

*Clinico-pathological Conferences***RENAL TRANSPLANTATION, RUPTURED RENAL ALLOGRAFT
AND TRANSPLANT LUNG**

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A CLINICO-PATHOLOGICAL CONFERENCE was held at the Princess Alexandra Hospital, Brisbane. The following is a report of the meeting.

CLINICAL HISTORY

The patient was a married man, aged 47 years.

He was first admitted to the Princess Alexandra Hospital, Brisbane, in November, 1965, with malignant hypertension. There was a history of intermittent albuminuria for six years and mild hypertension for 12 months prior to admission. There were no symptoms of renal disease, and no family history of kidney trouble or hypertension. Of possible aetiological significance was a very high ingestion of Worcestershire sauce. On his admission to hospital, the serum creatinine level was 4.0 mg/100 ml.

The hypertension was treated, and he was discharged. He presented again in February, 1969, with severe renal failure. The blood pressure was 250/145 mm Hg, and the serum creatinine level 19.2 mg/100 ml. The renal failure persisted, and the patient was started on bi-weekly haemodialysis on May 26, 1969.

The main problems during this period were from hypertension, controlled by salt and fluid restriction, and repeated clotting of the arterio-venous shunt. The patient received five units of blood prior to the start of dialysis and 14 units during the course of dialysis. After 76 haemodialyses, renal transplantation was performed on February 16, 1970, a right cadaver kidney being grafted into the patient's left iliac fossa. The total ischaemia time was 182 min (31 warm, 121 cold, 30 anastomoses). The graft assumed a good colour after revascularization, but no urine was passed during the operation. The results of tissue typing before operation are shown in Table 1.

TABLE 1
Tissue Grouping of Donor and Recipient¹

Subject	Blood Group	First Sublocus		Second Sublocus		Misc. 4b
		HLA2	HLA3	HLA5	HLA7	
Donor ..	O+	+	-	-	+	+
Recipient	A+	-	+	+	+	+

¹ The following antigens were not detected in either donor or recipient: HLA1, HLA9, HLA8, Sly 1, LC17, LC20, 4a.

Treatment with azathioprine (200 mg daily) and prednisone (200 mg daily) was started before operation. After operation, the patient's general condition was satisfactory, but the urine output was only 100-200 ml daily.

On the second postoperative day, a six-hour coil dialysis was performed. The next day the arterio-venous shunt clotted, and after the clot had been removed, heparin therapy was started. On the fifth postoperative day, haemodialysis was repeated. On the sixth day there was some bleeding from the wound. The heparin dosage was reduced, and this was followed by re clotting of the shunt. On the eighth postoperative day the patient complained of pain over the transplanted kidney, and at operation two hours later it was found that the graft had ruptured. There was a split

from the upper pole along two-thirds of the anti-hilar border. The rest of the kidney was tense and swollen, but appeared viable. Haemostasis was obtained and the kidney left in position.

Peritoneal dialysis was started and continued for ten days, the urine output slowly increasing to 600 ml daily. The patient was discharged from hospital on the 25th day after operation. The urine output at that time was 3 l. daily, with a serum creatinine level of 5.7 mg/100 ml. Drug therapy was azathioprine (100 mg daily), prednisone (140 mg daily) with magnesium trisilicate and methyldopa (1 gm daily).

The patient's general condition improved slowly, and the urine output was maintained. By the 54th postoperative day the serum creatinine level had fallen to 1.4 mg/100 ml, with a creatinine clearance of 58 mg/min. The drug doses at that time were: azathioprine, 200 mg daily; prednisone, 80 mg daily; methyldopa, 1 gm daily; and chlorothiazide, 0.5 gm daily.

On the 61st postoperative day he developed a dry cough, associated with a rise in temperature to 38.6°C. There were no other symptoms. The patient had stopped smoking at the time of transplantation. Physical examination showed no abnormality, apart from some scattered rales throughout both lungs. The chest X-ray film showed cardiomegaly, but the lungs were accepted as being within normal limits. Serum biochemical and haematological findings were unchanged, and the urine was clear of infection. Ampicillin (2 gm daily) and cloxacillin (2 gm daily) were added to the treatment régime. Over the next week the temperature fluctuated, but the other symptoms were unchanged. The patient felt more general malaise. The chest X-ray picture was unaltered.

