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Transplantation of the heart and both lungs
I. Historical review

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Transplantation of the heart and both lungs is being considered as a clinical possibility in several surgical centres today. This paper reviews the experimental development of surgical techniques in this field. In the 1940s Demikhov in the U.S.S.R. succeeded in developing a technique by which he could carry out cardiopulmonary transplantation without the use of any artificial means of recipient support during the procedure. He obtained survivors for up to six days; late deaths occurred mainly from pulmonary complications. The techniques and results of subsequent workers using hypothermia or pump-oxygenator support are reviewed. Recent work has focused on the problem of the return of spontaneous respiration following denervation of the lungs which, of necessity, occurs during this procedure.

The very early work on heart transplantation was carried out by Carrel and Guthrie (1905), Carrel (1907), and Mann, Priestley, Markowitz, and Yates (1933), the donor heart being placed in the neck of the recipient dog, but it was not until Demikhov began his extensive studies in the 1940s that the heart and both lungs were transplanted into their orthotopic locus (Demikhov, 1949).

Demikhov's work embraced many aspects of transplantation and involved the study of many types of organs, but his studies on the heart and heart-lung preparation are particularly notable (Demikhov, 1950b, 1951, 1952, 1956, 1959, 1962). He developed 24 different methods of providing a recipient dog with an accessory heart within the chest (Demikhov, 1950a), using most of the available major vessels within that cavity, with survival for as many as 32 days. He subsequently (1951–55) went on to carry out orthotopic transplantation of the heart, though only two of 22 attempts were considered successful, the heart functioning for 'a few hours' (Demikhov, 1962). Much credit must be given to his achievements, particularly when it is remembered that neither in these experiments nor in his heart-lung transplantations was he able to use any form of recipient support, for example, hypothermia or the pump-oxygenator.

On 20 October 1946, Demikhov transplanted the heart and lungs of a dog, and the recipient survived for two hours without its own organs, but it was not until 1949 that more prolonged survival was obtained.

The technique used was ingenious (Fig. 1) as it enabled the blood supply to the brain to be maintained continuously throughout the operation, with the exception of two to three minutes at one critical stage. Demikhov took care to dissect out the phrenic and vagus nerves of the recipient with the intention of preserving the innervation of those structures, particularly the diaphragm, below the region of the heart and lungs. At this stage the right lung was removed to facilitate later parts of the operation.

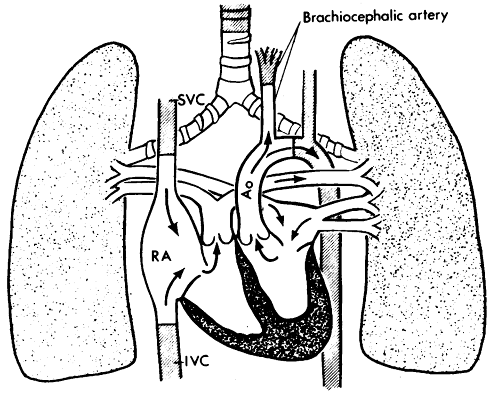

FIG. 1. *The completed operation of orthotopic heart-lung transplantation, using Demikhov's technique, after anastomosis of the donor tissues (white) to the recipient tissues (shaded).*

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After preliminary mobilization, the donor heart-lung preparation was removed from the animal by clamping and dividing the thoracic aorta, the inferior vena cava, brachiocephalic and subclavian arteries, and the superior vena cava. During transfer the donor heart-lung was kept viable by its own closed-circuit circulation, blood from the left ventricle being pumped into the arch of the aorta, from whence it passed through the coronary vessels supplying the myocardium and into the right atrium, the right ventricle, and the lungs; oxygenated blood was returned to the left atrium. This form of heart-lung preparation (Demikhov, 1950c) differed considerably from those described earlier by Pavlov and Christ-ovitch, and by Starling (Demikhov, 1962), and subsequently has been found to be a promising means of transporting and temporarily preserving the heart and lungs (Longmore, Cooper, Hall, Sekabunga, and Welch, 1969).

