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Human Lung Homotransplantation

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Left lung homotransplantation was performed in a 31-year-old man in terminal irreversible respiratory failure due to advanced silicosis. Within 10 minutes of completion of transplantation, arterial pO_2 rose from 52 to 211 mm. Hg, pCO_2 dropped from 90 to 43 mm. Hg, and pH rose from 7.15 to 7.42. On assisted ventilation, arterial O_2 tension was maintained within normal limits for the first four days. Thereafter, arterio-alveolar difference for O_2 increased to 300 mm. and that for CO_2 to 25 mm. Xenon-133 ventilation perfusion ratios confirmed differences between the two lungs. Terminally, bronchopneumonia and hypoxemia were present. Surfactant content of the lung was within normal limits. Postmortem examination revealed bronchopneumonia, bronchial infarction, lymphatic engorgement and mild rejection. Future efforts should emphasize selection of non-infected donors, minimal reliance on steroids for immunosuppression, cardiopulmonary bypass during transplantation, and more definite criteria for rejection.

On a entrepris une greffe homéoplastique du poumon gauche sur un homme de 31 ans parvenu à la phase terminale irréversible de l'insuffisance respiratoire relevant d'une silicose avancée. Dans les 10 minutes qui ont suivi la fin de l'intervention, le pO_2 est passé de 52 à 211 mm. Hg, le pCO_2 est tombé de 90 à 43 mm. Hg et le pH est monté de 7.15 à 7.42. Par une respiration assistée, on est parvenu à maintenir dans ses limites normales la pression artérielle de O_2, pendant les quatre premiers jours. Par la suite, la différence artério-alvéolaire en O_2 a augmenté à 300 mm. et celle du CO_2 à 25 mm. Les rapports des valeurs de la ventilation donnée en perfusion avec du Xénon^{133} comme élément marqueur ont révélé et confirmé des différences notables entre les deux poumons. A la phase terminale, on constatait de la bronchopneumonie et de l'hypoxémie. L'image des surfactants alvéolaires restait dans les limites normales. A la nécropsie, on a trouvé de la bronchopneumonie, de l'infarctus bronchique, un engorgement lymphatique et un début de rejet de la greffe. Les efforts futurs devraient porter sur le choix de donneurs non infectés, ne faire qu'un appel minimum aux corticoïdes pour la suppression des mécanismes d'immunité, le recours à la dérivation cardio-pulmonaire pendant la greffe et l'adoption de critères plus précis pour le rejet de la greffe.

FOLLOWING the first successful autograft of canine lung by Juvenelle *et al.*[1] in 1950, many investigators have established the technical feasibility of homotransplantation of the lung in several species.[2] Lung allografts in man using a cadaver donor have been reported by Hardy *et al.*[3] in 1963 and by Magovern and Yates[4] in 1964.

The present report represents the third attempt in man to transplant a lung from a cadaver source. This attempt was preceded by successful lung transplants in chimera twin calves* and in dogs.[5]† This experience, together with clinical experience in cadaver renal transplantation at the Royal Victoria Hospital, Montreal, since 1963,[6] prompted the authors to attempt left lung homotransplantation in a patient in terminal respiratory failure.

Clinical Evaluation of Patient

The Recipient

A patient with acute silicosis was admitted to the Royal Victoria Hospital, Montreal, for the first time in June 1963 at age 29 complaining of cough, fever, yellow sputum and hemoptysis of two days' duration. He gave a history of working for a sand blasting company since 1957. Between 1957 and 1960 he sand blasted only as an extra job during the evenings. From 1960 until June 1963, however, he had worked full time at sand blasting, often up to 100 hr./week. All of the sand blasting was done in large metal tanks with inadequate ventilation, improper safety hoods, and re-use of the sand as many as 10 times.

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On the first admission of the patient a diagnosis of pulmonary silicosis with superimposed bacterial pneumonia was made. While there was resolution of the pneumonia with treatment, dyspnea on exertion, a symptom that had been progressive over the previous six months, persisted. A lung biopsy was performed in October 1963 which confirmed acute silicosis. The ashed specimen consisted of 20% silica dioxide.

Between June 1963 and September 1965, the patient was treated with prophylactic isoniazid and para-aminosalicylic acid as well as antibiotics for bacterial pulmonary infections. During this period the patient's exertional dyspnea prevented active employment and he was readmitted on nine occasions for recurrent pneumonias, infected cervical lymph nodes and renal calculi and twice for spontaneous pneumothorax.

In November 1964, prednisone 20 mg. daily was started in an effort to reduce pulmonary fibrosis. Despite this treatment, however, dyspnea progressed to the point that the patient was unable to walk. In February 1965, he became dependent upon constant nasal oxygen, and even the simplest ventilatory testing was impossible. The patient was readmitted for the last time in September 1965, totally bed-ridden and requiring constant oxygen. He was pale and exhibited an acneiform rash due to steroid therapy. Extreme wasting was noted, reflecting weight loss from 145 lb. on his first admission to 77 lb. The chest showed decreased respiratory movements. The diaphragm moved 0.5 inch on maximal inspiration. Fine rales were heard throughout the chest and the fingers and toes were markedly clubbed, the nailbeds showing constant cyanosis.

In view of his impending terminal state, the decision was made jointly by the cardio-respiratory service of the Department of Medicine and the cardio-vascular thoracic service of the Department of Surgery to offer pulmonary transplantation to the patient. Elective tracheostomy was performed on September 12, 1965, and the patient was maintained on assisted ventilation using a Bird Mark VIII ventilator with 40% oxygen.

The downhill course is reflected in the deterioration of his lung function dating from 1963 onwards (Table I). Initial studies in June 1963 showed vital capacity to be reduced by about 25%, maximum voluntary ventilation by 20% and diffusing capacity by 35%. In September 1963, mechanical properties of the lung were still within normal limits; similarly, arterial blood gases were unaffected. In the course of the next year, there was a rapid progression of pulmonary fibrosis, shown by a progressive shrinking of the lung, affecting all subdivisions of lung volume; compliance fell by half between September 1963 and July 1964. Over the next five months, diffusing capacity fell dramatically and could no longer be tested on effort. From the beginning of 1965, arterial oxygen saturation was below 90%, except when the patient breathed an oxygen-enriched mixture; significant CO_2 retention was evident from February of that year (Fig. 1).