In the following week the temperature again rose, and the patient was admitted to hospital on the 73rd postoperative day. His symptoms were now lethargy and malaise, a dry cough and mild exertional dyspnoea. There was no evidence of cardiac failure or change in renal function. On physical examination the patient looked unwell and had slight dyspnoea at rest. His temperature was 38.4°C. and his pulse rate 100/min. The lungs were clear on clinical examination. A chest X-ray film showed bilateral basal pulmonary infiltration. The arterial blood gases were as shown in Table 2. The haemoglobin value was 9.0 gm/100 ml, and the leucocytes numbered 9,800/mm³, 50% being segmented neutrophils, 36% non-segmented neutrophils, 3% lymphocytes, 2% monocytes, 2% eosinophils and 7% myelocytes. The platelets numbered 200,000/mm³. The serum sodium level was 127 mEq/l., the blood urea level 47 mg/100 ml, the serum creatinine level 1.7 mg/100 ml, and the creatinine clearance 56 ml/min. The urine was not infected. The antibiotics were ceased. The prednisone had been reduced to 60 mg daily at this stage, but his drug treatment was otherwise unchanged.

The patient's dyspnoea worsened over the next 48 hours, so that oxygen was required at rest, and the temperature remained elevated. The chest X-ray film showed some progression of pulmonary infiltration, but there was still no sputum production, and the lungs were clear to clinical examination. Pulmonary function tests showed a considerable defect in gas transfer with a D_{50} of 7.6 ml/min/mm Hg at rest, and no increase on hyperventilation. The FEV₁ was 70% and the vital capacity 3,160 ml.

At this stage the dose of prednisone was increased to 200 mg daily. The temperature fell to normal and the patient felt better, no longer requiring oxygen support. The blood gases and chest X-ray picture were essentially unchanged. Blood cultures taken on the first and second days after admission to hospital were now reported as showing a growth of *Staphylococcus albus*, and treatment with methicillin was begun.

On the 78th postoperative day a renal biopsy was performed, showing mesangial thickening in the glomeruli and interstitial infiltration by chronic inflammatory cells. The serum creatinine level at this time was 1.6 mg/100 ml. The patient again felt unwell, and the dyspnoea at rest recurred. The patient was afebrile, but the blood gases and chest X-ray picture remained as before. After five days of prednisone in a dosage of 200 mg daily, a 10 mg/day reduction was commenced.

TABLE 2
Arterial Blood Gases¹

Days after Operation	pO ₂ (mm Hg)	pCO ₂ (mm Hg)	pH
74	55	27.8	7.52
76	Prednisone increased		
78	63	30.5	7.45
84	52	22	7.45
86	52	28	7.48

¹ The patient was breathing room air for 30 min before the arterial sample was taken.

His condition remained unchanged until the 84th postoperative day, when the serum creatinine level rose to 3.9 mg/100 ml. The prednisone dosage was increased to 300 mg daily. The serum creatinine level continued to rise, and the patient's general condition deteriorated rapidly. The dyspnoea worsened, and the oral administration of pentamidine isothionate was started at a dose of 300 mg daily on the 86th postoperative day. On that day, local external irradiation (150 rad) was given to the grafted kidney, but renal function did not improve. Peritoneal dialysis was started. The patient became markedly confused and disorientated and died suddenly during dialysis, 88 days after transplantation.

DISCUSSION

CHAIRMAN (DR J. FITZWATER): The main topic in this discussion will be the patient's terminal episode, but there are several interesting facets to discuss in the earlier parts of his life. The cause of his renal failure appeared to be related to his hypertension, but in addition he ingested a large amount of Worcestershire sauce. Would Dr Murphy like to comment on this aspect of the patient's illness?

