

Homotransplantation of the Heart in Puppies Under Profound Hypothermia: *

Long Survival Without Immunosuppressive Treatment

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SUCCESSFUL homotransplantation of any organ depends upon the solution of four main problems:

1. Procurement and preservation of the graft in a viable state.
2. Development of a satisfactory surgical technic.
3. Physiologic compatibility.
4. The host's immune response and/or homograft tolerance.

In regard to the last—and major—problem, the heart has certain advantages over other organ transplants:

1. Its histologic structure is rather simple in comparison with that of the kidney, liver or even the skin.
2. Its functioning can be followed precisely by comparatively simple observations.
3. Termination of graft functioning, or ultimate rejection of the donor heart, instantly terminates the life of the host.

Various means of handling the graft preoperatively and carrying out the actual transplantation have been advanced since Carrel⁶ kept an isolated heart viable for 2 hours in 1905. Most of these heart grafts have been heterotopic, imposing no burden on the host's circulation.

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Lower and Shumway¹⁸ were the first to achieve orthotopic homotransplantation of the heart (1960). After many attempts, five dogs survived 6 to 21 days with the transplanted heart completely supporting the circulation. Stimulated by this work, a number of other centers used the same technic but results were disappointing. In 1963, however, Blumenstock and co-workers⁵ reported survival of 8 of 50 dogs for periods ranging from 1 to 42 days. All their animals were treated with Methotrexate after operation. So far, because of technical difficulties, homologous heart transplantation by these two groups has resulted in only a limited number of survivals for more than 24 hours.

The present report is concerned with a reliable and effective method of heart transplantation under profound hypothermia without a pump-oxygenator.

Materials and Methods

Forty pairs of puppies weighing 3,000 to 4,800 Gm., previously immunized against canine distemper and hepatitis, were randomly selected on the basis of approximately matching weight. The recipient—premedicated with 0.15 mg. atropine sulfate, 3.0 mg. chlorpromazine and 10 mg./Kg. pentothal sodium intramuscularly—was anesthetized with ether to the third plane of the third stage and fixed in the supine position. Respiration was assisted by supplying 98% O₂ and 2% CO₂ via a respira-



FIG. 1. Total set-up for recipient (in immersion tub) includes recorder, respirator equipment, strain gauge and ECG leads.

tor and modified Ayre tube, and controlled by intermittent positive pressure breathing (IPPB) after the rectal temperature had dropped below 25° C.

Left femoral arterial pressure was continuously monitored through a polyethylene cannula by means of a Satham pressure transducer† and a Sanborn recorder.†† The electrocardiogram was similarly recorded throughout the procedure. Rectal and esophageal temperatures were taken by a Telethermometer and recorded. The left femoral vein was cannulated for a continuous drip infusion, and the right femoral vein was used for single drug injections.

After all preliminary preparations were completed, cooling of the recipient puppy was started by ice-water immersion (Fig. 1).

The donor puppy was also anesthetized and similarly managed except that femoral arterial pressure was not recorded. In our initial experiments, profound hypothermia (16°–17° C., rectal) was used for the donor in seven instances and normothermia in two. Moderate hypothermia (27°–29° C.,

rectal) was employed in the later experiments and yielded much better results. Cooling of the donor was started when the recipient's rectal temperature was 26° C. The fixation table was lifted and rested on the tub to stop cooling when the recipient's rectal temperature reached 19° C. and the donor's about 30° C.

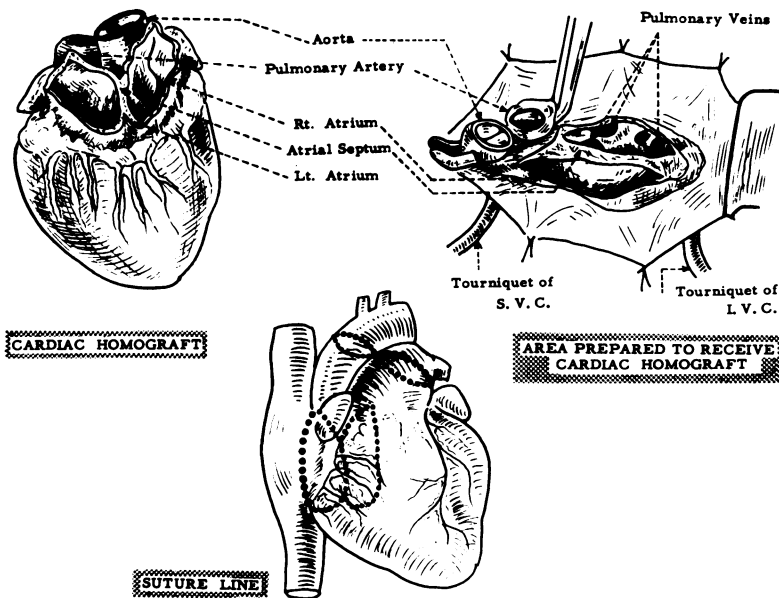
The recipient and tub were completely covered with a sterile vinyl sheet and both chest cavities were opened through the anterior 4th intercostal space. The azygos vein was ligated. The superior and the inferior venae cavae were dissected and taped for tourniquet. The pericardial sac was opened widely and partly fixed to the chest wall incision. By this time the body temperature was about 16° C. or 17° C. where it remained throughout the operative procedure.