TABLE I.—PREOPERATIVE LUNG FUNCTIONS

		1963		1964	
Test	*Predicted*	*June*	*Sept.*	*July*	*Nov.*
Lung volumes (l.)					
VC	3.85	2.87	2.80	1.58	1.11
FRC	2.85	2.79	2.94	2.59	1.69
RV	1.36	1.57	1.89	2.03	1.23
TLC	5.21	4.44	4.69	3.61	2.34
Lung mixing (%)	52.0	59.0	61.0	53.0	50.0
Ventilatory tests					
$FEV_{0.75}\times 40$ (l./min.)	123.0	96.0	100	62.0	30.0
MMFR (l./sec.)	3.95	3.47	3.32	2.39	0.92
$D_{LCO}SS_2$ (ml./mm./min.)					
Rest	21.1	13.6	11.4	16.4	8.5
Exercise	21.0		12.5		
Mechanics					
C_{ST} (l./ml.)	.123		.130	.062	
COVERALL	.178		.162	.090	
Flow res.	3.0		2.2		
F-V (l./sec./l.)	2.3		2.55	4.00	

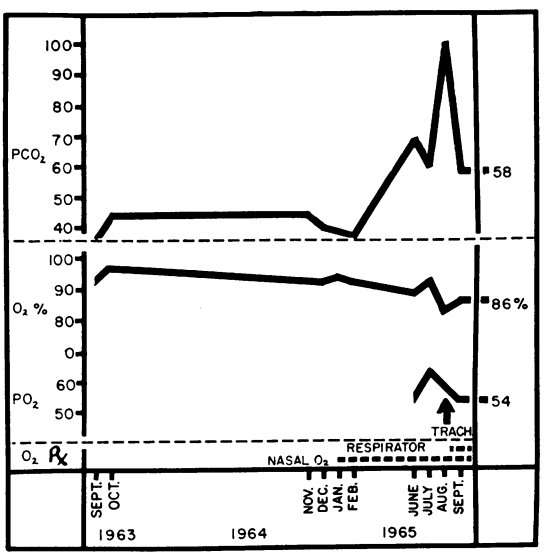

Fig. 1.—Preoperative blood gas values.

This decline is mirrored in a chest radiograph taken early in his disease (Fig. 2), compared with one taken just prior to transplantation (Fig. 3).

Once the decision to attempt lung transplantation had been agreed upon by all concerned, a suitable donor of the same major blood group was awaited.

The Donor

A 31-year-old white man was transferred to the Royal Victoria Hospital to be considered for a kidney transplant. He was in renal failure secondary to congenital ureterovesical obstruction, and had been maintained on hemodialysis at another hospital for approximately six months prior to admis-

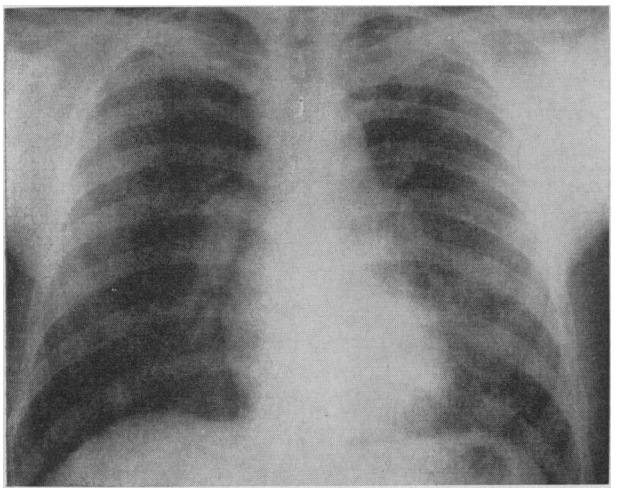

Fig. 2.—Chest radiograph of recipient early in his disease (March 1964).

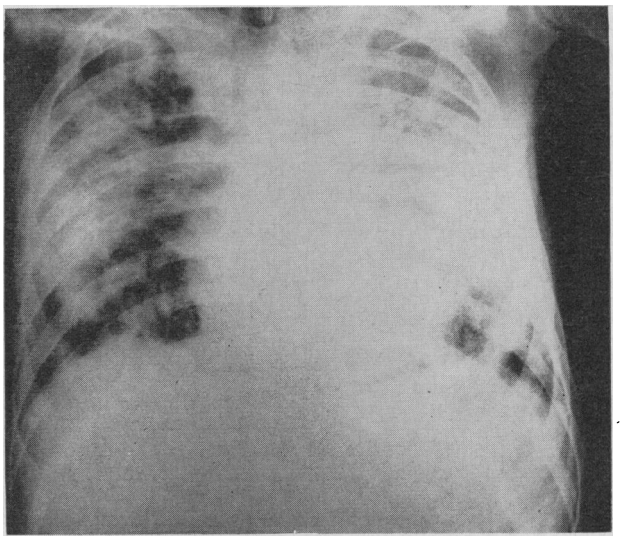

Fig. 3.—Chest radiograph of recipient two weeks before transplantation (September 1965).

sion. There was no history of unusual or severe respiratory disease and the patient was afebrile. During his investigations, he suffered a major convulsion associated with cerebral hematomas following an automobile accident three weeks before transfer. Severe neurologic damage was present, and he became completely dependent on the respirator. After repeated careful examinations and prolonged observation had demonstrated that there was no hope of recovery, permission was sought, and obtained, for lung donation after death. A chest radiograph taken shortly before death (Fig. 4) was interpreted as normal. The patient had been comatose for 48 hours and maintained on a respirator with an endotracheal tube for 24 hours prior to lung donation. He had a fever of 103° F. for the final 12 hours of his life.

Postmortem examination following transplantation revealed acute bronchitis and early bronchopneumonia in the remaining right lung.

PREPARATION FOR TRANSPLANTATION

When the prospect of human lung transplantation became apparent, a protocol was formulated for the preoperative, operative and postoperative periods.

While awaiting transplantation, the recipient was maintained in a single room on protective technique. Constant positive pressure respiratory assistance with a Bird respirator was required. Aerosol humidification was administered, as well as tetracycline to which the *Aerobacter aerogenes* in his sputum was sensitive. The skin was washed daily with povidone-iodine (Betadine) solution. Blood from both donor and recipient was submitted to the Canadian Red Cross for complete typing. The donor and recipient were compatible in 11 of the 15 blood factors tested; this compatibility included four of the major factors. In addition, blood for operation was cross-matched for compatibility with both the donor and recipient. Blood samples were drawn from both donor and recipient prior to transplantation and submitted for lymphocyte matching according to the method of Bain, Vas and Lowenstein.[7] Unfortunately, the results were equivocal because of a paucity of cells in the donor sample.