DR K. J. MURPHY: In 1956 Douthwaite reported an association between renal disease and Worcestershire sauce ingestion. A patient, who had rising blood urea, hypertension, gross albuminuria, a low urinary specific gravity, pronounced cylinduria and a low urea clearance (18% of normal), had been taking from half to one bottle of Worcestershire sauce per day. The sauce was ceased for lack of any other advice to give; the albuminuria diminished, and the blood urea and the blood pressure returned to normal. It thus appeared that the patient had glomerular and tubular damage due to excessive intake of Worcestershire sauce. Our own experience (Murphy, 1967) began with patients who had bilateral and recurrent renal calculi for which no reason was apparent, and in whom there was this finding of excessive intake of Worcestershire sauce. The patients originally described appeared to benefit from ceasing the sauce, in so far as they did not form further stones when seen 12 months later.

This patient, on discharge from the Army in 1945, had no hypertension or albuminuria; it was after this that he developed his habit of drinking sauce neat while his friends drank gin or vodka. Also, the albuminuria appeared before the hypertension. No other cause of his renal failure was elicited, and it is postulated that the sauce was a causative agent.

CHAIRMAN: When the patient's kidneys became incapable of maintaining control of the internal milieu of the body, he was commenced on twice-weekly dialysis. Were there any problems at this time?

DR T. MORGAN: The patient's hypertension was controlled by dialysis and limitation of salt and water intake. For a period of time the patient found it difficult to adjust to the restrictive life of dialysis, but in the two months before transplantation he was adjusted and enjoying life.

CHAIRMAN: In February, 1970, a kidney became available and was transplanted into the patient. The postoperative course appeared to be stormy, and the surgeon may wish to comment on these events.

DR L. C. J. HARTLEY: The period of ischaemic insult to the donor kidney was probably in excess of that recorded as warm ischaemia, for the donor was maintained by external cardiac massage prior to death, and the prolonged ischaemia caused acute tubular necrosis with swelling of the kidney. On the eighth postoperative day he developed severe pain in relationship to the graft. He showed signs and symptoms of blood loss and local tenderness in the area of the recent operation. When the wound was explored, there was a rupture along the length of the antihilar border. Tamponade stopped the bleeding, and no further problems developed.

Murray *et alii* (1968) reported four cases of spontaneous rupture of the kidney in 110 transplants. Three were in kidneys from living related donors, and after the haemorrhage was controlled they went on to function well. The fourth case, a kidney from a cadaver donor, required nephrectomy. There have been other cases of spontaneous rupture reported by Salaman *et alii* (1969) and Lord *et alii* (1970); the last was most interesting, as the rupture occurred at five months in association with gross rejection. In all cases ischaemia or rejection has been present, but in one case the trauma of renal biopsy may have been causative.

There is no record that capsulotomy was performed in any of the cases mentioned, and it has been suggested that this operation can reduce the amount of ischaemic parenchymal damage by allowing swelling of the kidney and perhaps thereby reduce the chances of spontaneous rupture. Although our patient was receiving anticoagulant therapy, there was no evidence that this could be held responsible. In reported cases biopsy has been implicated, but in only one was the biopsy related to the rupture site, and here it may well have been only the initiating factor, for the kidney was undergoing rejection.

It is known that, in experimental animals, spontaneous rupture can occur from the gross swelling associated with both anoxia and rejection. It seems likely that allograft rupture is a final result which can be common to any pathological process producing significant swelling of kidney. I believe that the rupture of this kidney was related to ischaemia prior to transplantation. His subsequent recovery of renal function and relative absence of rejection episodes support this.

CHAIRMAN: In subsequent cases, would you remove the kidney, or try to arrest bleeding and leave it *in situ*?

DR HARTLEY: In general, I would try to preserve the kidney, as prolonged function after spontaneous rupture has been recorded. However, if there had been repeated episodes of rejection, I would remove the kidney.

CHAIRMAN: The final illness of this patient appeared to start two months after operation and persisted for one month. What was thought at the time to be the cause of this episode?

