problems : current design of the artificial heart for clinical use, durability of the device, acceptability of the physiological hemodynamic state with the TAH, and some of the rejection reactions including infection, pannus formation and neoplasm growth, against the foreign materials, or within the device etc., even when the animal experiments have achieved six-month survivals and 75% healthy survival rates. Development of an implantable power source and/or miniaturization of an extracorporeal driving control system are also an area of important research. Questions of efficiency, cosmetic and psychological acceptability and cost are just beginning to be considered[13].

First of all, to get an acceptable total artificial heart, one has to understand many different characteristics of the human, such as behavior, life style, psychological reaction and anatomical construction of the human circulatory system, as differentiated from an

Home(or hospital)Station

Substation-1 to 2 weeks

Human application
of pneumatically driven heart
(within 5 years)

Portable artificial
air diven heart
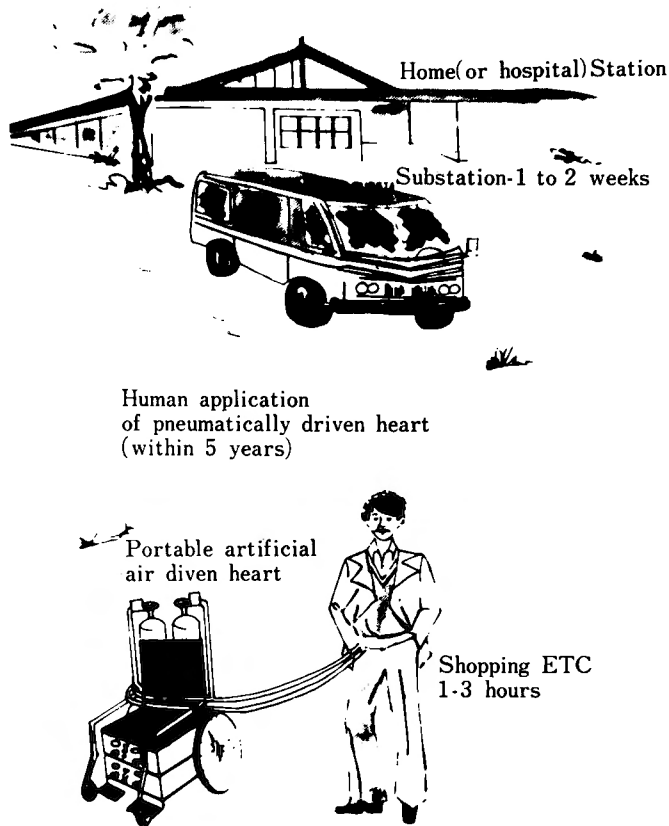
Shopping ETC
1-3 hours

Fig. 36 An illustrated idea for human application of the artificial heart, using the air-driven heart. The patient can leave his hospital for one or two weeks with a substation, and go shopping for one to three hours with his portable cart.

experimental animals. People spend much of their lives standing upright on their two legs, or resting on their backs, and enjoy life thinking about a lot of things. These human behaviors are quite different from that of experimental animals. An upright position on the two back legs, or a supine position, may drastically shift the operating point of the heart on the STARLING's curve. Also, the human being is psychologically so sensitive that people, especially sick people, may have trouble with limited mobility and high levels of noise caused by the artificial heart. Additionally, we have to consider the expectation of people for the artificial heart. A patient dies in a few minutes after the heart stops. Security for the TAH should be extremely excellent, or should be replaced with a new TAH, or others (such as a natural heart transplantation). Two years of longevity might not be sufficient. Five years of longevity might be required, although few man-made machines can be insured, with a high grade, for five years.

Since 1976, when many calves with a TAH started to survive for over three months, and especially during the last year, translation of the great advances in research has been conducted from experimental animals to clinical reality, and some of the alterations have made progress. Development of proper human-fit ventricles, the noiseless heart driver, portable heart driver, automatic feedback systems, surgical techniques for reoperation, computerized monitoring systems, and a new type of artificial heart (electrohydraulic heart) etc. have been started, or in some instances completed. Fig. 36 shows one of our illustrated ideas for the next human application of the TAH in the near future. In this picture, there are two big drive lines for pneumatically driven hearts. Those two drive lines will be soon replaced by a few small wires of the electrohydraulic heart, which is now in progress, or with other new types of electrically driven hearts including the DOE heart. There are two applications of the TAH : temporay use and permanent use. For either temporary or
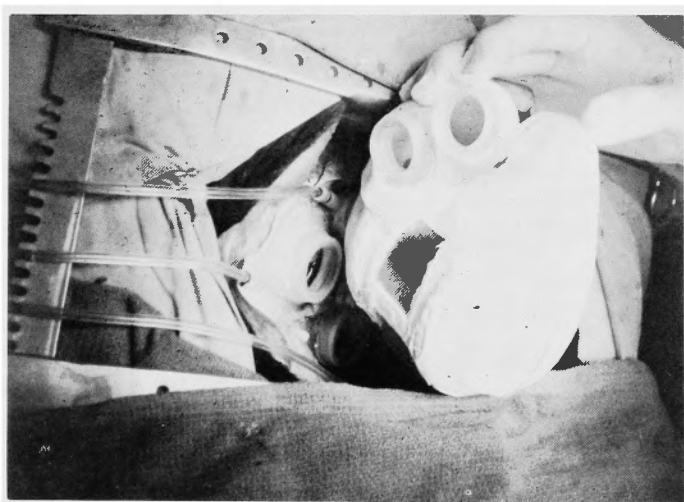