PROCEDURE

The left lung allograft was carried out in the early hours of September 29, 1965. After death of the donor, who had been systemically heparinized, a rapid left thoracotomy was performed through the bed of the fifth rib. The pulmonary artery was divided near the ligamentum arteriosum and the left main stem bronchus near the carina. A generous cuff of left atrium was removed, which included the pulmonary veins. The pulmonary artery was irrigated with 500 c.c. Ringer's solution kept at 4° C., to which 50 mg. of heparin had

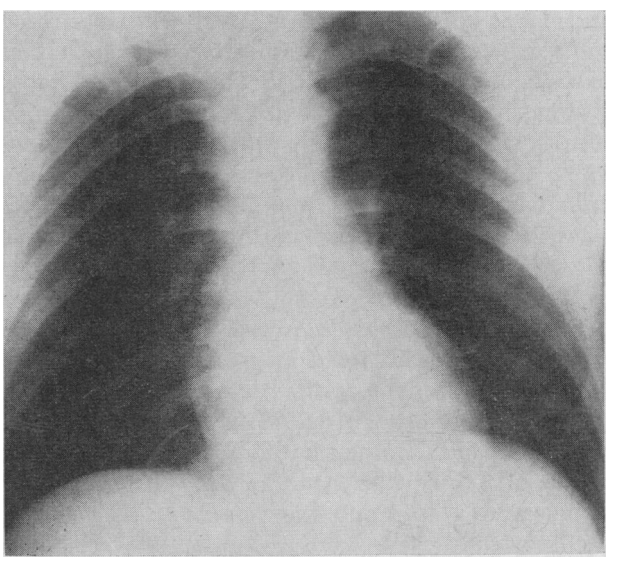

Fig. 4.—Chest radiograph of donor one day before he died. The lungs are large in size and there is no evidence of disease present.

been added, until clear fluid came from the pulmonary veins. A length of sterile Tygon tubing, 3/8 in. diameter, was gently tied into the bronchus with umbilical tape, and the lung was lightly ventilated with pure oxygen. Approximately 30 minutes elapsed from the cessation of the heart beat until the lung was removed, perfused and cooled.

Operation on the recipient was started after the death of the donor. The left chest was entered through the bed of the fifth rib and pneumonectomy performed. Approximately 4 cm. of the left pulmonary artery was mobilized prior to division, and the bronchus was transected through the upper and lower bronchi separately. The pericardium was opened and the common pulmonary vein was clamped at its junction with the left atrium; the superior and inferior pulmonary veins were divided with long cuffs.

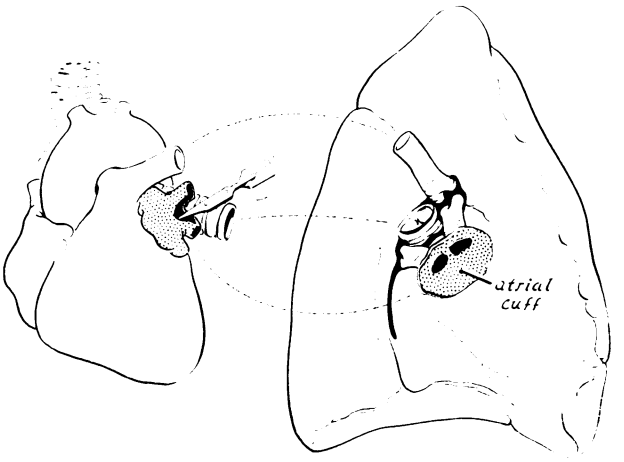

Fig. 5.—Illustration of operation.

Despite a striking discrepancy in size between the large lung of the donor and the fibrotic lung and contracted thorax of the recipient (Figs. 3 and 4), it was elected to proceed with total lung transplantation. The technique was basically that described by Magovern and Yates,[4] as illustrated in Fig. 5. The two recipient pulmonary vein cuffs were incised longitudinally on their opposing sides down through the contiguous part of the common pulmonary vein which joined them, providing a large "fish-mouth" cuff. The donor atrial cuff was trimmed to size and anastomosed with a continuous everting suture of 3-0 Tevdac. The donor bronchus was trimmed back just proximal to the upper lobe take-off and anastomosed to an appropriate length of recipient bronchus with a continuous over-and-over suture of 3-0 Tevdac. Finally the pulmonary artery was anastomosed with a continuous everting suture of 3-0 Tevdac. Anterior and posterior chest drains were placed and connected to mild negative suction. Total time from reception of the donor lung to completed anastomoses was 90 minutes, so that the transplanted lung underwent 30 minutes of "normothermic" ischemia, and 90 minutes of "hypothermic" ischemia.

ANESTHETIC MANAGEMENT

The patient arrived in the operating room in a somewhat apprehensive condition after transport from the ward, having been ventilated with an Ambu bag and oxygen. Oxygen, 100%, with assisted ventilation was administered via the tracheostomy. Rapid induction was accomplished using thiopentone 175 mg. intravenously; succinylcholine, 60 mg., was administered intravenously, and the ventilation controlled with 100% oxygen. A No. 39 Carlen's tube was inserted between the vocal cords and the tracheostomy tube removed. Two 30-mg. doses of laudexium sulfate, five minutes apart, were administered. A Ventimeter respirator was used throughout the operation.

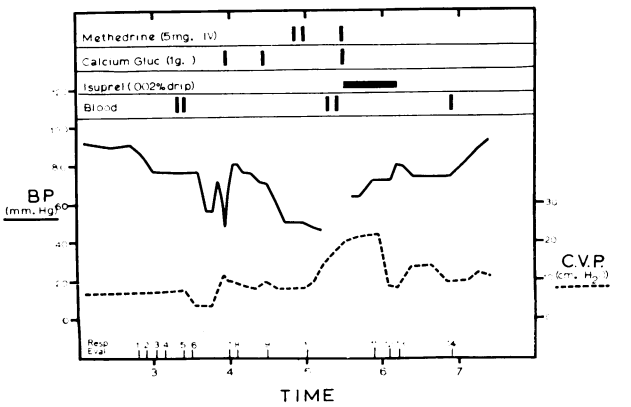

Fig. 6.—Anesthetic operative record. Respiratory evaluation numbers refer to the samples detailed in Table II.

The clinical course encountered during the operation is depicted in Fig. 6; Table II records the respiratory evaluation at the indicated times during the procedure. At the start of anesthesia at 2.10 a.m., the lungs were ventilated at a pressure of 30 cm. H_2O. This achieved a tidal volume of 380 c.c. measured by a Wright's spirometer, the resulting minute volume being 8360 c.c. With the patient breathing pure oxygen, blood gas determinations revealed a pO_2 of 278 mm., pCO_2 of 61 mm., pH of 7.34 and base excess of 4.5. The patient was tried on a 50% concentration of N_2O and O_2 for five minutes, by which time the arterial pO_2 had fallen to 78 mm.; for a further two minutes the right lung only was ventilated, resulting in clinical deterioration and an arterial pO_2 of 50.7 mm. Thereafter, he was switched to 100% oxygen with 0.25% halothane; a satisfactory arterial pO_2 (130 mm.) was achieved when only the right lung was ventilated. It was decided to maintain the patient on this mixture for the operation.