Principal modifications of the Lower and Shumway¹⁸ technic for removing and reimplanting the heart were as follows. Use of complete circulatory arrest—since there was no bleeding during the actual transplantation, permitting excellent visualization and maneuverability of the heart, we did not form the pericardial sac into a well. Also, the heart was sutured in directly opposite fashion, beginning with the superior

† Model P23 Db, Satham Instrument Co., Los Angeles, Calif.

†† Model 954 A-100, 4-Channel Recorder, Sanborn Co., Waltham, Mass.

FIG. 2. Attachment of vessels and atria of donor heart to their counterparts in recipient. (lower sketch) Suture started at superior aspect of right atrium is continued around chamber, through atrial septum and to left atrium, finishing at inferior portion. Aorta and pulmonary artery are then anastomosed.



part of the right atrium. This thin portion was handled without too much difficulty since the heart could be moved readily.

The venae cavae were occluded by tourniquet. The aorta and pulmonary artery were cross-clamped within the pericardial sac through the transverse sinus. The heart was excised at its posterior attachment to both atria and the atrial septum, about 1.0 cm. distal to the aortic and pulmonary valves. Artificial respiration was stopped at this time.

The second operating team had meanwhile opened the donor's chest cavity, injected 10 mg. heparin into the vena cava and similarly excised the heart. It was immediately placed in cold normal saline (4° C.) in the first 14 experiments, but in Tyrode solution (4° C.) in the last 26 experiments which gave much better results. The heart was kept in the solution 10 to 30 minutes.

To affix the heart, stay sutures of 4-0 silk were placed at both ends of the atrial septal ridge. Starting from the superior aspect, the right atrium was approximated with a continuous suture. The atrial septum

was sutured from the inferior to the superior aspect, with final closure of the left atrium at the inferior portion. The aorta was anastomosed with a continuous over-and-over suture of 5-0 silk. The left atrium and left ventricle were flushed with cold saline or Tyrode solution before the last suture was placed, to expel any air bubbles. Lastly, the pulmonary artery was anastomosed with a continuous 5-0 silk suture (Fig. 2).

After removal of the tourniquet and clamp, IPPB and blood transfusion were started. The duration of circulatory arrest to this point was 45 ± 5 min. For rewarming, the puppy was immersed in a 42° C. water bath, and the chest cavities were flushed with normal saline at the same temperature. Cardiac massage, begun at this time, was continued until the myocardium resumed good tonus and vigorous ventricular fibrillation. The temperature was raised to 26° to 28° C. (rectal) within about 20 minutes. The heart beat was readily started by applying countershock of 60 cycles/sec. frequency, 110 volts, and 0.1 sec. duration. In a few instances the heart beat was

FACTORS IN TRANSPLANTATION TECHNIQUE

RECIPIENT DOG NO. 1022 3200 Gm.
DONOR DOG NO. 2022 3300 Gm.