DR MORGAN: The onset of the illness was insidious and was marked by the absence of many definite signs. The patient was treated for a presumed respiratory infection, but antibiotic therapy did not seem to influence his symptoms. The most prominent of these was his dyspnoea, which progressed rapidly despite the treatment outlined. Chest X-rays were initially clear, but by the 12th day of the illness some changes occurred which the radiologist may wish to discuss. At no time could we culture any organisms from the lung, and by the time lung biopsy was considered he was too sick to survive the procedure. Thus, any diagnosis was being made on surmise without objective evidence.

DR K. SIDDLE: The first radiograph taken after transplantation showed clear lung fields with slight cardiomegaly. A chest X-ray on the 61st postoperative day was normal, but one on the 73rd day showed a bilateral basal infiltrate, more marked on the right, which by the 78th postoperative day had become more marked at the right base and left midzone. Adjacent areas were beginning to coalesce. Over the next five days the lesions showed progression.

The appearances were those of disseminated alveolar disease. Day-to-day changes were slight and variable, some films showing an apparent improvement. However, the overall picture was one of slowly progressive deterioration, with extension of the lung involvement and coalescence of adjacent involved areas. The changes are not specific and

may arise from a variety of causes. The most likely were: (i) a pneumonia due to bacterial, fungal, protozoal or viral infection; or (ii) the transplant lung syndrome.

CHAIRMAN: A prominent feature of this illness was the severe dyspnoea and anoxia. Blood gas studies were performed, and Dr Kennedy may wish to comment on these.

DR K. P. KENNEDY: The combination of a pO_2 of 55 mm Hg and a pCO_2 of 28 mm Hg indicated that by the 74th postoperative day there was quite a marked increase in alveolar arterial (Aa) oxygen gradient. In this particular case, one can calculate that the Aa gradient would have been approximately 60 mm (normal, 5 to 15 mm). An increase in Aa gradient of this order could occur as the result of a right-to-left shunt or a diffusion defect, or it could be due to ventilatory-perfusion ratio inequality. The presence of a right-to-left shunt could have been excluded if the patient had been given 100% oxygen to breathe over a period of several minutes. With regard to the possibility of a pure diffusion defect, one can say that pure diffusion defects practically never occur, and in fact changes considered in the past to have been due to diffusion defects are now known to be almost always caused by ventilatory-perfusion ratio inequality. In this particular patient, when the physiological findings are taken in conjunction with the radiological appearances, one can be reasonably confident in saying that the arterial gas changes would have been due to ventilatory-perfusion ratio inequality.

The simple ventilatory test did not reveal any evidence of airways obstruction or of any significant impairment of ventilatory function. The arterial pCO_2 of 28 mm Hg indicated, of course, that alveolar ventilation had in fact been in excess of normal. The carbon monoxide diffusion test had confirmed that there was considerable impairment of gas transfer—a finding which would be expected in the presence of a marked ventilatory-perfusion ratio inequality.

An initial slight improvement in arterial oxygen tension after prednisone was increased was not maintained (Table 2). It was not possible to make a diagnosis from these studies, but the lack of response to steroids suggests that it was not the classical pattern for transplant lung.

CHAIRMAN: The previous two speakers have mentioned an entity called transplant lung syndrome, and further information about this would be useful.

DR N. RIBUSH: A particular type of pulmonary disease occurring in patients who have undergone renal transplantation has been called "transplantation pneumonia" (Rifkind *et alii*, 1964) or "transplant lung" (Slopak *et alii*, 1968).

In 1968, Slopak *et alii* reported four survivors of transplant lung. In a review of the literature they found an additional 15, out of over 300 patients with renal allografts.

The majority of these patients have been under 21 years of age. The time of onset of the pulmonary disease is frequently during the third month following transplantation, and has been noted to occur when the prednisone dosage has been reduced to about 1 mg/kg body weight/day. Each of the four patients reported by Slopak *et alii* had had several rejection episodes, but this complication was not mentioned by Rifkind *et alii*.