The transferred heart and lungs, still functioning, were placed over the recipient's heart and lungs, and the brachiocephalic arteries of the two dogs were quickly connected over a tube, after which the superior vena cava of the transplant was sutured to the superior vena cava of the recipient. This procedure took only two or three minutes, thus preventing any undue stasis of venous blood in the brain. Consequently, the blood supply to the head was maintained by the transplanted heart and lungs, while the blood supply to the lower half of the body was still maintained by the recipient's heart and left lung. The two inferior venae cavae were then sutured together followed by anastomosis of the two aortae in the region of the arch. At this stage the transplanted heart and lungs provided the blood supply to the entire animal. During the inferior vena caval anastomosis the blood supply to the lower half of the body was temporarily interrupted for 15 to 20 minutes. Demikhov noted dilatation of the vessels of the lower half of the body as a result of this temporary occlusion, resulting in a sharp but easily correctable fall in blood pressure.

The tracheas of the transplant and recipient were then connected, either by means of a special tube or by silk sutures, using a technique which avoided interference with respiration. In later attempts tracheostomy was carried out prohylactically to prevent asphyxia from laryngeal spasm following damage to the recurrent laryngeal nerve.

Demikhov attempted this very considerable procedure on 67 occasions; of these, 23 were concluded with the recipient still on the operating table. Thirty dogs survived for less than 24 hours, six less than 48 hours, six less than four days, one less than five days, and one less than six days.

In those dogs which died soon after operation, technical problems and thrombosis at the various anastomoses, particularly of the brachiocephalic artery, were the common causes of death. The longer-term survivors died of bronchopneumonia, which was noted to be confined to the lower lobes of the lungs. Demikhov felt that this localization of the inflammatory process in the transplanted lungs could be explained by the anatomo-physiological properties of the lower lobes. He suggested that if the inflammation in the transplanted heart and lungs resulted from tissue incompatibility it must have affected both upper and lower lobes. In all cases the heart appeared to show no abnormality at necropsy.

Those dogs which did recover from the immediate effects of the operation appear to have been quite well for the few days until their demise. Respiration was generally slow, in the region of 12 per minute, and the pulse rate variable, though frequently fast. Certain dogs appeared to recover remarkably well, walked about their kennels, drank water, ate meat 'with a good appetite', and reacted briskly to their surroundings. One of them was even sent by train from Ryazan to Moscow on the fourth post-operative day and on arrival at its destination 'ran up the stairs by itself'.

Several important observations and conclusions have resulted from Demikhov's pioneering studies. Most significant is the fact that following total replacement of the heart and both lungs many of these dogs did breathe spontaneously, and apparently adequately, until death, which did not appear to be the result of respiratory insufficiency unless caused by bronchopneumonia. This is a particularly important finding and is not confirmed by all subsequent workers. Secondly, the respiratory rate was variable; one dog on the day following operation had a respiratory rate of 18 per minute. On the second post-operative day it drank some water and ate some meat but was noted to have a pleural effusion. Attempts to aspirate this led to vomiting for five minutes after which the dog was dyspnoeic 'and the respiratory rate rose to 135 per minute'. Four and a half hours later the rate had returned to 12 per minute. Thirdly, the transplanted heart was able to maintain an adequate circulation for six days, and, despite the fact that it was totally denervated and neither atrium had been left in situ, it also showed considerable variation in an individual dog, depending on the dog and its environment.

Demikhov's contribution to this experimental field has been considerable. Most subsequent workers have been unable to obtain survivors of more than a few hours, the failure of respiratory function being the major problem. A study of the authorized translation of Demikhov's own book (Demikhov, 1962) does not enlighten one as to why his results were better than other people's, neither his technique nor management differing in any crucial way from those of later workers.

During the period of Demikhov's studies, other workers, notably Sinitsyn (1948) and Marcus, Wong, and Luisada (1951 ; 1953), were studying the effects of cervical implantation of the transplanted heart. Sinitsyn (1945 ; 1951), working in the U.S.S.R., had also made studies on the transplanted frog's heart. Marcus *et al.* in the United States of America used similar techniques but also developed a technique for transplanting the heart and both lungs into the abdomen, thus giving the recipient two sets of heart and lungs.