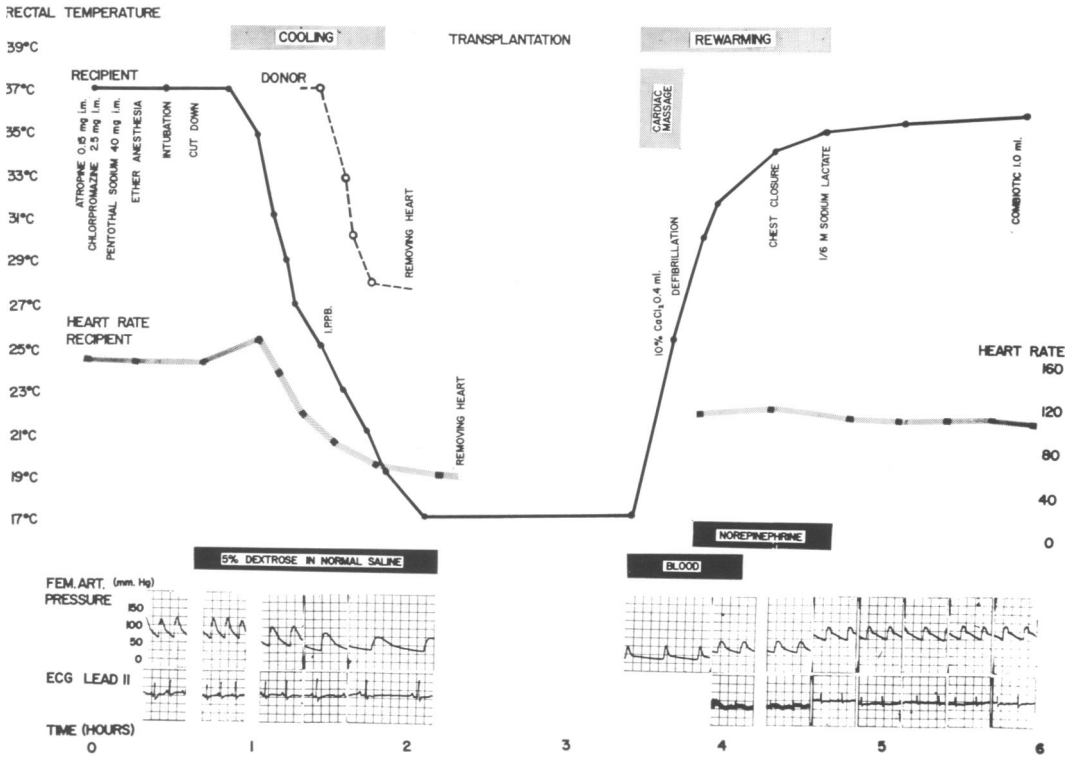


FIG. 3. Time scale (below) indicates relationship of procedure steps. Recipient's rectal temperature shown by solid line and donor's by dotted line; heart rate before and after grafting shown by shaded line. Lower left and right: femoral arterial pressure and ECG.

resumed without countershock. Additional heart massage for a few minutes was usually required. A slow intravenous drip of *l*-norepinephrine in 5% dextrose or an intraventricular injection of calcium chloride was sometimes necessary to support the blood pressure.

Rewarming was continued until the rectal temperature reached 35° or 36° C. The chest cavities were closed in three layers with a chest tube on each side for drainage. Blood (30–50 ml.) was transfused to replace the amount lost. Factors and time relationships of the total procedure appear in Figure 3.

The animal was fed liquids through the first postoperative day and thereafter a

normal diet. Antibiotics were administered daily for 1 week.

No attempts were made to suppress the immune reaction. ECGs, blood samples and chest x-rays were taken at intervals. Post-mortem histologic examinations were done on all animals.

Results

Survival Time

Twenty-four of 40 animals lived more than 24 hours; 13 lived more than 7 days. One is alive and well on the 112th day without immunosuppressive treatment. The other 12 survived 57, 25, 20, 20, 17, 15, 15, 15, 12, 12, 10 and 8 days, respectively, without immunosuppressive treatment.

In 13 animals, effective circulation was restored for more than 8 hours but death occurred within 24 hours. Three animals died in the immediate postoperative period. The causes of death in these groups, shown in Figure 4, were: brain damage from prolonged circulatory arrest due to technical failure (5 cases); ineffective circulation due to graft failure (8 cases); other technical failures such as intractable hemorrhage (1 case), faultily applied hypothermia (1 case) and air embolism (1 case).

As shown in Figure 5, all transplants in the last 26 experiments supported effective circulation during the immediate postoperative period. With the donor kept under moderate hypothermia and the graft preserved in Tyrode solution, 20 of these puppies (77%) lived more than 24 hours. Experience as well as improvements in technic undoubtedly contributed to the higher survival rate.

Postoperative Course

In successful experiments, spontaneous respiration had been started before the rectal temperature returned to normal. The

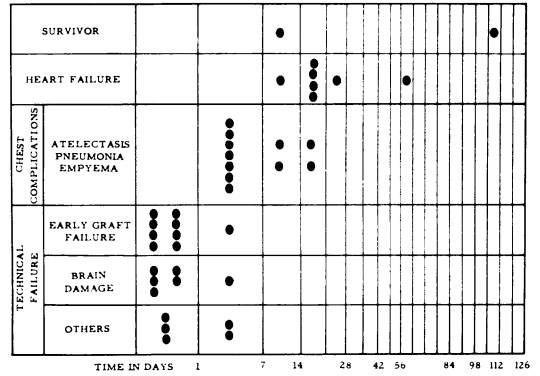
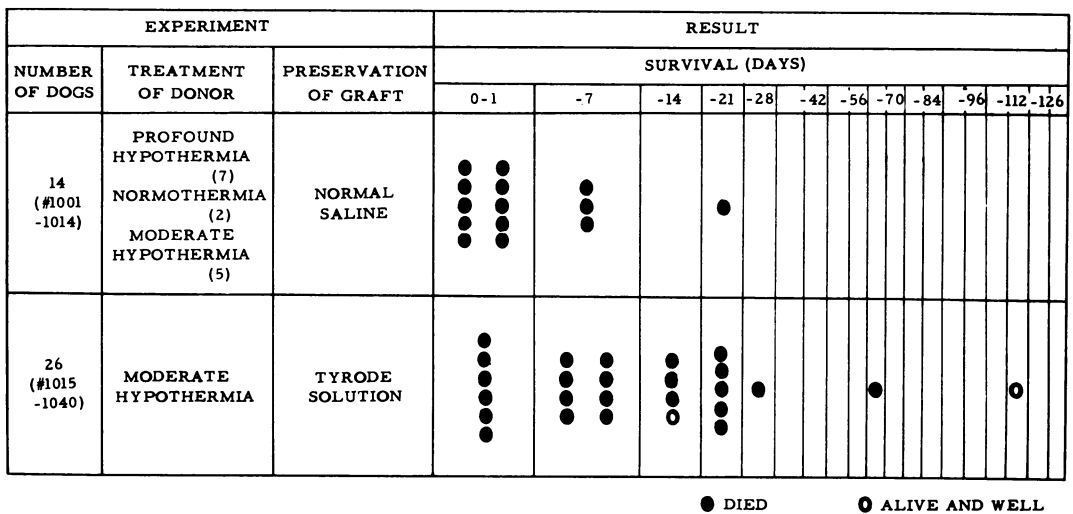