The main clinical features include cough, fever and cyanosis. In general the lungs are clear on physical examination, but the chest X-ray shows diffuse, bilateral pulmonary infiltrates, mainly basal or hilar in distribution. Pulmonary function studies show there is a defect in gas transfer. Some cases have been reported in which abnormalities of blood gases are detectable before clinical or radiological evidence of lung disease (Slopak *et alii*, 1968).

Most of the patients have recovered, showing no residual pulmonary abnormalities. Autopsy findings on those who have died of lung disease have shown a thickened alveolar capillary membrane, fungal infection and cytomegalic inclusion bodies. One patient who recovered from the transplant lung, but later died of massive gastro-intestinal haemorrhage, had no such autopsy findings.

The aetiology of this condition is not known, but infective and immunological bases have been suggested.

The pathogenicity of the frequently found *Pneumocystis carinii* and cytomegalovirus is disputed. These agents may be detected in the lungs of many immunosuppressed patients in whom there is no evidence of pulmonary disease (Kanich and Craighead, 1966). In other patients where they have been thought to be the cause of pneumonia, the clinical features and blood gas studies differ from those of patients with transplant lung (Gajdusek, 1957; Berven, 1962).

The response of patients with transplant lung to an increased dosage of steroids tends to suggest a non-infective cause for the disease, and patients with *P. carinii* pneumonia in other clinical situations do not usually improve with

steroids (Gajdusek, 1957; Sheldon, 1959; Berdnikoff, 1959).

This response to steroids has been put forward as evidence for an immunological aetiology (Slopak *et alii*, 1968). Other factors favouring an immune basis are the antigenic similarity between the alveolar membrane of the lung and the glomerular capillary membrane (Goodman *et alii*, 1955), and the demonstration, in two patients dying of rejection with lung complications, of antibody adherent to the alveolar wall in one, and the bronchial epithelium in the other (G. M. Williams and D. M. Hume, quoted by Slopak *et alii*, 1968).

Rifkind *et alii* (1964) have suggested that with higher doses of steroids the signs of infection are masked, and that, as the dose is reduced, the infection may become apparent. Another alternative is that a lower dose of steroids may precipitate an immune response to the transplanted kidney, and the lung is involved in a nonspecific way. This insult then renders it more liable to infection.

The hypothesis of Slopak *et alii* (1968) is somewhat similar: immunological damage causes a thickened alveolar wall with impaired oxygen diffusion. Steroids will suppress this reaction. Organisms are favoured by the local conditions, and by the patient's general state of immunosuppression.

Factors which may help combat infection are the administration of oxygen, use of specific antifungal therapy such as amphotericin and pentamidine, and decreasing the dosage of azathioprine. Steroids will tend to suppress an antigen-antibody reaction, but could decrease resistance to infection.

Features suggestive of transplant lung in the patient presented here are: (i) onset in the third month post-transplant; (ii) dosage of prednisone reduced to about 1 mg/kg/day; (iii) symptoms of cough, fever and dyspnoea with relatively clear lungs on physical examination; (iv) chest X-ray showing bilateral basal infiltrates; (v) evidence of a pulmonary gas-transfer defect; (vi) lack of response to antibiotics, and initial (but transient) improvement with increased steroids; (vii) onset of rejection as steroids decreased.

CHAIRMAN: Dr Emmerson assisted in the management of this patient, and a comment from him would be appreciated.

DR B. T. EMMERSON: Clinically, he fitted the syndrome of alveolar-capillary block described as "transplant lung", but this did not advance us very far in knowing what to do. Practically, it seems that such patients fall into two groups, those who survive on an increased dose of prednisone and those who die of the condition. Those who die are usually found at autopsy to have a pulmonary infection. Those who survive on the increased dose of prednisone are regarded as having an immunological reaction against lung tissue which subsides because of the prednisone therapy. I am not convinced, however, that such a response to treatment necessarily differentiates these groups—it may be that the survivors were those who could come to terms with their pulmonary infection.

DR M. D. INNIS: During this period of time, we examined the patient's blood for anti-kidney, anti-lung and anti-leucocyte antibodies, but none were detected by our methods. However, this does not exclude an immunological reaction causing lung disease.