Several problems were encountered during the course of the operation. At 3.00 a.m. arterial hypo-

TABLE II.—RESPIRATORY EVALUATION AT OPERATION: BLOOD GAS AND VENTILATORY ASSESSMENTS DURING ANESTHETIC INDUCTION AND THE TRANSPLANTATION OPERATION

Sample	*Time (a.m.)*	*Lungs ventilated*	*pO_2 (mm.Hg)*	*pCO_2 (mm.Hg)*	*pH*	*Base*	*Pressure to ventilate (cm. H_2O)*	*Tidal vol. (c.c.)*	*Resp. rate*	*Min. vol. (c.c.)*	*O_2 conc. (%)*	*Anesth. mixture*
1	2.50	Both	278.0	61.0	7.338	+4.8	30	380	22	8360	100	
2	2.55	Both	78.0	67.0	7.328	+5.9	30	250	22	5500	50	$N_2O:O_2$ 4-4
3	3.02	Right	50.7	89.5	7.221	+4.1	34	220	17	3740	50	$N_2O:O_2$ 4-4
4	3.10	Right	130.5	81.8	7.239	+3.0	34	250	20	5000	100	+Halothane 0.25%
5	3.25	Both	234.0	61.3	7.305	+2.1	31	280	20	5600	100	+Halothane 0.25%
6	3.30	Right	71.5	79.0	7.262	+4.6	32	400	20	8000	100	+Halothane 0.25%
7	3.58	Both (L) lung retracted	60.3	71.2	7.265	+2.1	30	300	22	6600	100	+Halothane 0.25%
8	4.08	Right	46.0	78.0	7.253	+3.2	31	300	22	6600	100	+Halothane 0.25%
9	4.30	Right	59.8	74.0	7.280	+4.1	33	300	26	7800	100	+Halothane 0.25%
10	5.00	Right	51.2	63.5	7.35	+6.9	3	300	26	7800	100	+Halothane 0.25%
11	5.55	Right	52.4	90.0	7.15	−1.3	32	250	18	4500	100	+Halothane 0.25%
					Lung transplant							
12	6.05	Both	211.0	60.1	7.249	−2.9	20	700	18	12,600	100	+Halothane 0.25%
13	6.10	Both	158.0	43.5	7.426	+3.7	21	600	18	10,800	100	+Halothane 0.25%
14	6.55	Both	189.0	38.4	7.50	+6.7	26	600	18	10,800	100	+Halothane 0.25%

tension of 50 mm. Hg systolic, which was associated with a fall in central venous pressure, responded to rapid infusion of two units of blood. Shortly afterwards, a second precipitous fall to 40 mm. Hg responded to the administration of 1.0 g. of calcium gluconate. With the isolation of the left lung from perfusion and ventilation at 4.02 a.m., there was a gradual fall in systolic blood pressure to 50 mm. Hg. About 30 minutes later, the systolic pressure suddenly became unobtainable; a sharp rise occurred in the central venous pressure and the hitherto strong pulse of 120 per minute slowed to a feeble 40 per minute. Ineffectual contractions were noted and cardiac massage was started. Interim administration of calcium gluconate and methamphetamine hydrochloride was ineffectual. Finally an isoproterenol drip was started, with dramatic improvement in the patient's cardiovascular status. The systolic pressure returned to 60 mm., although the central venous pressure remained elevated. The transplanted lung was opened to perfusion and ventilation at 6.00 a.m.

The deterioration of arterial blood gas values through the operation is detailed in Table II. Sample 11, taken immediately before opening the transplanted lung and at the end of the period of ventilation and perfusion of the silicotic right lung only, revealed a pO_2 of 52.4 mm., a pCO_2 of 90 mm., and a pH of 7.15. At a ventilation pressure of 32 cm. H_2O, the tidal volume was only 250 c.c. Upon opening the transplanted lung to circulation and ventilation, the central venous pressure dramatically fell to 3 cm. H_2O and the systemic pressure started its rise to normal. Blood gases five and 10 minutes later were within the normal range. A tidal volume of 700 c.c. was obtained with a ventilation pressure of 20 cm. H_2O.

The remainder of the anesthetic course was uneventful and the patient was awake at the end of the operation.

POSTOPERATIVE COURSE

Post-Transplantation Management

The recipient was nursed in a single room in an intensive care area using protective technique. From the surgical point of view, the postoperative period was uncomplicated. There was minimal chest drainage and no air leak; both chest tubes were removed on the third day. As can be surmised from the immediate post-transplant blood gas and ventilatory values obtained by the anesthetists in the operating room, the patient was able to breathe restfully and easily for the first time in several months. He did not require assisted ventilation for periods as long as 30 minutes, but was maintained on a Bird respirator on "40% oxygen" air leak to ease the work of breathing and ensure full inflation of the transplanted lung. He enjoyed a good appetite and was cheerful from the first day. Blood pressure was maintained within the normal range throughout the postoperative period, but a tachycardia of 110-130 per minute was constantly present. A low-grade fever (99°-100°) was present from the first day, rising to 102° on the sixth and 103° on the seventh days. Pleural and blood cultures were sterile. Culture of tracheal aspirations repeatedly grew *Pseudomonas aeruginosa* and *Aerobacter aerogenes*. The patient was allergic to penicillin. From the day of transplantation, the patient was given pyrrolidinomethyl tetracycline (Reverin), 275 mg. intravenously daily, and isoniazid, 100 mg. orally daily. Cephaloridine (Ceporin), 500 mg. intramuscularly every 12 hours, and colistin (Coly-Mycin), 75 mg. intramuscularly every 12 hours, were started on the fourth day.

Bronchoscopy via the tracheostomy was carried out on the fifth postoperative day. No evidence of obstruction or excessive secretions was noted. The mucosa of the bronchus for about 2-3 cm. distal to the anastomosis was noted to be a pale grey colour.

The hemoglobin value averaged 12 g. and the hematocrit 40%, with a normal reticulocyte count daily. The erythrocyte sedimentation rate (ESR) was elevated to 45 mm./hr.; the platelet count was 175,000. The white blood cell count (WBC) was 12,000/c.mm. early in the postoperative course, rising to 25,000/c.mm. on the seventh day. The lymphocyte count dropped from 17% initially to 2% from the third to seventh days. Daily serum and urine electrolytes, blood urea nitrogen (BUN), serum creatinine, bilirubin, alkaline phosphatase and uric acid values were consistently within normal limits. Serum glutamic oxaloacetic transaminase (SGOT) was mildly elevated at 60-80 units, and lactic acid dehydrogenase (LDH) at 450-700 units.