FIG. 4. Survival time and causes of death in 40 experiments.

puppies were almost completely conscious within 12 hours. Serum electrolyte balance was not significantly altered. To adjust the pH, which dropped slightly just after operation, 5-10 ml. of 1/6 M sodium lactate was administered intravenously. On the first postoperative day the puppies walked around and took fluids well. Body weight increased gradually. Chest complications including pneumonia, atelectasis or empyema—the most annoying problem in canine thoracic surgery—sometimes resulted, fatally, within 3 weeks. In such cases the infectious process may well have



● DIED ○ ALIVE AND WELL

FIG. 5. Survival data according to depth of hypothermia and type of graft preservation in 40 experiments.

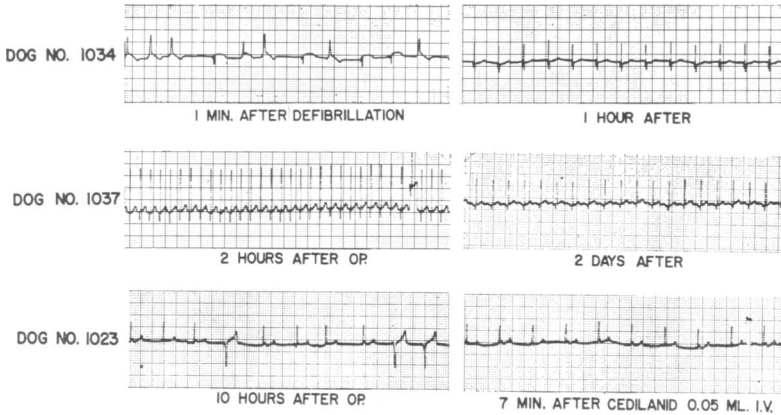


FIG. 6. Extrasystole noted after defibrillation in Dog 1034 had disappeared 1 hour later. Ventricular tachycardia after operation in Dog 1037 was not evident 48 hours later. Extrasystole disappeared shortly after I.V. Cedilanid injection in Dog 1023 although A-V dissociation persisted, a common finding. (Lead II)

masked the rejection phenomenon at the postmortem examination. Details of the postoperative course of the two longest survivors will be given later.

ECG, Arterial Pressure and Pulse Rate

ECG and femoral arterial pressure readings shortly after operation for the most part showed regular cardiac activity. In some cases, however, the ECG revealed low voltage and various irregularities such as premature ventricular contraction, A-V dissociation or ventricular tachycardia shortly after resuscitation (Fig. 6). Except for A-V dissociation, these changes usually disappeared on the first postoperative day and thereafter the pulse was fairly regular with a constant rate of 110–150/min.

The transplants were quite sensitive to *l*-norepinephrine (Levophed). In several cases the graft could maintain sufficient blood pressure only if this intravenous drip were continued for several hours. The prognosis was not good in these animals.

Follow-up ECG data are shown in Figure 7. The transplanted heart usually maintained an almost constant rate even after the puppies exercised.

As shown in Figure 8, the final fate of the transplants was evident from the ECG record in several cases before the puppy's general condition suggested that death was imminent.

Data on Long-Term Survivors

Dog 1022: On April 24, 1964 a 3,200-Gm. female German Shepherd type puppy

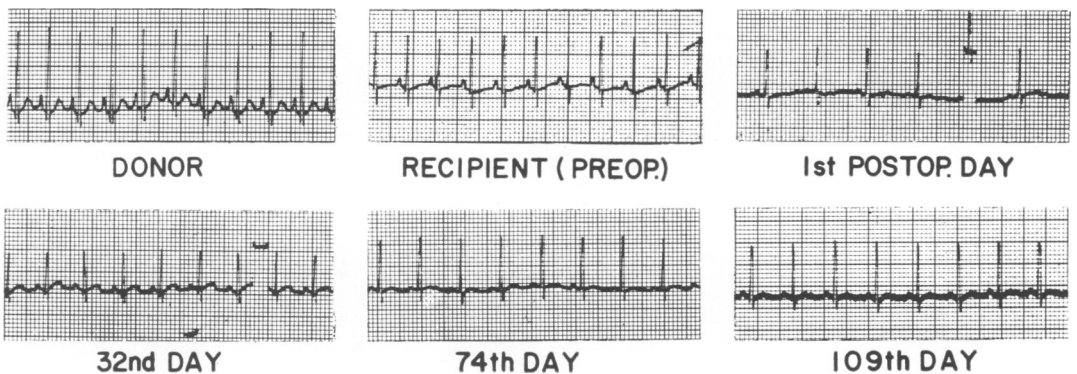


FIG. 7. Follow-up ECGs in Dog 1022. (Lead II)

