Transplant Lung—a New Syndrome

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[WITH SPECIAL PLATE BETWEEN PAGES 82 AND 83]

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"Transplant lung," a condition seen after homotransplantation, has only recently emerged as a recognizable syndrome (Rifkind *et al.*, 1964; Hamburger *et al.*, 1964, 1965). The episodes often follow a rejection crisis or a reduction in the dosage of prednisone. Clinically it is characterized by fever, at the onset of which the patient may feel surprisingly well. The commonest radiographic appearance consists in diffuse bilateral pulmonary infiltrates mainly at the base or the hilum. The main dysfunction in lung physiology is alveolar capillary block, while at necropsy a thickened alveolar membrane, fungal infection, and the presence of cytomegalic inclusion bodies have been frequently observed features.

This communication describes two cases of renal homotransplants in which pulmonary function tests revealed an alveolar-capillary block at a time when there were no clinical symptoms or signs of chest disease, and the chest x-ray film was normal. One patient developed the full picture of transplant lung. Two other patients who had undergone renal homotransplantation showed the characteristic pattern of alveolar capillary block associated with classical diffuse bilateral pulmonary infiltrative changes. One of these patients is alive, the other died of a non-pulmonary cause.

By January 1967 104 non-twin transplants in 95 patients had been performed at the Medical College of Virginia. Thirty-two of these patients had a variety of lung complications—in 15 these were the primary cause of death or a major contributing factor, while 17 survived, including the four reported

below. The other lung complications in this series have recently been described (Madge *et al.*, 1965; Slapak *et al.*, 1967).

Case 1

A 34-year-old white man with nephrosclerosis underwent bilateral nephrectomy, splenectomy, and renal homotransplantation on 27 November 1964, his 42-year-old brother being the donor. On the 74th postoperative day he became febrile, 22 days after his second rejection crisis (see Charts 1 and 2). Renal function and pulmonary function were normal. On the 82nd postoperative day, despite normal renal function tests and normal clinical and radiological appearances of the lung, pulmonary function tests showed a significant hypoxaemia (P_{O_2} 51 mm./Hg, Hb O_2 87%),‡ hypocapnia, and alkalosis with a CO_2 diffusion rate of 6 ml./min./mm. Hg (steady state) suggesting a definite alveolar capillary block (Chart 2). Six days later, on the 88th day, the chest x-ray film showed diffuse bilateral infiltrates (Special Plate, Fig. 1). Though there were no positive sputum cultures, he was given Staphicillin (methicillin sodium) and the prednisone dosage was further reduced. Nevertheless his temperature continued to rise, becoming 103.2° F. (39.6° C.) on 2 March (95th post-transplant day), when a rejection crisis was diagnosed on the basis of a rise in blood-urea nitrogen (B.U.N.) and serum creatinine concentrations and a fall in creatinine clearance, ^{57}Co vitamin B_{12} clearance (Slapak and Hume, 1965; Slapak, *et al.*, 1965), and urine output. On that day another arterial gas study showed a marked worsening of his alveolar capillary block. He was dyspnoeic and ill with concomitant pulmonary and renal problems (Special Plate, Fig. 2). Sputum and tracheal cultures continued to be negative for pathogens. He had been deriving considerable benefit from positive-pressure breathing with 40% O_2 . At this point the prednisone dosage, which had been reduced to 10 mg. daily, was increased to 200 mg. daily with subjective benefit, lessening of dyspnoea, and slight clearing of the chest x-ray film.

Renal function recovered by the 101st day and pulmonary function tests showed steadily increasing improvement. Over the next six weeks he made gradual progress, his dyspnoea progressively diminishing. Chest x-ray films showed residual abnormalities until the 151st day and his arterial gases did not become normal until the 171st day, three months after the beginning of his pulmonary condition. During the next six weeks the prednisone dosage was gradually tapered until the 159th day, when he reached his present maintenance dose of 15 mg.

CHART 1.—Case 1. Time relation between the blood urea nitrogen, serum creatinine, temperature, creatinine and ^{57}Co vitamin B_{12} clearances, and immunosuppressive therapy over nine months. The rapidity of the recovery of renal function is in contrast to the slowness of pulmonary function recovery seen in Chart 2. (CXr=chest x-ray picture.)