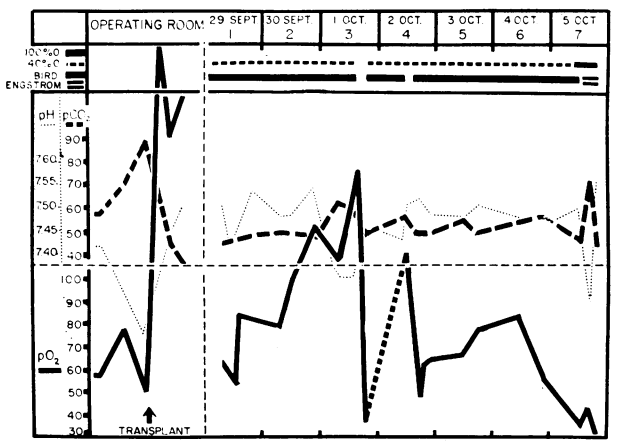

Fig. 7.—Postoperative respiratory course. The pH, pCO_2 and pO_2 values are shown for immediately following transplantation in the operating room and for the subsequent seven days.

Minute ventilation was measured with a Wright's spirometer, and frequent blood gas evaluations were made. The postoperative respiratory course is depicted in Fig. 7.

Immunosuppression

An immunosuppressive regimen similar to that for renal transplantation was used:

1. Azathioprine (Imuran).—A loading dose of 150 mg. (4 mg./kg.) was administered preoperatively and continued daily.

2. Corticosteroids.—An oral loading dose of hydrocortisone (300 mg. intravenously) was given preoperatively and repeated on the first postoperative day. Thereafter, prednisone was administered, starting at 100 mg. on the third day and increased to 300 mg. on the seventh day.

3. Actinomycin C, 400 mg. intravenously, was given immediately preoperatively and repeated on the first and fourth days.

Radiographic Examinations

Initial chest radiographs showed a fully expanded transplanted lung, occupying the whole of the left hemithorax. The central zone of the lung demonstrated irregular patchy areas of increased density containing an air bronchogram. The heart and mediastinum were shifted considerably to the right (Fig. 8). The central area gradually increased in size, and on the seventh day patchy densities appeared in the left lower lobe which progressed on to consolidation (Fig. 9).

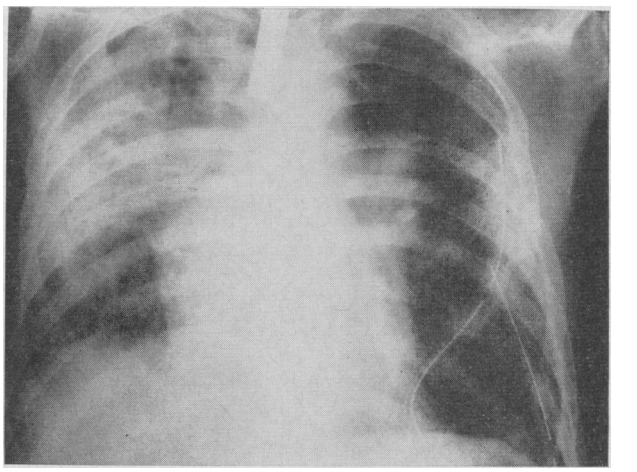

Fig. 8.—Chest radiograph of recipient three days post transplantation.

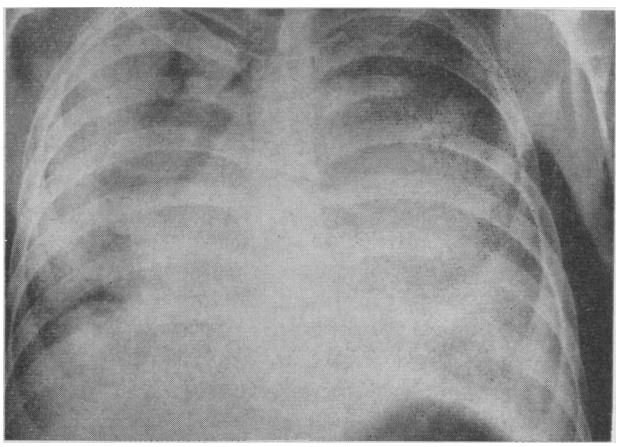

Fig. 9.—Chest radiograph of recipient seven days post transplantation.

PHYSIOLOGICAL TESTS

Alveolar-Arterial Differences

End tidal and mixed expired air were sampled for one minute while the patient was assisted by the Bird respirator. Minute volume was measured

TABLE III.—ALVEOLAR-ARTERIAL OXYGEN AND CO_2 GRADIENTS

	Days postoperative			
	3rd	*4th*	*6th*	*7th*
P_{AO_2}	455	546	422	317
P_{aO_2}	127	111	83	40
Diff.	338	435	349	277
P_{ACO_2}	25	28	27	21
P_{aCO_2}	60	56	55	46
Diff.	35	28	28	25

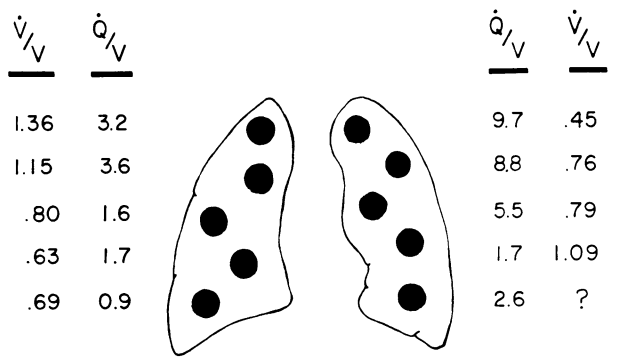

Fig. 10.—Xenon-133 ventilation perfusion ratios. The dark areas represent the lung fields scanned by the individual counters.

on a gas meter and the samples were analyzed by the micro-Scholander technique. Simultaneous arterial blood samples were drawn for analysis of respiratory gases. Significant (A/a) differences for O_2 and CO_2 existed (Table III).

Xenon-133 Studies

Evaluation of ventilation and perfusion of the lungs was made on the fifth postoperative day using xenon-133 (Xe^{133}). The patient was studied in the supine position with five scintillation counters placed over each lung posteriorly. He was given two intravenous injections of Xe^{133} in saline, and rebreathed from a closed spirometer circuit containing trace amounts of the isotope. Relative ventilation and perfusion values are depicted in Fig. 10. Ventilation as estimated from washout curves was abnormal throughout, but was best preserved in the right upper zone. Perfusion, on the other hand, was preferentially distributed to the upper zone of the graft, and was strikingly diminished elsewhere.