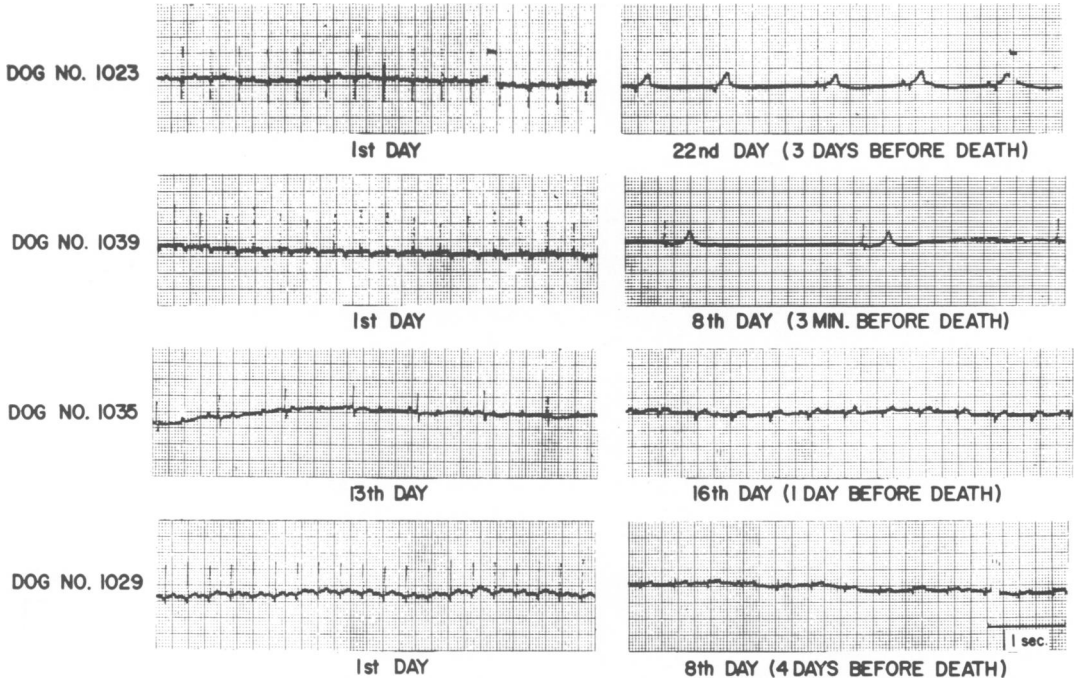


FIG. 8. ECGs in four animals shortly before death (Lead II).

received the heart of a 3,300-Gm. female of the terrier type. The operation was performed as described. The period of total circulatory arrest was 60 minutes (Fig. 3). Since the postoperative course was uneventful, the only drug used was an antibiotic agent for 1 week. Follow-up ECG and laboratory findings appear in Figures 7 and 9. This animal has moderate anemia, hypoproteinemia and lymphocytosis, but body weight increased steadily with proportional growth of the heart, as shown by x-rays. On the 112th postoperative day, physical activity is completely normal.

Dog 1018: On April 2, 1964 a 3,900-Gm. female mongrel puppy received the heart of a 4,000-Gm. unrelated female. The homograft functioned smoothly at the start and the postoperative course was uneventful. She suffered from a dry cough but seemed otherwise well until the 53rd day when ascites rapidly appeared. Breathing difficulty developed and the dog became torpid. The ECG showed regular sinus