CHAIRMAN: Dr Rao, could you inform us of the various bacteriological tests you performed.

DR A. RAO: Numerous microbial cultures, mainly for bacteria and fungi, were carried out during the patient's association with this hospital. Apart from isolated occasions of relatively superficial infections in association with or in proximity to the arterio-venous shunt, no consistent pathogen from any particular site was cultured.

Approximately ten days previous to the patient's death, two out of three blood cultures grew *Staph. albus*. As this is not an obligatory pathogen, the pathogenic role of this isolate is usually considered together with the clinical state of the patient. In an immunosuppressed patient, this isolate was considered to be a potential pathogen.

A battery of serological tests were carried out during this period as a screening procedure, and a high titre to *Salmonella paratyphi* B H antigen was obtained. It was positive at 1:128, and at post-mortem two weeks later the titre had risen to greater than 1:2,048. There would appear to be no direct bacteriological interpretation of this finding, as the antibodies to *S. paratyphi* B O antigen remained totally undetectable on both occasions, and no *Salmonella* species were isolated from the faeces during life or from any other tissues at post-mortem. In the absence of a definite explanation, it is possible that non-specific stimuli may have induced this unique antibody rise in this patient,

and that this could be an example of non-specific stimulation of an antibody response in an immunosuppressed patient.

CHAIRMAN: At this stage it may be best to return to the people in charge of his management and find out their final views.

DR MORGAN: I believe I can most satisfactorily give my views by quoting some figures to indicate the results of transplantation. A large number of people die in the first year, but more particularly in the first three months after transplantation (Table 3). The following list indicates the percentage incidence of causes of death in these patients (Australian figures), and the most common organ infected is lung:

Infection:	
Bacterial	35%
Viral	4%
Fungal	7%
Transplant lung syndrome	4%
Rejection	9%
Myocardial infarct	6%
Cerebrovascular accident	6%
Miscellaneous	29%

These infections may be bacterial, viral or fungal, and frequently there are several organisms present. The combined effect of immunosuppressive drugs, debilitating disease and destruction of normal bacterial flora with antibiotics allows organisms usually non-invasive and harmless to become serious pathogens.

TABLE 3
Percentage of Patients Alive After Renal Allograft¹

Period	World Figures	Australian Figures	Princess Alexandra Hospital
3 months ..	69	70	80
6 months ..	57	61	80
9 months ..	53	—	—
1 year ..	52	57	75
2 years ..	40	50	—

¹ Figures obtained from the eighth report of the Human Kidney Transplant Registry and the Australian Dialysis and Renal Transplant Survey.

DR G. J. A. CLUNIE: Other speakers have illustrated the difficulty we found in the diagnosis and treatment of this patient suffering from a defect in gas transfer, which is a relatively common non-renal cause of death in recipients of kidney allografts. We must accept the published reports of other groups who have found clinical response to increase in steroid dosage, although the evidence for the immunological nature of this process is equivocal. However, the experience with the syndrome of transplant lung in Australasia suggests that, in the majority of such cases, a major factor has been infection with *P. carinii*. Other organisms such as *Nocardia* or *Aspergillus* undoubtedly contribute to, and may even cause, the syndrome without *Pneumocystis* infection. Confirmation of the infective nature of the process is given in the report from Denver that several cases of transplant lung occurred in patients treated in one hospital, but not in another some half a mile distant (Rifkind *et alii*, 1964). The Auckland group, who have had 14 patients with one or other form of the syndrome, have seen no cases since moving the site of their unit (P. Doak, personal communication).

Our experience, and that of others in Australasia, suggests that we should be more aggressive in reaching a definite diagnosis, even though this will usually require lung biopsy, a procedure not without risk in such heavily immunosuppressed patients. The alternative of empirical treatment adopted in this case proved unsuccessful. The large number of deaths in renal transplant recipients suffering from transplant lung compares badly with reports of the successful outcome of the more active diagnosis and treatment of *P. carinii* pneumonia in patients suffering from neoplastic diseases (De Vita *et alii*, 1969; Goodell *et alii*, 1970). If we follow this approach in future, we may then be able to avoid unnecessary deaths from one of the potentially treatable non-renal causes in our own patients, and thus improve the already reasonably satisfactory results of cadaveric renal transplantation.