The purpose of this latter experiment was to determine whether the heart and lungs as a pump-oxygenator unit could deliver self-oxygenated blood to a delimited part of the host's body. The heart-lung preparation was interposed either into the aorta-vena caval circulation just above their

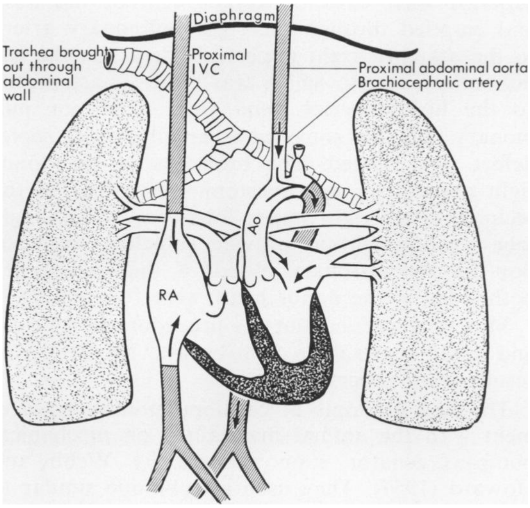

FIG. 2. *The donor heart-lung preparation (white) transplanted into the recipient aorta-vena caval circulation (shaded) in the abdomen, using the technique described by Marcus, Wong, and Luisada. The transplanted organs were able to function in accessory support of the host animal.*

bifurcations (Fig. 2) or into the common iliac circulation. Blood was brought from the host's inferior vena cava to the right atrium of the transplant, passed through its own lungs, which were attached to an artificial respiration apparatus for oxygenation, and returned via the pulmonary veins to the left heart, which supplied part of the host's body and its own myocardium. This hypothesis was tested by (1) connexion of the host's trachea to a source of nitrogen only, (2) temporary ligature of the host's main pulmonary artery, providing an empty left atrium and ventricle, and (3) occlusion of the tricuspid valve in an attempt to empty both sides of the host's heart.

Eight heart-lung preparations were transplanted. Attached to its own ventilator such a heart-lung transplant lived for 75 minutes after the heart of the host animal had died. On one occasion the heart beat and pumped oxygenated blood to a portion of the host's body for 61 minutes after the host's lungs were purple by virtue of inhalation of 100% nitrogen. On another occasion the heart-lung preparation lived within the abdominal cavity of the recipient for over nine hours, during which time it was necessary to defibrillate it three times.

On two occasions, when the heart-lung preparation was working in the aorta-vena caval circulation, the chest of the host was entered and the main pulmonary artery was temporarily occluded to empty the left side of the heart. The host's heart was then opened through the left atrial appendage and manipulations of the mitral valve were made under direct vision. After seven minutes the atrium was closed and the appendage amputated. The pulmonary artery remained occluded once for 15 minutes and once for 48 minutes and was then released. The coronary arteries, in the meantime, had been supplied with oxygenated blood from the heart-lung transplant in the abdomen.

Among the difficulties that Marcus and his associates met were disturbances of rhythm of the donor heart by reflex or mechanical causes. The former, they felt, could usually be prevented by means of bilateral cervical vagotomy in the heart donor at the beginning of the experiment, and the latter cause was usually consequent upon varying degrees of overdistension of the right heart, which they therefore took steps to prevent.

In an attempt to minimize tissue incompatibility, the recipient and the donor animal's blood were crossmatched in many cases, but maximal survival time of the transplanted organs did not increase.

Among the conclusions on their work, the authors suggested the possibility of using a heterologous heart–lung preparation as an extracorporeal pump during intracardiac procedures. They also commented that the transplanted heart might act as an accessory pump to decrease the work load of the central heart, even if only temporarily.

With the advent of supportive techniques total heart–lung excision and replacement became more feasible. In 1953, Neptune, Cookson, Bailey, Appler, and Rajkowski used hypothermia to sustain life in the recipient while the transplantation was proceeding. They estimated that, by cooling the recipient to 21–24° C. rectally, they allowed themselves approximately 15 minutes to perform the critical stages of the transplantation. It is of interest to note that they obtained this low body temperature by placing the recipient in an ordinary beverage cooler.

Their technique involved rapid anastomosis of the ascending aortae by suture, and of the superior venae cavae over a polythene tube, after which the cerebral circulation could be resumed. The inferior venae cavae were then joined similarly, allowing restoration of the complete circulation.