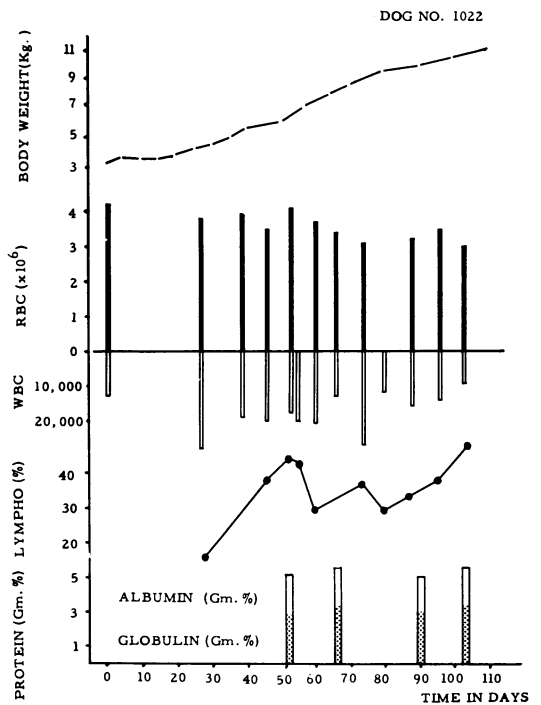
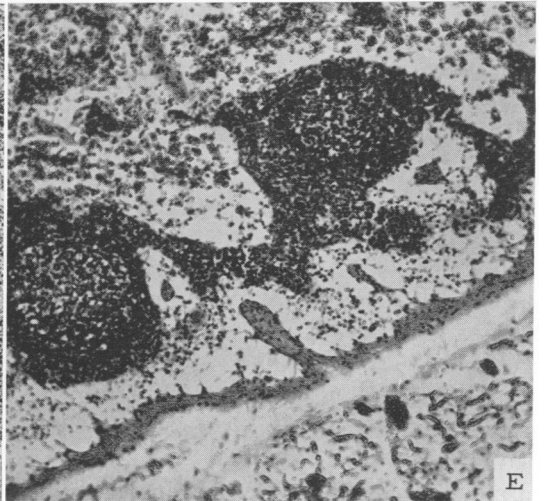
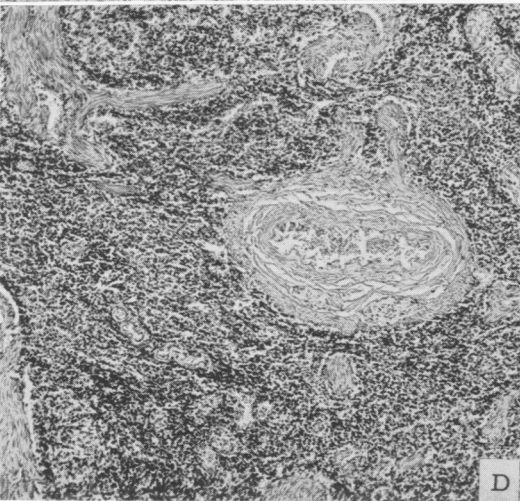
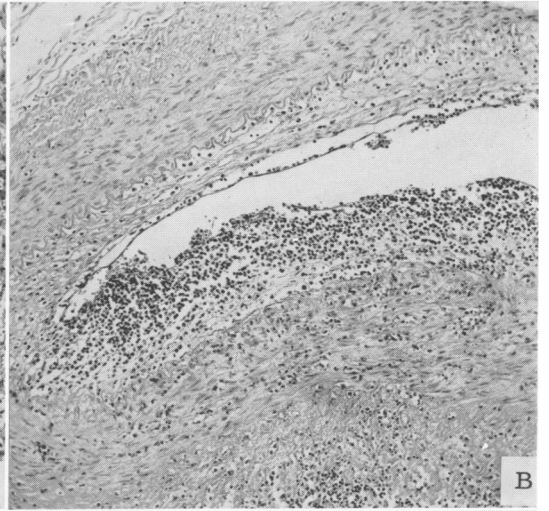
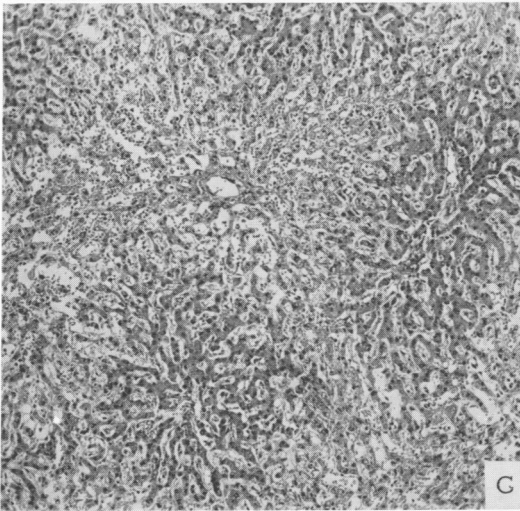
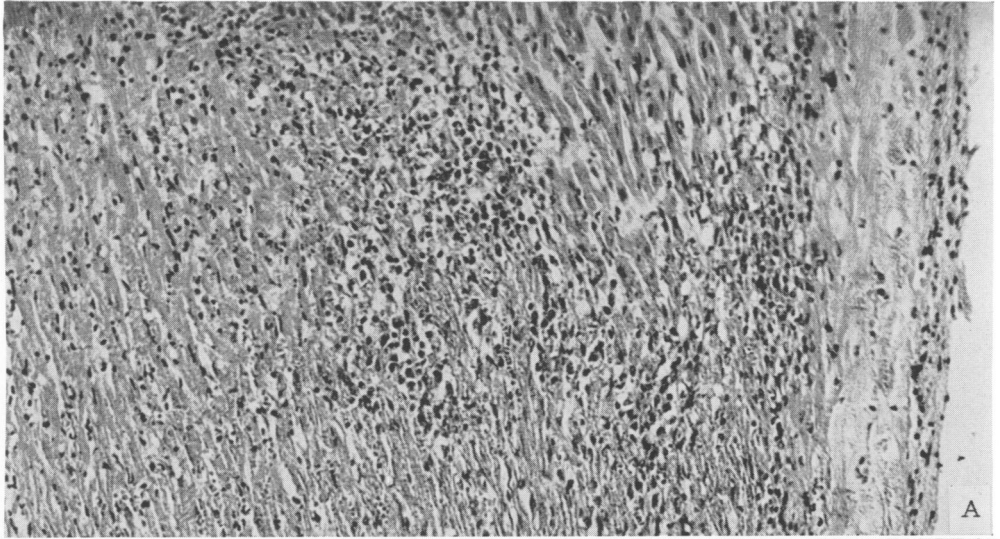


FIG. 9. Postoperative course in Dog 1022 (living on 112th day).



rhythm with a tall P wave and low voltage. Death on the 57th day was caused by congestive heart failure. Autopsy revealed a slightly enlarged heart, severe congestion of the liver and spleen with 1,000 ml. of ascitic fluid, and 100 ml. of pleural effusion.