CHAIRMAN: Dr Little will now present the autopsy findings.

Autopsy Findings

DR J. H. LITTLE: At autopsy, external examination revealed herpetic facial lesions and scars on the left forearm and left

iliac fossa at the sites of the haemodialysis shunt and the kidney transplant. Extensive haematomas were present in the right groin and both cubital fossae.

The patient's kidneys were markedly reduced in size, but the atrophic and fibrotic changes were so marked that it is not possible to indicate the cause of the kidney damage.

The donor kidney was swollen, weighing 190 gm and measuring 12.5 cm long. The capsule stripped easily, to reveal a haemorrhagic mottled surface which was also evident on the cut face of the swollen cortex. At the upper pole there was a healed linear scar, the site of the post-transplant rupture. Histologically there was marked interstitial oedema. The glomeruli showed only a slight increase in cellularity, but the basement membrane region showed increased width and an indistinct appearance. Red cells and eosinophilic material were present in the glomerular spaces and also in numerous tubules. The tubules show degenerative changes varying from hydropic change to shedding of tubule cells into the tubule lumen. A sparse inflammatory infiltrate of plasma cells and mononuclear cells was present in the interstitial tissue. Examination of the arcuate and interlobular arteries showed separation of their muscle bundles by oedema, but no fibrinoid change was evident, and stains for fibrin were negative. Although some histological features are missing, and other factors such as previous irradiation and hypoxia may have influenced the microscopic picture, it is considered that the kidney's changes are mainly due to rejection.

Both lungs were heavy; the right weighed 895 gm and the left 850 gm. The lungs were firm, but not hard, and when cut were reddish in colour. A number of segmental bronchi were plugged by grey, non-purulent mucus. Histological examination of the bronchi showed varying degrees of ulceration of the mucosa, with necrosis of the bronchial wall extending down to the muscle coats. Their lumens were blocked by excessive mucus, and in the mucus and necrotic bronchial wall mycelial hyphae and conidophores could be found which on culture proved to be *Aspergillus niger* and a *Candida* species (Figure 1¹). The alveoli showed areas of collapse and over-distension, suggesting obstructive and ball-valve effects of the bronchial mucus. In addition, the alveoli contained eosinophilic material, varying in staining from thin to dense eosinophilic material. In distended alveoli the material was flattened against the alveolar walls, resembling hyaline membranes. In the eosinophilic material numerous clumps of *P. carinii* can be seen, even in the haematoxylin and eosin stains. These were further identified by the use of special stains and by imprints of the unfixed lung tissue (Figure 2). Cytomegalovirus infection was also present, but was relatively sparse (Figure 3). The large intranuclear inclusions appeared to be in swollen pneumocytes which were shed into the alveoli. Negative features were the lack of any cellular infiltrate in the alveolar walls, and the absence of any thrombi or stainable fibrin in the vessels.

There were degenerative changes in the central nervous system, with drop-out of cerebellar Purkinje cells, probably due to hypoxia. In the duodenum, a peptic ulcer extended down to, but did not penetrate, the muscle coat. There was little evidence of inflammatory reaction or fibrosis in the base of the ulcer, and no evidence of a recent bleed. The adrenal cortices were atrophic. There were no germinal centres in spleen and lymph nodes, but numerous lymphocytes were present. The bone marrow was hypocellular. The bone was osteoporotic, and there was some atrophy of voluntary muscle fibres. The heart showed concentric left ventricular enlargement and weighed 500 gm.

A number of post-mortem cultures were carried out.

DR RAO: Post-mortem cultures for bacteria, fungi and viruses were carried out from numerous sites. The transplant kidney tissue cultured no significant growth of pathogenic bacteria, and no fungi or viruses were isolated. Though no virus was isolated from the lung tissue, a moderate growth of *Klebsiella pneumoniae*, a potential pathogen of the respiratory tract, was cultured from the bronchus and the peritoneum.