When the heart was thought to be in good condition, as evidenced by E.C.G. studies, the tracheas were anastomosed end-to-end and the cavae were individually clamped, the polythene tubes removed and suture anastomosis performed. The animal was then rewarmed to normal body temperature.

This technique has similarities to that used by Demikhov, particularly in the need for early resumption of the circulation to the brain. The importance of the phrenic nerves was again realized and care was taken to preserve them.

The authors pointed out that by keeping the heart and lungs together the problem of the pulmonary circulation was solved, and, in addition, by keeping this circulation intact, the coronary circulation was maintained throughout the procedure. In fact, Neptune and his colleagues, like Demikhov before them, had realized the potential of this heart–lung preparation as a means of retaining cardiac viability during the transfer of the heart from donor to recipient.

Only three attempts to perform this procedure were reported by these authors. The first resulted in poor cardiac action which was maintained for 30 minutes. On the second occasion cardiac action was good, though there were E.C.G. irregularities, and there was a return of pupillary and knee reflexes, but the dog died after four hours as a result of haemorrhage from the posterior suture line of the aorta. In our own experience (Longmore *et al.*, 1969), this is a crucial region, and one that is more likely to bleed if the anastomosis is made hurriedly, as was necessary when hypothermia was the only available means of support of the recipient.

The third dog had normal cardiac action, as evidenced by the E.C.G., and had return of reflexes and spontaneous respiration, an observation of great importance. Normal body temperature was restored and the animal did well for six hours, at which time it died. The cause of death was not fully explained, other than probable shock.

Matejiček in 1956 briefly reported a study of the transplantation of the heart and right upper lobe of the lung into the chest; the recipient's heart and lungs (except for the right upper lobe) remained intact and continued to function. The donor heart was placed in position in such a way that its left atrium filled with oxygenated blood from its own left pulmonary vein. The coronary arteries were filled by the action of its own left ventricle. The transplant aorta was anastomosed to the central or distal end of the host brachiocephalic vessel. The donor right heart received desaturated blood through an anastomosis between the donor superior vena cava and the superior vena cava or azygos vein of the host, and emptied through the right pulmonary artery to the attached right upper lobe, and via the left pulmonary artery, which was either anastomosed to the host superior vena cava or donor pulmonary vein. In some cases an interatrial septal defect was created. The bronchus of the donor right upper lobe was anastomosed to that of the recipient after right upper lobectomy. The single lobe was thought to provide sufficient oxygenation for the coronary blood of the transplant; both sides of the donor heart were functioning.

Matejiček carried out his procedure in 21 dogs and noted survival up to five days. No details of results were reported.

The first attempts at cardiopulmonary replacement with the animal maintained on mechanical pump-oxygenator support were by Webb and Howard (1957). They used a technique similar to that of Neptune *et al.*, suturing the aortae, but using couples to anastomose the cavae. They differed in causing 'inflow and outflow stasis' of the donor heart, which was then 'perfused with lactated Ringer's solution to wash all blood from the coronary and capillary beds', thus negating the value of the heart–lung preparation as a means of maintaining cardiac viability.

Webb and Howard reported six such procedures, and found that it was possible to restore the heart to relatively normal function with acceptable E.C.G. patterns. These animals lived from 75 minutes to 22 hours. The early deaths were caused by continued oozing from the extensive raw surfaces developed during the dissection. In none of these animals was there a return to spontaneous respiration.

The authors also described a second series of experiments in which autotransplantation of the heart and both lungs, in four cases, and of the heart alone, in three cases, was attempted, and a third series in which the heart and one lung were homografted.

In the autotransplant experiments the heart–lung preparation was not perfused but was allowed to perfuse itself. The technique in the four autotransplants of the heart and both lungs was as in the homograft series just described. In two of these the coronaries were occluded by the aortic clamp with resulting fibrillation which could not be corrected, but in the other two, normal cardiac function was obtained for as long as four hours. It was again observed that these animals were unable to breathe spontaneously. Where the heart alone was transplanted there was an immediate return to spontaneous respiration.