Histopathology

The following findings were typical of the series. The heart in Dog 1016 (15-day survivor) showed endocarditis, focal myocarditis and epicarditis with focal calcific deposits. Changes in the arteries were comparable to those occurring in human polyarteritis. Bronchopneumonia had developed and moderate reticulum cell hyperplasia was found in the spleen.

The heart in Dog 1018 (57-day survivor) showed a recent myocardial infarct of the anterior wall, focal necrosis of the papillary muscle, acute endocarditis and thromboangiitis of the left circumflex artery. Mild bronchopneumonia, chronic passive congestion of the liver, passive congestion of the spleen without follicular hyperplasia, sinus catarrh of the mediastinal lymph nodes with hemorrhage and interstitial round-cell infiltration of the kidneys were also evident. Several of these sections appear in Figure 10.

All heart sections in Dog 1029 (12-day survivor) showed fairly extensive myocarditis. As seen by the myocardial section crossing the suture line, this condition was much more severe in the graft than in the host (Fig. 11). Other findings were acute interstitial pneumonitis, acute splenitis and acute lymphadenitis with clusters of histiocytes.

The myocardium was normal in Dog 1003 (5-day survivor).

Sections from the anterior wall of the heart in Dog 1011 (20-day survivor) revealed acute epicarditis and a normal myocardium. Other findings were early bronchopneumonia with moderate congestion, edema and atelectasis, reticulum-cell hyperplasia and sinusoidal dilatation of the lymph nodes, and increased numbers of reticuloendothelial cells in the spleen.

Signs of severe bronchopneumonia were found in Dog 1023 (25-day survivor) but the myocardium was virtually normal.

Discussion

Carrel *et al.*,⁶ pioneers in organ homotransplantation, placed a puppy heart in the neck of an adult dog (1905), but unfortunately did not report details of their technic. In 1933, Mann and co-workers²¹ re-established coronary circulation by anastomosing the host's carotid artery to the aorta of the homograft and the host's jugular vein to the pulmonary artery. Other investigators* later carried out similar experiments. In some instances the heart was transplanted to the abdomen or the groin.^{23, 32} It rarely beat in the new site more than 10 days.

Neptune and colleagues²⁶ were the first to report orthotopic homotransplantation of the canine heart, using hypothermia (1953). Their three dogs survived 3, 4, and 6 hours, respectively. Recent experiments of this kind performed with a pump-oxygenator by Webb *et al.*,^{33, 34} Blanco *et al.*,⁴ Berman *et al.*² and Cass *et al.*⁷ have yielded poor results. The first real breakthrough was by Lower *et al.* who used a pump-oxygenator. Five of their dogs with a heart transplant survived 6 to 21 days,¹⁸

* 1, 3, 8, 11, 22, 23, 29, 30, 31, 32, 35.

FIG. 10. Autopsy findings in Dog 1018 (57-day survivor) include: A. Focal necrosis of papillary muscle (H & E, $\times 400$); B. thromboangiitis of coronary artery; C. chronic passive congestion of liver; D. passive congestion of spleen; E. sinus catarrh of mediastinal lymph nodes with hemorrhage (H & E $\times 210$).

