SUCCESSFUL TRANSPLANTATION OF A healthy vital organ to replace a diseased one has been a long sought dream of mankind. Most transplantation work has been directed toward the kidney. In the short span of 14 years, human renal transplantation has progressed from developmental uncertainty to a therapeutic endeavor that has rehabilitated many patients in terminal renal failure, despite the numerous problems involved. As a result, the feasibility of attempting other whole organ transplants has received tremendous impetus.

Paired organs such as the kidney may be obtained from healthy living donors, whereas lung, liver, and heart homografts for human use can only be obtained from cadavers. Before we can routinely use such organs on a wide scale, methods for procurement and storage of whole organs must be realized. The purpose of this report is to emphasize and describe the importance of certain technical details that we encountered during experiments involving homotransplantation of stored lungs, and to outline pertinent features relative to postoperative management.

The bulk of experimental work in lung transplantation has been done with the left lung, since it offers less technical difficulty. Although there are several communications in the literature of autotransplants of the right lung, the only reports of homotransplants of the right lung, to our knowledge, are the recent experiments described by Gago, et al. However, it is obvious that in the clinical situation, the decision concerning the side to be operated is based on the needs of the patient and the existing pathologic condition, not technical considerations. The investigation of the technique of right lung homotransplantation is the second purpose of this communication.

MATERIAL AND METHODS

Animals: Adult mongrel dogs of either sex with weights ranging from 7.0 to 23.0 kg. were used in this study. One hundred and twenty experimental lung transplants were performed; 20 autotransplants (15 on the left side, five on the right side), and 100 homotransplants (85 on the left side, 15 on the right side). Ninety of the homotransplants were preserved for at least 24 hours.

Graft Procurement and Its Management: All donors are heparinized (1.5 mg./kg. heparin sodium). In autotransplants, the heparin is injected into the pulmonary artery immediately before clamping it. The lung is excised with an atrial cuff. Immediately after removal, a polyethylene catheter is inserted into the pulmonary artery and the lung is perfused for five minutes (gravity perfusion), the pressure not exceeding 40 cm. of water, using...
250 to 500 ml. of a refrigerated solution at 4° C. Pressures greater than 40 cm. of water may result in rupture of the media of the pulmonary artery, a mishap we observed in three instances. The fall in tissue temperature during perfusion, as registered with a thermistor probe, is shown in Fig. 1.

The perfusate consists of a balanced salt solution (Tis-U-Sol)†† with 5 per cent low molecular weight dextran (40,000) (Rheomacrodex),‡ heparin sodium 100 mg./l., buffered with tromethamine (THAM)‡‡ and sodium bicarbonate titration to a pH of 7.4. If the lung is to be stored. The lung is wrapped in moist cold towels. The rise in tissue temperature as registered by a thermistor probe, is shown in Fig. 1.

Operative Technique: For transplantation of the left lung, the chest is entered through the fifth interspace. The pericardium is opened and the hilar structures are dissected free. Care is taken to leave the phrenic and vagal nerves intact. The pulmonary artery is clamped, the veins are doubly ligated and divided, and the main stem bronchus is clamped and divided at its distal end. The next very important step is to free the posterior wall of the left atrium, by ligating and dividing the tissue between the atrium and right pulmonary artery.

Anastomosis is started on the bronchus, using interrupted sutures of 4-0 silk or Tevdek. If both bronchi are equal in diameter, an everting mattress suture is used; if unequal, the smaller bronchus is invaginated within the larger. After suturing, the suture line is covered with a pericardial flap. Next, an opening is created in the left atrium, excising the atrial appendage and enlarging the opening by incising beyond the the stump of the superior pulmonary vein. This step provides an ample free border without obstructing the atrium or the right inferior pulmonary vein with the clamp. The anastomosis is carried out using a continuous everting suture of 6-0 silk. The arterial anastomosis is next effected with continuous 7-0 suture. Both vascular anastomotic sites are reinforced with methyl 2-cyanoacrylate monomer (Eastman No. 910 Monomer).¶¶

Homotransplantation of the right lung employs the same techniques with the following exceptions: (A) the aygos vein is ligated and divided, providing better exposure of the bronchus and the artery; (B) the short right main stem bronchus prohibits the use of a clamp, so it is simply divided and the endotracheal tube advanced forward into the left main stem bronchus; (C) the left atrium is carefully dissected free from the right until there is adequate room to clamp the left atrium without disturbing the right atrial or vena caval flow (Fig. 3). Incision of the atrium through the venous entrances then allows a sufficient free border for anastomosis with the atrial cuff of the transplant (Fig. 4).