In the series of heart and unilateral pulmonary transplants the donor heart and left lung were perfused with lactated Ringer's solution, excised, and then refrigerated at 4° C. in Tyrode's solution with 10% serum during preparation of the recipient animal. These organs were exteriorized for two to four hours before their function was restored by suture anastomosis of the aortae and couplings of the cavae and right pulmonary artery and veins. Cardiac action was restored prior to the bronchial anastomosis. To prevent blood flow through the functionless left lung, the left pulmonary artery was clamped until the bronchus was re-anastomosed.

The authors do not state how many such operations they performed but note that satisfactory cardiac function was easily restored in all, though in one case a twisted inferior vena cava caused complete obstruction and proved fatal before it could be corrected. Another died early from oozing. The other dogs recommenced spontaneous breathing as soon as the chest was closed and artificial respiration discontinued.

As they were unable to obtain restoration of normal respiratory function in the presence of total denervation of the lungs, Webb and Howard concluded that transplantation of the heart and both lungs was not practicable, as denervation resulted in respiratory paralysis. They did suggest that while transplantation of the heart with one lung was technically more difficult, the technique might be feasible for use in cases with pulmonary hypertension. Such transplantation circumvented the respiratory paralysis by leaving one innervated lung in the recipient.

In a later study Webb, together with deGuzman and Hoopes (1961), reported a study of the autotransplanted heart. The heart and lungs were completely dissected free from all mediastinal attachments except the trachea, superior and inferior venae cavae, and the aorta. The major vessels were then divided one by one, and rejoined by nylon couples, each procedure being performed quickly enough to allow the entire operation to be accomplished without the use of cardiopulmonary bypass. The trachea was transected at the carina and immediately anastomosed, much care being taken to leave undisturbed the tissues around the proximal trachea. Respiration was maintained throughout this procedure.

Four animals successfully underwent reimplantation of the heart and both lungs. Each was able to return to the maintenance of a normal blood pressure and apparently normal cardiovascular function. In spite of a well-innervated lower tracheal segment, respiratory insufficiency was apparent in all, with none living longer than 14 hours.

Four further dogs were subjected to the preliminary dissection requisite for cardiac transplantation. The phrenic nerves were carefully dissected off the pericardium, and the vagal branches to the heart and lungs were divided. The dissection was continued until only the trachea, aorta, and venae cavae supported the heart and lungs. The trachea was divided immediately proximal to the carina and anastomosed without interruption of ventilation at any time. As the cough reflex was abolished, tracheostomies were performed for frequent endotracheal aspiration.

None of these dogs was able to maintain the continuing adequate ventilation necessary for permanent survival; the animal surviving longest breathed spontaneously for only 16 hours postoperatively. One dog was able to make only gasps during the post-operative period. The authors came to the conclusion that continuing respiration was dependent on 'feedback' afferents from the respiratory system, and felt that their studies indicated that respiratory paralysis was not due to phrenic nerve damage, excessive vagal or sympathetic dissections, or periods of shock accompanying the extensive dissection and trauma of the actual transplant. Accordingly they concluded that transplantation of the heart combined with both lungs was probably a physiological impossibility.

In 1958 Blanco, Adam, Rodriguez-Perez, and Fernandez reported eight attempts at orthotopic homotransplantation of the heart and lungs, maintaining the recipient on a pump-oxygenator. The surgical technique used was that described by Neptune *et al.* Two such attempts were terminated during the procedure because of technical difficulties. In the other six, cardiac contractions supported the circulation for one-half to four-and-a-half hours, with an average survival time of only two-and-a-half hours. In two dogs spontaneous respirations appeared and corneal reflexes were active at that time. Death followed a period of weakened cardiac contractions and ventricular fibrillation.

In the late 1950s several groups were attempting transplantation of the heart alone into the orthotopic locus. Notable among these were Golberg, Berman, and Akman (1958), Webb, Howard, and Neely (1959), and Cass and Brock (1959), but in no case was long-term survival achieved. In 1960, however, Lower and Shumway reported the first really significant breakthrough in the technical aspects of cardiac homotransplantation, and since that time they and their co-workers have contributed massively to our knowledge of this subject. They have reported one study of transplantation of the heart together with both lungs (Lower, Stofer, Hurley, and Shumway, 1961).