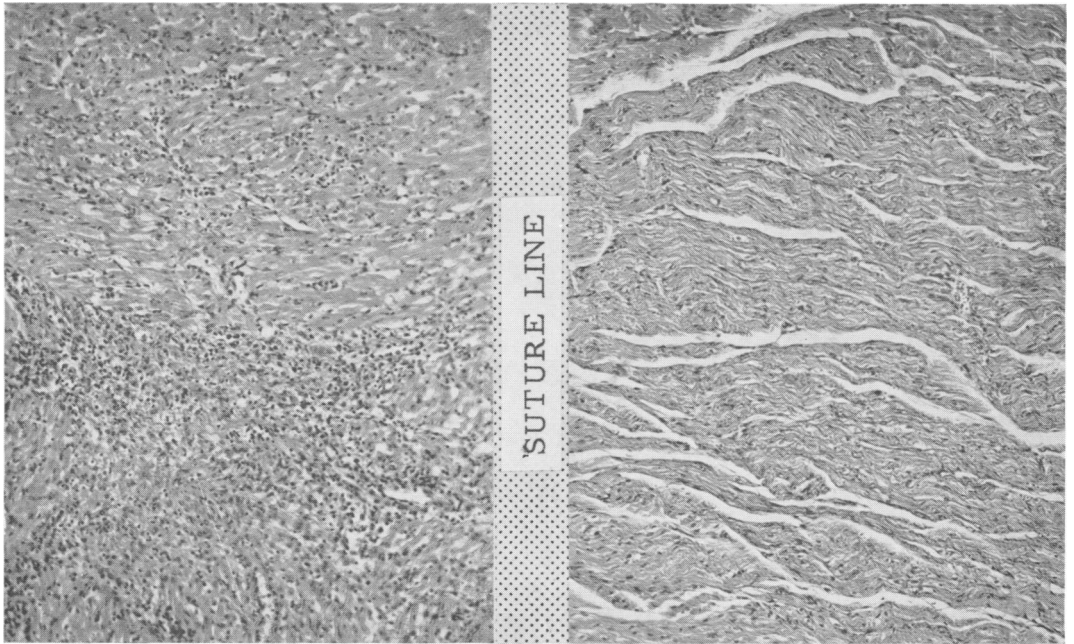


FIG. 11. Myocarditis in Dog 1029 (12-day survivor) was more severe in graft (left) than in host (right).

²⁰ and two with a transplanted heart and lung survived 5 days.¹⁹ Many other investigators using these technics have reported no long-term survivors.^{12, 13, 15} However in 50 such experiments by Blumentstock *et al.*,⁵ 8 dogs lived more than 1 day and one lived 42 days. Methotrexate was administered after transplantation.

In preliminary studies we transplanted the heart by the same method, using a pump-oxygenator, but had no long-term survivors. Intractable hemorrhage after operation, a major problem, has been avoided by relying on profound hypothermia and no pump-oxygenator.

In the last 26 experiments, all transplanted hearts supported adequate circulation in the immediate postoperative period, and 77 per cent of the animals survived more than 1 day.

One puppy is living on the 112th day and another survived 57 days—to our knowledge a record for heart-transplant animals with or without immunosuppressive treatment. In common with others working with dogs,¹⁷ we found chest com-

plications such as atelectasis, pneumonia and empyema a continuing threat and lost many animals to these complications. The fact of a few unexpectedly long survivals without immunosuppressive agents, which may be explained by unpredictable histocompatibility,²⁴ is encouraging us to further efforts centered on graft-host grouping.

Microscopic examination of heart tissues from the long-term survivors revealed no unequivocal evidence of the rejection phenomenon. Some changes noted in Dog 1018 (57 days), Dog 1016 (15 days) and Dog 1029 (12 days) might indicate rejection, but in Dog 1011 (20 days) and Dog 1023 (25 days) the myocardium appeared normal. Previous studies in some laboratories using Mann's method²¹ suggest that rejection is usually manifest within 10 days. Since these groups also worked with puppy heart grafts, the discrepancy may be due to better toleration of a dynamically functioning heart than one merely beating without any load on the left ventricle.

Lee *et al.*,¹⁶ in experiments with renal homotransplantation in dogs, reported a

mean survival time of 19.2 days for the renal grafts in puppies and 10.2 days in adult animals, with immunosuppressive treatment. It is believed that young animals tolerate homologous transplants better than adults, perhaps another reason for our encouraging results.

The transplanted heart's steady increase in size, proportional to the body weight gain, suggests eventual use of the method for infants with congenital heart failure.

Possible clinical application, once the immunologic enigma has been solved, is strongly indicated by successful autotransplantation of the canine heart by Hurley *et al.*,¹⁴ Dong *et al.*,^{9, 10} and Willman *et al.*,^{25, 26, 27} Despite some discrepancies regarding the effect of denervation, several of their dogs survived more than 2 years with a well-functioning heart. This view is similarly supported by our long-term survivors.

In our basic studies of profound hypothermia in puppies, from which the present method of transplantation evolved, 70 minutes was demonstrated to be the safety limit of circulatory arrest for the brain at the temperature used. Our procedure falls well within this limit. In early experiments blood pressure during rewarming was often inadequate because of graft failure or time-consuming operation due to faulty technic, and the brain was sometimes damaged. However this complication has been very rare in later cases. Excellent results with clinical application of the same method of profound hypothermia have been reported by Niizu, Okamura *et al.*,^{27, 28} They performed open-heart surgery, *e.g.*, for total correction of tetralogy of Fallot, under profound hypothermia (17–20° C.) without a pump-oxygenator, stopping the entire circulation for 1 hour.

We are using immunosuppressive treatment (Imuran) in a few cases in an attempt to prolong the mean survival time. Also we have transplanted heart grafts preserved for 24 hours. The data will be reported in the near future.

Summary and Conclusions

A satisfactory technic for orthotopic homotransplantation of the heart under profound hypothermia without a pump-oxygenator has been presented. Twenty-four of 40 puppies survived more than 1 day; 13 lived more than 7 days. One dog is alive and well on the 112th postoperative day.

The transplanted heart showed some irregularity shortly after operation, but the beat usually became regular on the first postoperative day and remained constant even after exercise. The puppies were normally active, and most laboratory findings were normal. The follow-up ECG record appears to be a fair indication of the fate of the transplant.

Although histologic findings have not been uniform, homologous heart grafts have been accepted much better than expected. In long-term survivors the heart size increased proportionally with the body and was reinnervated gradually. Such cases can probably be explained by unpredictable histocompatibility. Possible clinical application of cardiac homotransplantation in the future has been discussed from several standpoints.

Acknowledgments

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