Culture for fungi yielded *Candida* species from both the bronchus and the lung tissue. In addition, *A. niger* was cultured from the bronchus. *Candida* and *Aspergillus* species are considered as fungi having low virulence, and the host resistance must be severely impaired before these fungi can proliferate sufficiently to produce a clinically manifest disease.

In a patient treated with cytotoxic agents, steroids and antibiotics, it is probable that these opportunistic fungi

¹ For figures, see art-paper supplement.

could have contributed in some degree to the already debilitated state of the respiratory tract, where the presence of *P. carinii*—another opportunistic invader—had caused obvious pulmonary damage.

DIAGNOSIS

DR LITTLE: The final post-mortem diagnosis was:

1. Infections (subsequent to immunosuppression): (a) *P. carinii* infection of lungs; (b) cytomegalovirus infection of lungs; (c) *A. niger* infection of segmental bronchi; (d) *Candida* infection of bronchi and lungs; (e) facial herpes simplex.

2. Changes subsequent to immunosuppression (or stress): (a) duodenal ulceration; (b) adrenal cortical atrophy.

3. Rejection of renal allograft.

4. Changes due to previous disease: (a) bilateral atrophic kidneys; (b) cardiac hypertrophy; (c) osteoporosis; (d) parathyroid hyperplasia.

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Medical Practice

DIETARY ALLOWANCES FOR USE IN AUSTRALIA (1970 REVISION)

At the Seventy-first Session of the National Health and Medical Research Council held in Canberra in October, 1970, the Council adopted a revision of the Dietary Allowances for Australia (1965 Revision), prepared by its Nutrition Committee. The title has been altered to "Dietary Allowances for Use in Australia (1970 Revision)". The complete 1970 Revision is to be printed in booklet form, and should be available about mid 1971.¹ An abridged version has been prepared, and is as follows:

DIETARY ALLOWANCES FOR AUSTRALIANS (1970 REVISION — ABRIDGED)

Purposes and Intended Uses

The Tables of Dietary Allowances for Australians are intended as a guide for compiling diets from foodstuffs. When a diet is designed to contain the nutrients listed, it is likely to contain all other dietary factors necessary for health but which have not been listed, such as the bulk factor, pantothenic acid, folacin, vitamin E, magnesium, etc.

The understanding of the many aspects of good nutrition is by no means complete, but it is known that fundamental defects in the overall pattern of a diet cannot be corrected with a few vitamin/mineral supplements. A balanced diet providing an adequate amount of each essential nutrient from foodstuffs should be planned for optimal nutritional health.

Specific Uses of Dietary Allowances

A dietary allowance may be used:

(i) As a guide to planning menus for individuals and groups.

¹ Copies can be obtained free of charge from: The Secretary, National Health and Medical Research Council, P.O. Box 100, Curtin, A.C.T., 2605.

(ii) As a guide to planning therapeutic diets. Although the tables are designed for normal, healthy people, they can help in planning diets for specific therapeutic purposes.

(iii) For a first assessment of the adequacy of the diet of a group or individual. Its use in this respect is limited, because of the wide "margin of safety" incorporated in values allowed for some nutrients, variations in the needs of individuals, and the need to consider sociological factors.

Reference Man and Woman

Man

The reference man is 25 years of age. He is healthy—that is, he is free from disease and exhibits a "normal" degree of physical fitness. He weighs 71 kg (154 lb) and lives in the warm temperate zone at a mean external annual temperature of 18°C (64°F).¹ He consumes an adequate well balanced diet; he neither gains nor loses weight. His activity is exemplified by the following average weekly schedule. On each working day, 8 hours of the physical work of the type referred to below; 4 hours of "sedentary" activity; walking slowly on the level for 2 hours and at least 2 hours out of doors; on each non-working day, the active pursuit of exercise and sport not of the extremely strenuous variety. The degree of activity involved in occupation in light industry or general laboratory work would represent approximately his working activity.

¹ Computed from mean annual temperatures of capital cities of all Australian States based on the mean of the daily maximum and minimum.