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daily. His renal function has steadily improved and he has remained well over three years after transplantation. Both his renal and pulmonary functions have been normal on repeated testing (Charts 1 and 2; Special Plate, Fig. 3).

CHART 2.—Case 1. Relation between arterial oxygen tension, haemoglobin oxygen saturation, and prednisone dosage.

Case 2

A 29-year-old white man had a pretransplant diagnosis of Goodpasture's syndrome, having presented with a seven-month history of dyspnoea on exertion, haemoptysis, haematuria, and progressive renal failure. Bilateral nephrectomy and renal homotransplantation was performed on 2 June 1965, his 24-year-old sister being a donor. He had four rejection episodes during the next six weeks, but only the last of these was accompanied by fever. The rejections were seemingly successfully reversed and by the 77th day his B.U.N. was 17 mg./100 ml. and creatinine 1.3 mg./100 ml. He was afebrile and the chest x-ray film was clear. Arterial gas analysis on the day that his fourth rejection was diagnosed was found to be normal. On the 80th day his temperature went up to 100.2° F. (37.9° C), though no cause could be found for this on investigation. Repeated chest x-ray films were normal. On the 84th postoperative day he was asymptomatic with a normal chest x-ray picture, but there was appreciable microscopic haematuria (Special Plate, Fig. 4) and arterial gas analysis showed a mild hypoxaemia, hypocapnia, and alkalosis. Renal function tests showed no abnormalities. No treatment was given, the prednisone dosage being held at 40 mg. daily, and the fever spontaneously remitted after three days. His pulmonary function tests became normal. He has been perfectly well for 18 months since transplantation. No more haematuria has been noted and the chest x-ray picture has remained within normal limits.

Case 3

On 23 September 1964 this patient, a 32-year-old Chinese man with a past history of healed tuberculosis of the left upper lobe of the lung, underwent bilateral nephrectomy. Renal homotransplantation was carried out on 12 October, the patient receiving a cadaver kidney. Having previously had two treatment rejection episodes, he developed fever on the 62nd post-transplant day. There were occasional crepitations at both bases, but the chest x-ray film was clear. Colistin sulphate, streptomycin, and penicillin were given without benefit. On the 82nd post-transplant day his temperature rose to 106.2° F. (41.2° C), and on that day arterial gas analysis showed hypoxaemia and alkalosis. There was neither cough nor sputum, while an x-ray film of the chest on the following day showed some increase in perihilar markings (Special Plate, Fig. 5), and a few crepitations were heard intermittently at both bases.

Prednisone dosage was now raised to 200 mg. a day and his penicillin dosage was also increased from two to five million units daily. Fourteen hours later he was afebrile and felt subjectively better. His respiratory rate fell from 32 to 24. Two days later arterial gas analysis showed improvement of the early capillary block pattern. By the 87th post-transplant day he was much improved and his chest x-ray film was normal. Antibiotics were discontinued five days later (92nd post-transplant day) and corticosteroids were reduced to maintenance levels.

During the course of the next six months he had a further eight rejection episodes. None of these was accompanied by pyrexia, nor were there any other abnormalities on the chest x-ray film or on further tests of pulmonary function. On the 315th post-transplant day, while he was afebrile and asymptomatic, with a normal B.U.N. and serum creatinine, a routine chest x-ray film showed a left pleural effusion. Pleural biopsy showed chronic granulation tissue, sputum culture was negative for acid-fast bacilli, and culture of the pleural fluid showed it to be sterile. Pulmonary function tests showed a vital capacity of 62% of the predicted value, a P_{O_2} of 72 mm. Hg, an Hb O_2 saturation of 92%, PCO_2 of 36 mm. Hg, and pH 7.42. The packed cell volume was 49% and the CO_2 combining power 18 mEq. On exercise the haemoglobin oxygen saturation remained at 92% while the P_{O_2} fell to 80 mm. Hg. In view of the large amount of prednisone which the patient had already received, and the presence of peptic symptoms, no increase in prednisone dosage was instituted. It was felt that the findings represented the onset of a possibly progressive fibrotic condition similar to the one seen in systemic lupus erythematosus (Hendry and Patrick, 1962).