Anesthetic and Postoperative Care: All recipients are given morphine sulphate and 0.4 mg. atropine sulphate 30 minutes before the operation is started. General anaesthesia is induced and maintained with thiopental sodium. Overdosage must be carefully avoided because dogs undergoing this procedure usually will not recover if anaesthesia is excessive. Ventilation with a positive-pressure respirator is maintained during the operation. During occlusion of the

††Kindly supplied by Baxter Laboratories, Morton Grove, Illinois.
‡§Kindly supplied by Pharmacia Laboratories, Newmarket, N.J.
¶¶Kindly supplied by Ethicon, Inc., Somerville, N.J.
pulmonary artery, pure oxygen is given. Adequate muscular relaxation is provided by succinyl-choline (it is especially important that complete muscular relaxation be present at the end of the actual transplantation procedure). The tracheobronchial tree is suctioned upon release of the bronchial clamp. Preserved lungs secrete fluid; inadvertent contralateral aspiration of this fluid may initiate suboxygenation and subsequent death. Thus, frequent suctioning both during the operation and postoperatively is an important step.

All blood loss is replaced with lung donor blood. Ten per cent low molecular weight dextran is infused (10 ml./kg.), during operation and for the first postoperative day, but no systemic heparin is given. Chest suction is applied for three to six hours postoperatively depending upon the amount of drainage; the tubes are left in place and suction is repeated the next day. All animals routinely are given parenteral chloromycetin or tetracycline.

RESULTS

The first 24 lung transplants, including all 20 autotransplants, provided indeterminate results, since the techniques employed were not yet standardized. However, some conclusions may be drawn. Those lungs preserved for periods up to four hours by immersion cooling without previous perfusion were damaged after autotransplantation in the recipients, which usually died. The animals of this group which were systematically heparinized, showed marked parenchymal bleeding in the damaged lung at necropsy. After ten months, only one dog of this series (autotransplant left side) is still living. This animal is healthy, has a normal chest film and tolerates occlusion of the contralateral main stem bronchus without stress.

Sixty-four left lung homotransplants were performed to investigate the preservation of the lung by hypothermia (3°C.) and hyperbaric oxygenation (3.0 or 8.0 atmospheres absolute). Six dogs died of causes unrelated to the preservation. Constant homograft survival was achieved with intermediate transplantation or with those lungs preserved 24 hours by hypothermia (3°C.) and 3.0 atmospheres absolute of oxygen, whereas 48-hour preservation with the same parameters showed a 50 per cent lung survival. Twenty-four hour preservation with hypothermia alone resulted in less than 50 per cent survival. Details of this study are reported elsewhere."

The same operative technique was used for transplantation of 22 lungs (17 left, 5 right) preserved with continuous hypothermic perfusion and continuous ventilation. There was no death due to technical failure. This method permits dependable storage of the lung for 24 hours and sometimes even for 48 hours. Details of the results are reported elsewhere, also."

Finally, an additional ten right lung homotransplants were performed. All dogs were treated with azathioprine (7-4 mg./kg. daily). During the postoperative period, these dogs were weaker than recipients of left lungs, and they died with less damage of the transplant. Six dogs received immediate transplants. One died after the operation (mechanical failure of the respirator), the others died within four or five days, one because of early rejection, the other because of drug toxicity. The transplants were viable in every case, and there was no thrombosis of the anastomoses. Four dogs received a transplant preserved for 24 hours with hypothermia and 3 atmospheres of oxygen; two died because of a damaged transplant, and two died from drug toxicity or septicemia after six days, with a perfectly viable transplant. Chlorpromazine had been added to the preservative solution of one of the successfully and one of the unsuccessfully preserved lungs.

DISCUSSION

The technique of lung transplantation was first described in 1950 by Lanari and co-workers, Metras, and Staudacher and colleagues. Technical improvements and results were reported by Juvenelle, et al.}

![Kindly supplied by Burroughs Wellcome & Co., Tuckahoe, N.Y.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21427/ on 06/09/2017)
in 1951, Neptune, et al., Davis, et al. and Hardin, et al. in 1952. Since the pioneering framework of these investigators, the technique has been applied successfully in many laboratories. However, a few remarks concerning the special situation of the transplantation of a preserved lung are in order.

It is our experience that a lung is altered during storage, but that these alterations (edema, congestion, and decreased distensibility) are generally reversible. If such a lung distends incompletely after transplantation, or should it collapse during the postoperative period, it is impossible despite any measure to obtain adequate inflation again. This exemplifies the extreme necessity for an airtight bronchial anastomosis for a successful result. Some authors prefer to do the vascular anastomoses first, in order to reduce the ischemia time. However, since the bronchial anastomosis is much more difficult to perform after the vascular anastomoses are done, we favor the bronchial anastomosis first. In our hands, using this method, circulation is still reestablished within 45 minutes, so that the ischemia time is not unduly prolonged.