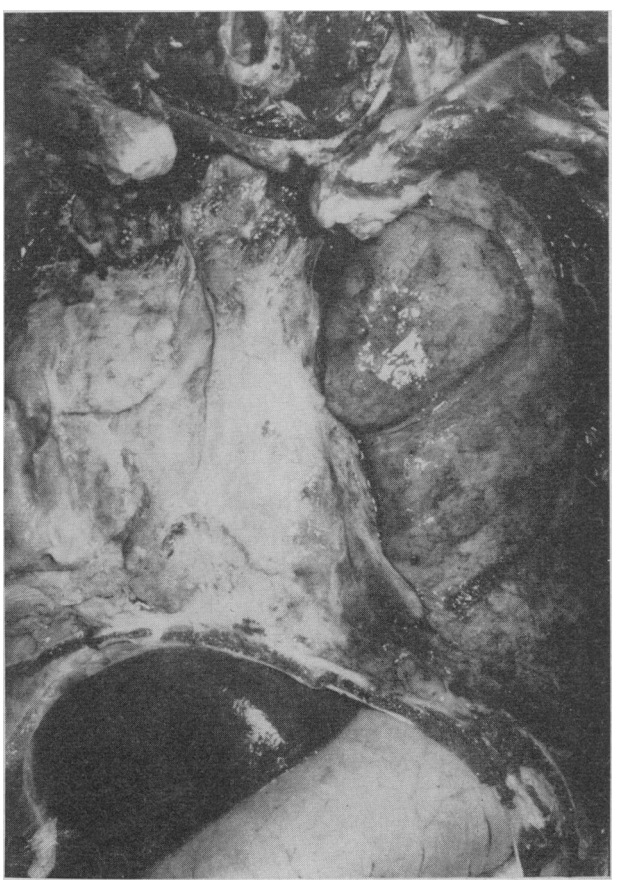

Fig. 11.—Overall view at postmortem examination. The transplanted left lung was boggy and bulged out of the thorax. The silicotic right lung had been shifted further to the right thorax.

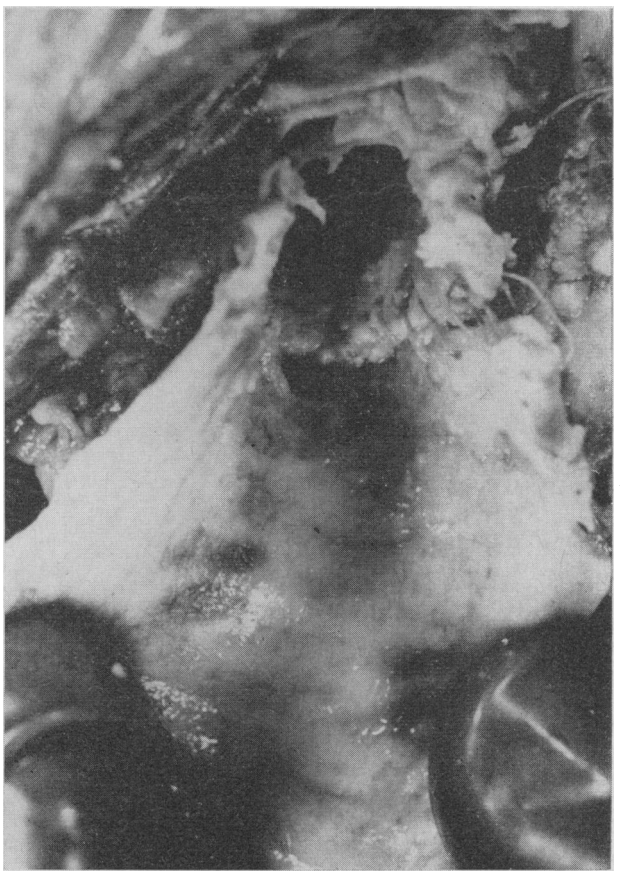

Fig. 12.—Bronchus at postmortem examination. The slightly inflamed but otherwise normal host bronchus has been opened to demonstrate the infarcted proximal aspect of the transplanted bronchus.

POSTMORTEM FINDINGS

The patient died on the seventh postoperative day and autopsy was performed within three hours of death. The transplanted left lung bulged out of the thorax and had shifted the mediastinum and heart toward the right side. The residual lung was whitened and fibrotic; the transplanted lung had a boggy feel and considerable pallor (Fig. 11). The vascular anastomoses were intact with no thromboses at the suture line. The transplanted bronchus for 2-3 cm. distal to the intact anastomosis had a grey white appearance contrasting greatly with the normal-appearing host bronchus proximally (Fig. 12); distal to this area the smaller transplanted bronchi showed inflammation and edema with some plugs.

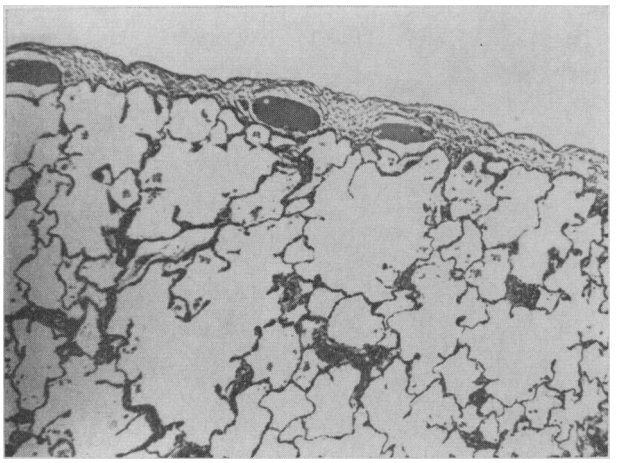

Fig. 13.—Severe engorgement of subpleural and intra-alveolar lymphatics is demonstrated.

Microscopic sections of the transplanted lung demonstrated infarction of the main-stem bronchus to the level of the left upper lobe bronchus take-off, with acute pseudomembranous bronchitis in the viable bronchial tree. There was severe interstitial edema of protein-rich fluid in the perivascular, interstitial proper and subpleural lymphatics (Fig. 13). Within the substance of the lung, nearly all in the lower lobe, was an extensive pneumonitis. The alveolar septa contained little blood, and alveolar lining cells were often swollen and sloughed into the lumen. Large mononuclear cells were present in the lung, often surrounding small venules; unfortunately, these were not stained for pyronine (Fig. 14).

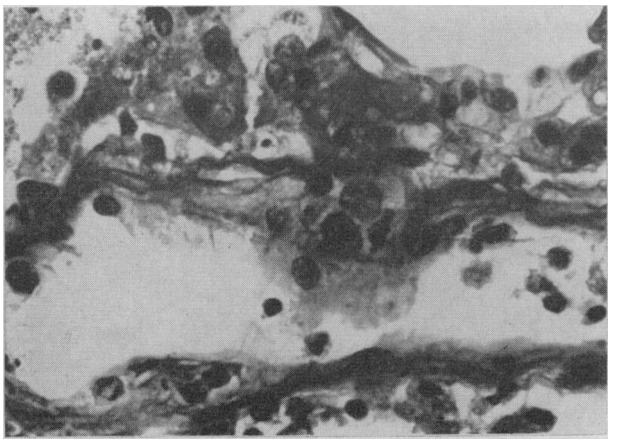

Fig. 14.—Large mononuclear cells in alveoli and surrounding small venules.