The patient remained asymptomatic for a further two months. On the 375th post-transplant day he had a massive haemorrhage from a duodenal ulcer, from which he ultimately died. Necropsy revealed hepatomegaly with intrahepatic focal necrosis, cardiomegaly, and acute pulmonary oedema. Pulmonary complications were not thought to be a major contributing factor in this patient's death.

Case 4

A 17-year-old youth received a kidney from his sister on 2 March 1964. After good renal function in the early postoperative stage, his temperature rose on the 31st post-transplant day. On the 42nd day an x-ray film showed pneumonia in the apical segment of the right upper lobe. By the 59th day (24 April) the process had become diffuse and miliary tuberculosis was considered (Special Plate, Fig. 6). Arterial gas analysis on 1 May showed an O_2 tension of 70 mm. Hg, a CO_2 tension of 31, and a pH of 7.52. Corticosteroid dosage was increased and the fever abated, the patient improving symptomatically. Repeated arterial gas studies eight months later were normal. Fig. 7 (Special Plate) shows his chest x-ray picture to be normal one year after his illness. Thirty-six months after his illness his chest x-ray picture and pulmonary tests were still normal. His renal function was excellent, the ^{51}Cr clearance being 106 ml./min. He has had three rejection crises, the average for live donor series being 2.01 (Slapak *et al.*, 1965).

Discussion

The clinical course in Case 1 illustrates the difficulty of sorting out the roles of infection and autoimmune mechanism in the pathogenesis of pulmonary dysfunction in a patient who has received a homotransplant. Nevertheless, the response of both the renal rejection and the pulmonary abnormality to increased prednisone dosage was very impressive, and subsequently the vital capacity was found to be within normal limits. Whatever process had caused the lung condition was clearly functionally reversible, as shown by the steady improvement of the arterial gas values over the next four months. The slowness of its reversal contrasted, however, with the speed of the reversal of the renal rejection. Though infection as the primary cause of the pulmonary condition cannot altogether be excluded, the response to corticosteroids was the opposite to that expected in infection. The failure to isolate pathogenic organisms from the sputum, despite marked lung involvement, is unusual, and though hypoxaemia with hypocapnia occurs with some of the

viral pneumonias (Austrain *et al.*, 1951) it is unusual in those due to bacteria or to fungi.

Like the first patient, Case 2 had a relatively long period of acute tubular necrosis and an uncommonly large number of rejections in the first six weeks, 2.01 being the average total for living donors in our series (Slapak *et al.*, 1965). His febrile episode, beginning on the 80th day, occurred at a time when his prednisone dosage was 40 mg. a day. The phenomenon of fever on gradual withdrawal of prednisone had been previously noted by us and by other observers (Hamburger *et al.*, 1965). It occurs most commonly when the 50–30 mg. dosage level is reached, after treatment of a rejection episode with doses of 200 to 400 mg. of prednisone daily. The fever may be accompanied by joint or bone pain, but is often asymptomatic. At times it is accompanied by diffuse bilateral infiltrates in the lung (Rifkind *et al.*, 1964). Our patient's vital capacity was 100% of the predicted value but his F.E.V.₁/V.C. was 78%, showing a mild degree of restriction. The oxygen tension fell from 79 to 76 mm. Hg on exercise and his haemoglobin oxygen saturation from 94 to 90%, the packed cell volume of 33% not being low enough to influence the quoted figures to a significant degree (Ryan and Hickam, 1965). These findings in the absence of any radiological abnormality are therefore of diagnostic significance. It is of great interest that at this time he had microscopic haematuria in the absence of pyuria. Whether this represents a recurrence of Goodpasture's syndrome, or whether it signifies a sharing by the transplanted kidney and the lung of the effects of an immunological onslaught by the host, is not clear.