Fig. 37 The integrated electric heart (DOE heart). This type of heart has only a few electric wires through the skin. The longest survival time with this type of heart has been thirty-seven days in calves.
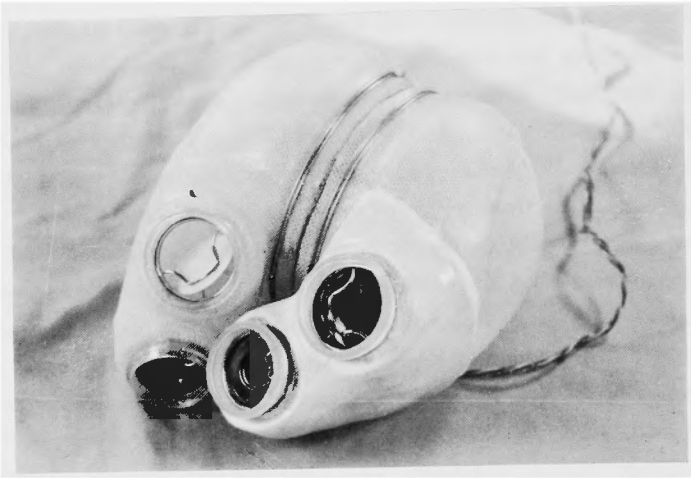
Fig. 38A
An axial flow pump with
DOE-type ventricles.

Fig. 38B
An axial flow pump with
Jarvik-5 ventricles.

Fig. 38　Electrohydraulic hearts. Recently, a small, reversing, axial flow pump is utilized in
the artificial heart. The mock circulation testing has demonstrated the function of
these electrohydraulic hearts.

permanent usage, elimination of infection or pains around the large drive lines is necessary.

J.　*Electric and electrohydraulic hearts*

　　　The electrically powered devices are the most promising for eventual human use, as a United States governmental agency, the National Heart, Lung and Blood Institute (NHLBI) recommends. The electromechanically driven heart (ERDA heart) has successfully developed an effective and reliable blood pump[45], which requires only 14 watts of electrical power, and has been effectively implanted in the calf since 1972. The longest survival time achieved with this type of electrically driven heart was 37 days and recently, we have eliminated the abdominal electric motor, by replacing it with a small, brushless DC motor

which attaches directly to the blood pump in the chest, and requires no cooling system[17,57] (Fig. 37).

We are also devloping an electrohydraulically driven heart[17] using an axial flow pump energy converter (Fig. 38). The main advantage of this system over the other is its great simplicity. There is only one moving mechanical part ; that is, the reversible motor with the rotor of the axial flow pump attached to it, and there are only two sets of ball bearings. This flow pump with reversible motor pumps hydraulic fluid back and forth, and can be attached to both ventricles. The diaphragm that separates the hydraulic fluid from the blood can be pulsated with the hydraulic fluid flow. If one uses two axial flow pumps with the J5 ventricles, one can control the right and left ventricles separately, just as the pneumatically driven heart can be. The power consumption of this system will be as low as, or less than other electrically driven hearts. Higher than 25% efficiency might be possible on power utilization.

Summary

The long-term survival of up to six months, and a healthy survival rate up to 75% have been achieved in animal experiments by 1978. These achievements have been due to the effective infusion and/or adaptation of technologic advances in a wide variety of disciplines. Some of the important disciplines have been biomaterials, engineering, heart manufacturing, surgery and postoperative management.

With this achievement the translation of the great advances in the experimental animals to clinical reality is continuing with great optimism. It is only after two decades of continuous research on the TAH. With these advances, the surgical and postoperative treatments for the total natural heart replacement with the artificial heart are not complex, but easy and stable. We can say now that the artificial heart is more reliable than the natural heart, for at least a certain period of time.

Further development of the TAH is now in progress for clinical use. The human has quite different characteristics of behavior, life style, psychological reactions, as well as anatomical construction of the circulatory system, than the experimental animals. So, there are still a number of problems and questions which should be solved or well answered before the artificial heart becomes a clinical reality. To get more suitable artificial hearts, the electrohydraulic heart is now under development.

After all, we hope to create happiness—not prolong misery of the patients with a artificial heart.

Acknowledgements

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和文抄録

完全置換型人工心臓の実験的研究

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完全置換型人工心臓の研究は1957年コルフ教授，阿久津教授らの研究によって開始された．その後20年の才月を経て初めて，近い将来臨床応用可能な人工心臓が開発されるだろうと予想されるまでに至った．過去の動物実験においても3カ月に及ぶ長期生存の症例が得られたが，その記録は普遍的なものでなく15%以下の確率で得られたものであった．完全置換型人工心臓が臨床応用可能であるためには，常に高い確率で長期の生命維持がなされなければならず，しかもその生命維持の質が高いものでなければならない．本研究はこの要求に答えるためのものであった．人工心臓の現実の姿と生体側からの要求のギャップを，植え込み動物実験の場において単純化し，明確化することによって，現実の人工心臓の欠点を明らかにする必要があった．結果は75%以上の確率で，動物実験の長期生存例を得ることが出来た．動物死体を利用してデザインした人工心臓は生きた生体内で解剖学的にしばしば適合するものでないことが明らかにされた．ポリウレタン製の人工心室は抗血栓性にすぐれ，血液接触面の人工心室内面を全く結ぎ目のないものにする様デザインされたジャルビック型人工心臓は人工心臓内にほとんど血栓を認めることなく仔牛の生命を長期に維持し得た．仔牛を使用した実験では，3カ月以上7カ月に及ぶ長期生存例を得るに至って，自然心血管組織と人工心臓材料の接点の部分で，異常結合組織性の増殖反応（パヌス形成および結合組織芽細胞性増殖）が認めるに至った．この異常増殖反応は解決されなければならない．その他の主な実験動物の死亡原因は仔牛の急速な成長に伴う相対的低心拍出量によるものであった．本研究の結果，近い将来，臨床応用可能な完全置換型人工心臓が確実に開発されるであろうことが示唆された．