Surfactant Assay

Wedges of the transplanted lung were frozen within three hours of death for subsequent surfactant assay. The pieces of lung were minced in saline, and the extract was studied with a Wilhelmy balance. According to the method of Clements *et al.*,[8] the stability index ($\bar{S}$) can be calculated from the formula:

$$\bar{S} = \frac{2\ (\max \gamma - \min \gamma)}{\max \gamma + \min \gamma}, \text{ where}$$

max γ represents maximum surface tension and min γ minimum surface tension. Two samples were analyzed, both from the upper lobe of the transplanted lung which was relatively unaffected by the terminal pneumonitis. No bronchus large enough to cannulate was apparent in either specimen. However, by gently blowing through a No. 18 needle inserted into the parenchyma, an indication of the inflation and collapse characteristics of the samples was obtained. A wedge sample from the lingula weighed 4.26 g.; only half of the sample could be easily inflated, the remainder appearing grossly atelectatic. Its max γ was 41.5 d/cm., and the min γ was 14.6 d/cm. The $\bar{S}$ was 0.91. The specimen from the upper lobe proper weighed 2.2 g. and retained the air blown into it. Its max γ was 47.1 d/cm. and its min γ was 23.2 d/cm. with a $\bar{S}$ of 0.68.

In our laboratory, a minimum surface tension less than 15 d/cm. at 20% of maximum area can be considered normal. The abnormalities of the upper lobe sample might be attributed to the small amount of tissue submitted for testing. The lingular specimen had a min γ of 14.6 d/cm. with a $\bar{S}$ of 0.91 which is within normal limits. These figures are compatible with those reported by Waldhausen *et al.*,[9] but are just outside the range acceptable to Yeh, Ellison and Ellison.[10] The pneumonic lower lobe was not sampled, but surfactant assay suggests that loss of surface activity was at a minimal level in the relatively non-infected upper lobe of the transplanted lung.

DISCUSSION

Decision

The natural history of this degree of silicosis is one of rapid and relentless downhill progression. This outcome was only too apparent to those who cared for the recipient clinically; he had required constant nasal oxygen for the eight months before transplantation. The final consideration that prompted the decision for transplantation was the onset of acute respiratory failure in September, secondary to bronchopneumonia. Tracheostomy was performed and assisted ventilation supplied. These measures tided the patient over until transplantation was performed on September 29, 1965. In view of the terminal bronchopneumonia, the success of the lung transplantation might have been better assured if the decision had been taken earlier when infection was not a major problem and tracheostomy was not essential for respiration.

Selection

Proper selection of a donor is of the utmost importance in undertaking lung transplantation. Not only must the lung function be optimum, but infection must also be absent. Endotracheal tubes or tracheostomies easily introduce infection into the tracheobronchial tree, and these measures should probably be avoided. Necessity may demand the

use of such a donor, as in this case, but the possibility exists of transplanting an infected lung. Bronchopneumonia was present in the non-donated lung of the donor post mortem; sputum cultures of the recipient, however, consistently grew bacteria which were indigenous to him preoperatively. In the contracted chest of the silicotic patient, placement of an overly large transplanted lung may have interfered with proper ventilation. In these circumstances, transplantation of a lobe may be preferable.

Immunosuppression

The current management of immunosuppression in patients undergoing renal transplantation consists of azathioprine, steroids, actinomycin C and localized radiation therapy. The latter is not applicable to such a large organ as the lung; of the former, steroids should probably be used very minimally, if at all. The use of heavy doses of steroids in association with the other immunosuppressive agents seems to fan the fires of infection if present in the organ—a significant danger in the case of the lung. In the Royal Victoria Hospital series two kidneys with latent infection, one with histoplasmosis and one with smoldering pyelonephritis, have been transplanted. Overwhelming sepsis resulted in the deaths of both recipients. In the present case, the administration of large doses of steroids in addition to preoperative steroids may have contributed significantly to the overwhelming terminal bronchopneumonia. In patients undergoing lung transplantation, steroids should probably be reserved for rejection crisis and not routinely administered.

Criteria for Rejection

While for renal transplantation there are several varied criteria to determine the onset of rejection, the criteria for rejection of a transplanted lung are uncertain. The lung cannot be palpated; fever and leukocytosis may be indicative of pneumonitis no less than rejection. The diminution of function shown by blood gas analysis and ventilatory function studies can also be due to edema and/or infection. Reduction of lung compliance as an indicator of diminished surfactant production by the alveolar cells and, consequently, of rejection activity has been noted.[9, 11] Compliance was not measured in our patient, but surfactant assays were performed seven days post transplant. In the upper lobe, which was relatively unaffected by pneumonitis, surfactant activity was within the normal range for this laboratory. Rejection activity at the time of death was at a minimum by this criterion. Compliance can be modified as well by edema and pneumonitis; the poor ventilation of the transplanted lung relative to the silicotic residual lung as demonstrated by Xe^{133} testing may have been due to these factors, rather than to rejection. Steroid administration in this case was increased terminally in fear that the fever was due to rejection crisis. No specific criteria for rejection in lung transplantation were available, and it would seem necessary to elucidate these criteria for future transplantations.

Anesthesia

The No. 39 Carlen's tube proved most satisfactory in ventilating each lung individually. Assessment of respiratory function before beginning the operation itself showed that the patient's right lung could exchange gases adequately when both lungs were being perfused. It became evident when the left lung was isolated during the period of transplant that there was a tremendous load imposed on the right ventricle, which had to pump the entire stroke volume through the one residual lung with its marked increase in vascular resistance. Gas exchange deteriorated and the right heart failed; it recovered only by means of the isoproterenol infusion. Where the disease process itself is as extensive as encountered in this case it would seem judicious to carry out the transplant with the patient on heart-lung bypass, obviating the possibility of heart failure developing. The use of cardiopulmonary bypass during pulmonary surgery has been recommended where ventilatory support seems necessary.[12]

No attempt was made to correct the respiratory acidosis present during the transplantation proper because the base value was within normal limits, and because it was anticipated that this respiratory acidosis would be corrected when the transplanted lung was opened to ventilation and perfusion. Had it been corrected with sodium bicarbonate, the possibility of metabolic alkalosis would have been present in the post-tranplant period.