The inevitable lung damage which occurs during preservation forbids the use of heparin. Therefore, extra care must be taken to avoid thrombosis which may result from inaccurate or substandard techniques. Anastomosis of an atrial cuff instead of the pulmonary veins (first described by Métras, and later by Neptune, et al. and Hardin et al. has been universally accepted for left lung transplants. However, for right lung reimplantations, all authors (Alican and Hardy, Juvenelle, et al. Slim, et al.) but one (Nigro, et al.) describe separate anastomosis of the veins for improved technical simplicity. It is our experience that in right-sided lung homotransplants, the atrial anastomosis is much easier, faster, and more reliable, when delicate preparation of the left atrium is completed carefully as described above.

![Comparison of Fall in Tissue Temperature of Perfused Lung with Fall in Temperature of Lung Immersed in Perfusate at 4°C](attachment:comparison_of_temperature_graph.png)

**Figure 1:** Fall in lung temperature during cooling. Average values of six determinations; mean weight of the lung 60 gm.
Rise in Tissue Temperature of Lung During Transplantation Procedure

Figure 2: Rise in lung temperature during transplantation. Average values of six determinations; mean weight of the lungs 60 gm.

Figure 3: Left atrium, in the right thorax, after dissection from the right atrium, and removal of the right lung.
Furthermore, our data suggests that the success rate of right lung homotransplants is about the same as that on the left side, as far as technique is concerned. No deaths resulted from bleeding or thrombosis, but this type of procedure is more poorly tolerated by the recipients, as shown by their behavior during the postoperative period, and by the fact that they die with less extensive damage of the lung than do recipients of left side transplants. Perhaps the size factor may account also for the fact that preservation did not achieve the same degree of success as on the left side. However, the number of experiments is too small for definitive conclusions.

The rationale of perfusing an organ prior to transplantation is to obtain cooling in order to decrease tissue metabolism, remove waste products of metabolism, and to prevent thrombosis. It is acknowledged today, for every organ, that decreasing the metabolic requirements by cooling is an important step in successful transplantation, even for immediate grafting experiments. In the case of a thin organ like the lung, both surface and parenchymal cooling can be achieved almost as fast by immersion in a refrigerated solution as by cold perfusion (Fig. 1). The limitation of the cooling process to 10° C. after five minutes is due to the rapid rewarming of the solution in the infusion line by the room temperature.

Despite the factors mentioned above, our results indicate that perfusion is more desirable. Our own work with kidneys\(^1\) has shown the importance of cleaning the vascular tree for maintaining functional integrity of the organ. Moreover, unfavorable results with autotransplants stored only a few hours without perfusion tend to confirm this conclusion. Furthermore, Blumentock and co-workers\(^2\) in studies with 24-hour hypothermic preservations of lungs with continuous ventilation, achieved better results with flushing the lung with pH-adjusted serum than with mere hepariniza-

**Figure 4:** Opening in the left atrium, ready to be anastomosed with the atrial cuff of the right lung homograft.
tion. The perfusate used in the study in this report has proved to be superior to several other perfusate combinations screened in our experiments with the kidney. In the case of the lung, the importance of perfusion during ventilation must be stressed. Perfusion is never complete nor uniform if not combined with ventilation.

SUMMARY

One hundred and twenty canine lung transplants have been performed. Ninety of these were preserved transplants. Details of handling the transplant, operative technique and management of the recipient are described with special reference to preserved transplants.

Right-sided lung homotransplants were performed. The results of this procedure are similar to those done on the left side, insofar as postoperative complications are concerned.

RESUMEN

Ciento veinte y nueve transplantes de pulmones caninos han sido realizados. Noventa de estos pulmones han sido conservados por algún tiempo antes de ser implantados. Se describe en detalle la manipulación del traspante, la técnica operatoria y la preparación del recipiente, con referencia especial a los traspantes conservados.

Los resultados del homotrasplante del pulmón derecho han sido similares a los del izquierdo, en lo que a complicaciones postoperatorias se refiere.

ZUSAMMENFASSUNG

Es wurden 120 Transplantate von Hunde-

lungen gewonnen. Bei 90 von ihnen handelt es sich um konserviertes Material. Beschreibung der Einzelheiten der Handhabung solcher Transplante, der operativen Technik und der Betreuung des Empfängers und zwar unter besonderer Berücksichtigung konservierter Transplan-
tate.

Es wurden Homotransplantate der rechten Lunge vorgenommen. Die Ergebnisse dieser Eingriffe ähneln denjenigen der linken Seite, jeden-
falls war die postoperativen Komplikationen angehen.

REFERENCES

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