Cases 3 and 4 differ from the preceding cases in that the abnormality in the arterial blood gases was found concomitantly with a central pneumonitis. In both patients the differential diagnoses considered were pulmonary tuberculosis, septic pneumonia, and transplant lung. The radiological appearance was suggestive of pulmonary tuberculosis in Case 4. Both had negative findings on sputum culture and both recovered without specific antituberculosis chemotherapy. A septic process was made less likely by the lack of change in either the type or number of bacterial organisms on repeated sputum cultures, by the negative blood cultures, and by the unconvincing response to penicillin and colistin. In Case 4 the response to prednisone was equally brisk and antibiotics were not given. Both patients demonstrate the remarkable reversibility of transplant lung, which in Case 4 is apparently permanent.

Other Reports of Transplant Lung

Rifkind *et al.* (1964) described the cases of six renal homotransplant patients with diffuse symmetrical bilateral infiltrates and fever; five recovered and were alive and well at the time of the report. Pulmonary function studies performed on three of them showed marked arterial desaturation with a normal carbon dioxide content. The carbon monoxide diffusion capacity was low in the patient in whom it was measured. Five of the patients had oral candidiasis. The protozoan parasite *Pneumocystis carinii* and cytomegalic inclusion bodies were identified in the lungs of the patient who died. Hamburger *et al.* (1964) reported pulmonary infiltrations associated with fever and dyspnoea without apparent bacterial infection in three patients after transplantation. In one patient the illness was of short duration and disappeared rapidly during prednisone administration. The other two patients died, one of them after severe deterioration of the homotransplanted kidney. In this patient *P. carinii* was found in the lungs at necropsy. This group also reported the presence of a fever of unknown origin 27 times in 13 patients. This was initiated either by withdrawal of corticosteroids or by diminution of the dose. In a report by Hedley-Whyte and Craighead (1965) of 22 patients from the Peter Bent Hospital who came to necropsy, eight were found to have had cytomegalic virus inclusion bodies in the lungs.

In four of these patients the virus was recovered by tracheal washings and subsequently grown in tissue cultures. Arterial gas studies performed on one of these patients five days before death showed a Po_2 of 25 mm. Hg, and HbO_2 saturation of 54%, and a PCO_2 of 25 mm. Hg. X-ray examination showed bilateral mottling. S. Nakamoto and W. J. Kloff (personal communication), at the Cleveland Clinic, have had two renal homotransplant patients with diffuse bilateral pulmonary infiltrates and fever who recovered from their condition.

Thus out of a combined total of over 300 patients studied after renal transplantation, 15 have been reported to have survived a lung condition, which suggests a definite clinical entity. In nine of these single or repeated arterial gas studies are reported to have been made, all of which have shown the presence of a so-called alveolar capillary block. The distinctive feature of two of our patients is the presence of abnormal values of arterial gas, suggesting a generalized defect in alveolar diffusion preceding any other clinical and radiological abnormalities, and the correlation between radiological and functional aspects as determined by repeated arterial blood gases.

The observed relation to corticosteroid dosage is intriguing. The condition occurs in patients who (in our series), by virtue of having a high rejection index, receive a greater than average amount of corticosteroids. Conversely, it usually takes place when prednisone dosage is being reduced and, furthermore, specifically responds to sharp increase of the dose. Experimentally it has been shown by Berkheiser (1963) that marked alveolar proliferation with thickening of the wall can be produced in rabbits by daily injection of 12.5 g. of cortisone. Necropsy studies of 44 patients receiving high doses of corticosteroids showed 22 of them to have definite thickening of alveolar walls (Hendry and Patrick, 1962). Conversely, it was clearly demonstrated by McClement *et al.* (1953) that corticosteroids can have a specific effect on the alveolar capillary block syndrome, as well as on the histological improvement on lung biopsy, present in some patients with Boeck's sarcoid.

Significance of Pulmonary Function Tests

There is little specific about the alveolar capillary block syndrome, which Austrain *et al.* (1951) first used to describe a condition characterized by an alveolar respiratory insufficiency resulting from an impairment of adequate diffusion of respiratory gases across the thickened alveolar septa. Methods of measuring the separate components of the syndrome have been devised (Finley, 1961; Ball *et al.*, 1962; Ryan and Hickam, 1965).