In 1961 this group reported the resumption of spontaneous respiration in six dogs after complete homograft replacement of the heart and both lungs. The actual number of operations attempted is not mentioned. During preparation of the donor the phrenic and vagus nerves were carefully preserved and the bronchial vessels ligated. The donor organs were immersed in saline solution at approximately 4° C. for 10 minutes and, after being cooled in this manner, were placed in the recipient, and anastomoses of the aorta, trachea, and venae cavae were carried out with fine silk sutures. After rewarming, the animal was electrically defibrillated.

In the six dogs who respired spontaneously post-operatively, it was observed that oxygenation remained adequate but the respiratory pattern was altered in that tidal volume was increased and the respiratory rate diminished. There was an occasional marked prolongation of the expiratory phase. Four of the animals died of surgical complications 5–24 hours after the onset of spontaneous breathing.

The remaining two animals recovered fully except for temporary gastro-intestinal ileus, presumably due to vagus nerve injury during dissection and ligation of the bronchial vessels. They were ambulatory, active, and eating until they became lethargic on the fourth post-operative day, at which time the arterial oxygen content of one animal was 14–21 vol. % with an oxygen capacity of 18–19 vol. % (78·2% saturation). The arterial CO_2 content was 48·8 vol.% (method of van Slyke and Neill). Both animals died (of respiratory insufficiency) on the fifth post-operative day.

At necropsy the lungs of the dogs were found to be heavy and firm. Microscopically there was considerable atelectasis, but the most striking finding was an extensive infiltration of large mononuclear cells which appeared to be histiocytes. Grossly the heart appeared normal, but microscopically it showed infiltration of the myocardium with mononuclear cells, chiefly of the plasma-cell variety. These changes of the myocardium were less extensive than the authors had observed previously with cardiac homografts of longer duration.

Lower and his colleagues felt that this study confirmed earlier work by others (Juvenelle, Citret, Wiles, and Stewart, 1951; Neptune, Redondo, and Bailey, 1952; Portin, Rasmussen, Stewart, and Andersen, 1960), that the bronchial arterial supply to the lungs could be sacrificed without resulting necrosis, but that the question of the possibilities of prolonged survival after pulmonary denervation remained unanswered. It was evident that the sacrifice of peripheral innervation, which necessarily accompanied pulmonary transplantation, resulted, in the cases reported, not in respiratory paralysis but in an altered respiratory pattern which resembled that observed after bilateral cervical vagotomy. The adequacy of this pattern for normal ventilation over prolonged periods, and for the maintenance of respiratory equilibrium under various stresses, remained to be demonstrated.

The authors concluded that complete homograft replacement of the heart and lungs was technically feasible, and that spontaneous respirations with an altered pattern remained which would sustain life until homograft rejection supervened.

Sen and his colleagues in India have experience of several techniques of cardiac and cardiopulmonary transplantation (Sen, Parulkar, Panday and Kinare, 1965). Using the technique originally described by Neptune *et al.*, they carried out five homologous cardiopulmonary transplants, and succeeded in obtaining survivors of 5–12 hours in which the systemic blood pressure was maintained at levels of 80–120 mm. Hg. Three of these five animals breathed spontaneously post-operatively; but two required ventilatory support. The causes of death were not discussed by the authors, but haemorrhage from the suture lines was found to be a major problem, as it has been in most reported series.

De Bono, working in England but reporting his studies in a French journal (De Bono, 1966), also used Neptune's technique. He obtained six survivors in whom spontaneous respiration of an apparently normal pattern occurred for periods of from two to 10 hours, at which times the dogs were sacrificed. Although no conclusion regarding prolonged survival could be drawn from these studies, De Bono felt that adequate spontaneous respiration was certainly possible following heart–lung transplantation, but it was rarely achieved because pulmonary oedema, caused by a number of factors, diminished the ventilatory capacity and compliance of the lungs. Damage to the lymphatic drainage of the lung might also bring about significant changes in lung function. It was suggested that the innervation of the chest wall and trachea might be sufficient to furnish an afferent respiratory stimulus following cardio-pulmonary transplantation.

In his paper, De Bono also reported a type of anaphylactoid reaction (immediately following transplantation) which he had observed in a number of cases.