Bronchial Infarction

Evidence of ischemic infarction of the transplanted bronchus was noted at bronchoscopy on the fifth day and confirmed at autopsy. This has not been reported in the two previous cases of human lung transplant, but has been noted on occasion in animals.[13] Experimentation has demonstrated that bronchial transection, and thereby bronchial artery interruption, can generally be carried out with impunity. Extensive bronchopulmonary arterial precapillary anastomoses have been demonstrated in humans;[14] it has been further observed that the bronchial arteries seem to function to provide pulmonary nourishment *in utero*, retaining the same size in adult life and enlarging only in response to pulmonary need in the face of pathological process.[15] By virtue of the dual pulmonary blood supply and anastomoses, pulmonary tissues and bronchi peripheral to the hilum retain viability if one or the other circulation is interrupted; the bronchial arteries are necessary for the

nutrition of the proximal main-stem bronchus only.[16] Bronchial anastomosis performed too proximally or interference with hilar adventitial arteries may deprive the proximal portion of the bronchus of blood supply and lead to infarction or late stenosis.[13, 17] Pulmonary resections with bronchoplasty have not demonstrated compromise of circulation to the bronchus.[18, 19] In this case, the anastomosis may not have been close enough to the first bronchial bifurcation, or sufficient damage may have been done to the hilar adventitial arteries to compromise the circulation.

Pulmonary Function

Immediately following transplantation, there was instantaneous correction of the heart failure and, within minutes, correction of the severe acidosis and respiratory failure. This followed upon the threefold increase in minute ventilation (from 4.5 to 12.1 l./min.), at a reduced delivery pressure (from 32 cm. H_2O to 18 cm.); such a change can be anticipated following replacement of a stiff lung with one of normal compliance, and ventilation and perfusion of both lungs. Subsequently during the postoperative period, delivery pressures of 15-20 cm. H_2O maintained ventilation at 8.5-11 l./min.

Despite the large ventilation volumes, however, blood gases could not be controlled within normal limits, a probable consequence of disturbances of ventilation *vis-à-vis* perfusion within the lungs. Arterial pCO_2 (ranging from 45 to 65 mm.) was, however, lower than the values recorded in the three months before operation. With bicarbonate values between 30 and 40 mEq./l., the H^+ concentration was somewhat below normal, and the pH slightly on the alkalotic side. End tidal pCO_2 measured on the third, fourth, sixth and seventh postoperative days was consistently lower than simultaneously measured arterial pCO_2, the difference ranging from 25 to 35 mm. These differences can be attributed to areas in the lung in which ventilation was excessive in relation to perfusion (i.e. areas of virtual dead-space ventilation).

In the first six postoperative days, the patient's ventilation was assisted by a Bird ventilator (Mark VIII) connected to an oxygen pressure source; alveolar pO_2 (as reflected in endtidal samples) ranged between 455 and 546 mm. Despite this, simultaneous measured values for arterial pO_2 never exceeded 127 mm. These high alveolar-arterial O_2 differences were thought to be produced by areas of virtual blood shunting where ventilation was low in relation to perfusion (i.e. low $\dot{V}/\dot{Q}$ ratio). This also was demonstrated in the precipitous fall of arterial pO_2 to 40 mm. when the patient was allowed to breathe room air for short periods on the third and fourth days. The high A/a O_2 difference dictated the need for high inspired levels of oxygen in order to maintain arterial pO_2 above an arbitrary minimum of 60 mm.; the theoretical hazard of potential damage to alveolar structure from high O_2 tension was accepted.

On the afternoon of the sixth postoperative day there was a further precipitous fall in arterial pO_2 despite increasingly high inspired O_2 levels. The final measurement of 31 mm. was taken when the patient was being maintained on the Engstrom respirator run on pure O_2.

Observations in the operating room had suggested that the transplanted lung was well perfused and ventilated at the end of operation. The A/a differences for O_2 and CO_2 which had developed by the third postoperative day indicated that this state of affairs did not persist. By the fifth day the only well-perfused area was the left upper lobe (i.e. in the graft). It was anticipated that the more compliant transplanted lung would have continued to receive the bulk of the ventilation as well. The Xe^{133} studies on the fifth postoperative day, on the other hand, demonstrated reduced ventilation to the entire graft, with maximal ventilation in the patient's own right upper lobe which was severely diseased. It is tempting to regard this area as the one with a greater than optimum ventilation/perfusion ratio and responsible for the observed A/a CO_2 difference, and the transplanted lung as the area of reduced ventilation *vis-à-vis* perfusion (and responsible for the A/a O_2 difference). This latter became greatly aggravated when pneumonic consolidation developed within the graft. The reason for the poor ventilation in the transplanted lung is not clear. It is possible that the graft became turgid with lymphatic edema; dilated lymphatics observed as the chest was closed at operation, and still present at autopsy, as well as the daily radiographs, support this suggestion. Such edema would presumably persist until regeneration of the lymphatic drainage to the mediastinum occurred, which from animal work might be anticipated at about 14 days.

Gas exchange in autotransplanted dogs is reduced for the first two to three weeks, during which time compliance is likewise low; improvement seems to take place concurrently with lymphatic regeneration. In experimental lung transplantation, the animal can rely on the function of his other good lung for this period. For a patient to be considered for lung transplantation, however, his remaining lung must be the site of considerably impaired function. This will undoubtedly continue to be a major problem as long as transplantation is postponed until the late stages of bilateral lung disease.

SUMMARY AND CONCLUSIONS

Left lung homotransplantation was performed on a 31-year-old man in terminal irreversible respiratory failure due to advanced silicosis. Initially, fair respiratory function was achieved, but terminal pneumonitis interfered significantly with perfusion and ventilation, and, consequently, with gas exchange. Surfactant assay

suggested that there was minimal rejection activity in the non-infected areas of the transplanted lung.

Inasmuch as experience has shown that observations from animal transplantation experiments with other organs are not fully applicable to humans, it is felt that selective human lung transplantation should continue. Complete function studies, including A/a gradients, xenon-133 testing and surfactant assay where available, should be done. From the experience of this human lung transplantation, it is felt that success can be better assured if the decision to operate is taken earlier and particular care is taken to avoid infected grafts in selecting the proper donor. Immunosuppression measures should rely minimally on steroids, and patients should be weaned from steroids preoperatively. Cardiopulmonary bypass should probably be used during transplantation. Finally, specific criteria for rejection must be elucidated to guide immunosuppression therapy in lung transplantations. Pooling of information and critical analysis of all cases from various centres must be encouraged to guide future efforts.

This lung transplantation could not have been possible without the co-operation of the nursing, medical and ancillary services of the Hospital. Particular acknowledgment is made of the contributions of: Dr. G. F. Brindle, Department of Anesthesia, McGill University, and Miss E. Munro and the Operating Room Staff, Royal Edward Chest Hospital, for their assistance in the animal experimental phase; Dr. J. Henderson, Department of Medicine, Royal Victoria Hospital, for the clinical care of the patient; Dr. R. G. Fraser and the Department of Radiology, Royal Victoria Hospital; Dr. E. Rosenberg, Department of Experimental Surgery, Royal Victoria Hospital, for the surfactant studies; and Drs. J. Gagnon and W. Thurlbeck, Department of Pathology, McGill University, for postmortem studies.

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