Dickie and Rankin (1960) named 28 clinical disorders under this heading. Nevertheless, the syndrome is uncommon with either fungal or bacterial pneumonias (Berven, 1962) and its presence in lung conditions after transplantation has been sufficiently prominent to have been noted by several observers (Rifkind *et al.*, 1964; Hamburger *et al.*, 1965; Hedley-Whyte and Craighead, 1965). We have shown that the syndrome is present before any other detectable abnormalities, and this may be of future diagnostic and therapeutic importance.

Is Transplant Lung Due to Infection?

Over 30 adult renal homotransplant patients have died a terminal respiratory death in which cytomegalic viral inclusion bodies were found in the lung. Thus of 47 renal transplant patients whose lungs were specifically examined at necropsy for the presence of cytomegalovirus, inclusion bodies were found in eight. In five of these the virus was regarded as a coincidental finding, since death was due to other causes (Kanich and Craighead, 1966).

The evidence suggests (Rowe *et al.*, 1961; Levine *et al.*, 1964) that the presence of localized or even disseminated

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FIG. 1

FIG. 3

FIG. 2

FIG. 1.—Case 1. 88th post-transplant day. Diffuse bilateral infiltrates of early transplant lung.

FIG. 2.—Case 1. 95th–96th post-transplant day. Full-blown transplant lung. Homograft rejection diagnosed the following day. PO_2 35 mm. Hg.

FIG. 3.—Case 1. 185th post-transplant day. Patient fully recovered, with normal blood gases and renal function.

FIG. 4.—Case 2. 84th post-transplant day. Chest x-ray picture normal. PO_2 76 mm. Hg after exercise.

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FIG. 5.—Case 3. 82nd-83rd post-transplant day. Arterial desaturation with pulmonary infiltrates.

FIG. 6.—Case 4. 59th post-transplant day. Bilateral infiltrates with alveolar capillary block. This responded to corticosteroids.

FIG. 7.—Case 4. 419th post-transplant day. One year later the chest x-ray picture was normal. Normal renal function.

FIG. 1.—Intravenous pyelogram showing dilated calices in upper part of left kidney.

FIG. 2.—Selective renal arteriogram.

FIG. 3.—Artist's composite drawing to show relation of arteries and infundibulum.

FIG. 4.—Intravenous pyelogram 10 months after operation.

cytomegalic inclusion bodies is not irrefutable evidence that the virus plays some part in causing the patient's death. Local tissue factors may influence the appearance of the inclusion bodies in a particular organ (Levine *et al.*, 1964). Certainly this organism seems unlikely to have had an important place in the pathogenesis of the reversible disease in our four patients.

Fatal pulmonary complications due to fungi have been reported in most of the major renal homotransplant series (Hume *et al.*, 1963, 1965, 1966; Starzl *et al.*, 1963, 1964; Hamburger *et al.*, 1964; Ryan and Hickam, 1965; Huang *et al.*, 1965). *Candida albicans*, *C. stellatoidea*, *C. krusei*, *P. carinii*, *Nocardia asteroides*, *Mucor*, and *Histoplasma capsulatum* are among those found, *Candida* and *Pneumocystis* being by far the commonest. The part played by these organisms in the pathogenesis of transplant lung except as a terminal event is, however, doubtful. Pathogenic yeasts are commonly found in health and may be present in great abundance without contributing symptoms to pre-existing disease. While it is known that treatment with antibiotics and corticosteroids predisposes to candidiasis (Seelig, 1966), no beneficial effect has ever been recorded as a result of prednisone.

The role of *P. carinii* in transplant lung is also obscure. This protozoan parasite has been thought by European authors (Gajdusek, 1957) to cause interstitial plasma-cell pneumonia which occurs predominantly in immature or debilitated infants 6 weeks to 4 months old (Sheldon, 1959). Nevertheless, the parasite has been found in routine necropsy of the lung in man, and it occurs naturally in the lungs of animal species (Hendry and Patrick, 1962). The clinical manifestations of infection with *P. carinii* are unlike those of transplant lung (Gajdusek, 1957), and treatment with corticotrophin has not been effective in the cases reported (Gajdusek, 1957; Sheldon, 1959; Berdnikoff, 1959).