In a study of the preservation of cardiac viability using the heart–lung preparation, Robicsek, Lesage, Sanger, Daugherty, Gallucci, and Bagby (1967) performed orthotopic transplantation of the heart and both lungs on 12 occasions, using Demikhov's original technique. Eight of the 12 recipients lived longer than one day, with a maximal survival time of 37 hours. Better results were obtained with transplants of the heart alone. The authors considered that the main problems of their experiments in which both heart and lungs were grafted were respiratory rather than haemodynamic. The animals maintained satisfactory heart function, but their breathing appeared to be inadequate and had to be assisted by a respirator. Attempts to discontinue artificial respiration were followed by cardiorespiratory arrest.

As can be seen from the foregoing review, the major physiological problem is whether or not the totally denervated lungs will function spontaneously. That the denervated heart will function satisfactorily is a well-established fact, and our own studies (Longmore *et al.*, 1969) confirmed that a technically successful procedure leads to a satisfactorily functioning heart able to maintain an adequate circulation.

A great deal of work has been carried out on transplantation of the lung and the problems of denervation of that organ. Hardy and Alican (1966) have reviewed these subjects thoroughly in a recent paper. It is sufficient to say here that the majority of evidence leads one to conclude that in the dog, denervation or transplantation of one lung only does not affect the spontaneous respiration of the animal, but denervation or transplantation of both lungs (or removal of the second lung) generally leads to cessation of spontaneous respiration within hours, though a number of exceptions to this generalization have been reported. At least some dogs have spontaneously respired adequately for several months following denervation or autotransplantation of one lung and contralateral pneumonectomy. The problem with much of the reported work lies, however, in not knowing fully the extent of what each author terms 'denervation'. Total removal from the body and reimplantation of the lung is the only means by which one can be sure that full denervation has been carried out.

Nakae, Webb, Theodorides, and Sugg (1967) have recently followed up Webb's earlier work on heart–lung transplantation, and have made further studies of the effects of denervation of the lungs. They carried out four types of procedure. First, they performed cardiopulmonary autotransplantation by piecemeal division and reanastomosis of the major vessels and trachea, and division of all other tissues connecting the heart and lungs with the surrounding structures. All 10 dogs operated on resumed some type of spontaneous respiration, but with extremely slow respiratory rates and abnormal respiratory patterns. Arterial O_2 saturation and CO_2 tensions rapidly fell and rose respectively, and apnoea occurred within 4 minutes unless the dog was mechanically ventilated. If artificial ventilation was stopped, apnoea again occurred in all cases. One dog died when a ligature slipped off the inferior vena cava, but all other nine died from respiratory failure.

In the second group of experiments mediastinal denervation and tracheal transection were carried out, but the major vessels were not divided. The results were as for autotransplantation. A third group of dogs underwent mediastinal denervation without tracheal transection. They all recovered slow, gasping respirations which lasted from 40 minutes to 6 hours, but all ultimately died from respiratory failure.

A final group of dogs underwent only division of the major vessels (superior vena cava, inferior vena cava, and ascending aorta) which were anastomosed by vascular couplings, without pulmonary denervation. They all resumed spontaneous respirations and maintained normal respiratory patterns, surviving for three to 10 days, and dying from occlusion of the couples by thrombosis.

Nakae and his colleagues repeated the second procedure in cats, with the same results, and in monkeys. It is a very important finding that the monkeys resumed a relatively normal pattern of spontaneous respiration and maintained normal blood gases, in contrast to the findings in the dogs. Only one out of six survived for more than 24 hours, but none required respiratory assistance, all deaths resulting from intra-thoracic bleeding or air-leakage.

This work lends some degree of confirmation to the earlier work of Haglin, Telander, Muzzall, Kiser, and Strobel (1963) that total denervation of both lungs does not prevent a return of adequate spontaneous respiration in primates, though it does in dogs.

Although the experimental work in dogs has been disappointing, with few breathing adequately after heart-lung transplantation, much valuable information has been gained from these studies in regard to the technical and physiological problems involved. The encouraging results obtained following denervation of the lungs in primates lead one to hope that man will tolerate this procedure also. Some of the many lessons learned on the dog will then prove of value in overcoming the problems that man will undoubtedly provide.

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