Is Transplant Lung an Immunological Phenomenon?

An immunological basis for transplant lung has been suggested (Rifkind *et al.*, 1964; Hamburger *et al.*, 1965). The host lung may share with the transplanted kidney an immunological attack directed against the latter similar to the auto-immune mechanism concerned in the lung manifestations of diffuse systemic sclerosis, disseminated lupus erythematosus, and rheumatoid arthritis. In these conditions, interference with a similar pattern of alveolar function produces an alveolar capillary block syndrome. The syndrome may be present before clinical or radiological manifestations in the lung (Huang *et al.*, 1965).

Against an immunological explanation is the rarity of transplant lung—about 15 reported cases—and our inability at present to reproduce the condition experimentally in the dog after renal transplantation. Nevertheless, long-term studies in the dog are notoriously difficult and, clinically, transplant lung has not been reported until 41 days after transplantation.

In favour of an immunological basis for transplant lung is the close antigenic similarity between alveolar membrane of lung and glomerular capillary membrane (Goodman *et al.*, 1955). Thus intravenous injection of anti-lung antibodies can cause experimental glomerulonephritis (Seegal *et al.*, 1955). Read (1958) showed that pathological changes in the lung of a rat could be produced by injection of a specific anti-lung serum intratracheally. These changes were distinct from spontaneous infective disease occurring in the rat. Hager *et al.* (1964) found that during rejection of a renal homograft immunoprotein antibody was found adherent not only to the homograft kidney but also on the host's own kidney—so-called immunological suicide. G. M. Williams and D. M. Hume (personal communication) have demonstrated immunoprotein adherent to the alveolar wall in one patient and the bronchial

epithelium in another. Both these patients have died of rejection with lung complications.

The response to corticosteroids is a specific feature of transplant lung and one of the differentiating features between this condition and an infective process.

Tentative Hypothesis

In the evolution of transplant lung we envisage immunologically induced damage causing a thickening of the alveolar wall and consequent decrease in oxygen diffusion. In fortunate patients (such as Cases 1, 2, and 4) early treatment with corticosteroids suppresses and contains the reaction as it does renal homotransplant rejection. The lung then recovers over weeks or months.

In those patients in whom an antibiotic-resistant bacterial or fungal organism is present the local conditions together with the decreased resistance due to immunosuppressive therapy enable it to multiply rapidly and enhance its virulence. Virus elements, owing to the same cause, also emerge and proliferate, and by virtue of their identifiable inclusion bodies become visible.

In some cases, even at this stage, treatment with oxygen may make local conditions less favourable for the organism and increase general metabolic efficiency. Specific antifungal preparations like amphotericin or pentamidine isethionate (Robbins *et al.*, 1965) or measures aimed at increasing host resistance such as a decrease of Imuran (azathioprine) dosage may tip the balance in the patient's favour. Corticosteroids are a double-edged weapon, known to be invaluable in damping the effect of antibody-antigen reaction but dangerous in their effect of decreasing resistance to infection. In those patients who succumb the unfavourable local conditions and the low resistance tip the balance in favour of the organism, and widespread terminal dissemination of normally contained organism takes place with death.

Earlier methods of diagnosis of the basic immune phenomenon by the use of pulmonary function tests are described; and methods to demonstrate any secondary viral or fungal invader, such as serological tests (Kanich and Craighead, 1966), might be of great importance. Clearly, the most effective measures are those designed to suppress the immune mechanism concerned and to combat hypoxia as well as specific therapy aimed at the secondary invaders.

Summary

Four patients are documented who developed a new recognizable syndrome—transplant lung—after renal homotransplantation. The syndrome is described and the evidence for its causation on an autoimmune basis summarized. This includes a specific response to corticosteroids and a close temporal relation to renal rejection in some instances. All four patients recovered from their lung condition, though one died later of another cause.

The fact is stressed that in two of the patients the diagnosis was made on a characteristic pulmonary function abnormality which was detected by arterial gas studies before there were any clinical or radiological manifestations. Earlier diagnosis by means of serial pulmonary function tests, and treatment aimed at the postulated underlying immune mechanisms, are suggested.

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Simultaneous ^{51}Cr Edetic Acid, Inulin, and Endogenous Creatinine Clearances in 20 Patients with Renal Disease

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The estimation of endogenous creatinine clearance is the method most widely used to measure the glomerular filtration rate. Unfortunately, in many patients with renal disease this method gives unreliable results, as has been noted by Berlyne *et al.* (1964) in patients with the nephrotic syndrome and by Miller *et al.* (1952) in patients with impaired renal function. The laboriousness of the chemical estimation of inulin inhibits the use of inulin clearance for routine clinical work. For this reason various workers have looked for an alternative method (*Brit. med. J.*, 1967). Nelp *et al.* (1964) reported that ^{57}Co -cyanocobalamin clearance showed good correlation with inulin clearance in man, but Breckenridge and Metcalfe-Gibson (1965) pointed out that it was necessary to give a large dose of the unlabelled vitamin in order to saturate the binding sites of the plasma proteins. Despite adopting this technique, other workers encountered inaccuracies due to protein binding (Foley *et al.*, 1966). In practice it is necessary to estimate the degree of protein binding of the labelled vitamin B_{12} during the mid-point of each clearance period (*Brit. med. J.*, 1967).

Downes and McDonald (1964) described the preparation of ^{51}Cr complexed with edetic acid, and Stacy and Thorburn (1966) compared the renal clearance of this substance with that of inulin in sheep. They found a ratio ^{51}Cr edetic acid clearance to inulin clearance of 0.95. Garnett *et al.* (1967) studied patients with a wide range of clearances and found a correlation coefficient between ^{51}Cr edetic acid clearance and inulin clearance of 0.995. These authors have not reported simultaneous creatinine clearances on their patients.

This paper describes experiments in dogs in which the clearance of ^{51}Cr edetic acid was compared with the simultaneous clearance of inulin over a wide range of plasma concentrations of Cr edetic acid. In addition, simultaneous

^{51}Cr edetic acid, inulin, and endogenous creatinine clearances were studied in 20 patients with renal disease. The group studied includes many subjects in whom the ratio creatinine clearance to inulin clearance was high.

Material and Method

Dog Experiments.—Six dogs weighing from 8 to 25 kg. anaesthetized with pentobarbitone sodium (20 mg./kg.) were used. A bladder catheter was inserted and 0.9% saline infused to establish a high urine flow. Arterial blood samples were collected by a catheter in the femoral artery. Each dog received a loading dose of ^{51}Cr edetic acid (20 μCi) and of inulin (60 mg./kg.). A solution containing ^{51}Cr edetic acid and inulin diluted in saline (0.9%) was then given at a rate of 0.5 ml./min. After 30 minutes for equilibration urine was collected for two clearance periods of 10 minutes. In order to increase the plasma level of Cr edetic acid, a further loading dose of 20 ml. of a second solution containing a higher concentration of ^{51}Cr edetic acid but the same concentration of inulin was then given quickly, and after a further equilibration period with this more concentrated solution two further clearance periods were carried out. Each dog underwent two to four stepwise increments in this way. In order to get a high edetic acid blood level without an excessive increase in radioactivity, ^{51}Cr edetic acid (approximately 300 μCi) was mixed with a concentrated unlabelled Cr edetic acid solution. Thus blood levels of Cr edetic acid from 0.02 up to 2.9 mg./100 ml. were obtained.

Studies in Patients.—Twenty patients were studied. The diagnosis of each of these patients is given in the Table. In each patient simultaneous ^{51}Cr edetic acid, inulin, and endogenous creatinine clearances were estimated. A priming dose of 40 μCi of ^{51}Cr edetic acid and of 60 mg. of inulin per kg. was given, followed by the infusion of a solution containing 40 μCi of ^{51}Cr edetic acid and 6 g. of inulin diluted in 120 ml. of either 0.9% saline or 5% dextrose. The speed of the

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