donors, the significance of the association was much reduced. This he found perplexing, though perhaps insufficient sibships had been collected. Finally, he wondered whether genes always exerted their effect through enzyme action only—could the Hapsburg lip (apparently a dominant trait) be due to a single enzyme? Payr assumed the latter and postulated a strong inherited component—for example, bronchial asthma, with capriciousness as its main feature—were also difficult to explain. He wondered whether another Einstein could give us a new conception which would explain those partly inherited diseases where the mind–body relationship was one which would be difficult to comprehend on the theory of genes being solely responsible for enzymes.

Dr. Clarke and Dr. P. M. Sheppard showed an exhibit of butterflies and moths demonstrating basic genetic principles.

SYMPOSIUM ON RENAL DISEASE
ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH

The Royal College of Physicians of Edinburgh held a symposium on "Some Aspects of Renal Disease" in the Hall of the College on March 25. We report here a summary of the proceedings, which included Sydney Watson Smith lectures by Dr. J. S. Robson (Edinburgh) and Dr. J. P. Merrill (Boston, Mass.). Dr. J. D. S. Cameron, President of the College, presided.

Patterns of Renal Insufficiency
Dr. J. S. Robson took this as the subject for the first Sydney Watson Smith lecture. He pointed out that renal insufficiency was associated just as often with the loss of essential body constituents as with the retention of metabolites. Many discrete tubular syndromes were now recognized, but it was only recently that water-losing renal conditions had become susceptible to any systematization which took into account the hypothesis that implied that the kidney functioned as a single medullary organ with respect to water transport and related intrarenal water transport to the reabsorption of sodium in the loops of Henle and of urea in the collecting ducts. The effect of interfering with these two functions was illustrated by the concentration defects seen after mersalyl, in hyperparathyroidism, in potassium depletion, and in the newborn. In acute and chronic pyelonephritis which primarily affected the medulla, concentration was impaired as a result of tubular cell damage without nitrogen retention, whereas the polyuria of glomerulonephritis or hypertensive renal disease resulted from a urea diuresis and paralleled the reduction of filtration rate.

The evidence that renal ischaemia was the cause of tubular and cortical necrosis in acute renal failure was not entirely convincing. Recent studies of renal blood flow in these conditions, using radioactive krypton, gave values of 25–50% of normal, comparable to those found in severe congestive failure. However, estimates of renal blood flow made at the onset of acute renal failure were not available and there was much circumstantial evidence to support the ischaemic theory. The primary role of septicaemia with Gram-negative organisms in producing acute tubular necrosis had probably been underestimated, and in a series of sixty patients in Edinburgh there were fourteen in whom this seemed the most likely aetiological factor. Six of these were jaundiced. A coliform septicaemia might be the cause of many cases of the "hepato-renal syndrome," in which infection was the most important cause of mortality. The continued widespread use of prophylactic broad-spectrum antibiotics was contributing to this.

Other problems arising in these patients and in those with chronic renal failure were hyperkalaemia and acidosis. Dr. Robson described the mechanisms of these complications, and stated that the incidence of convulsions, cardiac irregularities, and death after dialysis was higher in severely acidic patients. Rapid restoration of serum bicarbonate levels led to extracellular alkalois due to continued hyperventilation. The stimulus for this hyperventilation was obscure, but, since bicarbonate ions did not penetrate cells rapidly, the intracellular acidbase deficit either persisted or fell. This pattern was certainly seen after dialysis in the cerebrospinal fluid, into which bicarbonate ions passed only slowly. The acidity was not relieved.

The speaker discussed the place of intermittent dialysis in chronic renal failure using an exterized tefon arteriovenous fistula.

Management of Renal Failure
Dr. J. S. Robson was the moderator in a panel discussion of renal failure and its management. The members of the panel were Dr. David Band (Edinburgh), Dr. F. M. Parsons (Leeds), and Dr. K. G. Lowe (Dundee). Dr. Lowe outlined the history of the artificial kidney in acute renal failure. In Great Britain, after the second world war, the emphasis had been on conservative treatment, for reasons which included the hazard of infection during haemodialysis and lack of antibiotics, apart from penicillin. The implied success of the Hammermillich conservative regime in many patients delayed the development of haemodialysis in the treatment of traumatic anuria, which still caused a high mortality. Now, however, there was an adequate national haemodialysis service. In the many units there was an aggressive attitude towards further reduction of mortality by earlier "prophylactic" dialysis in acute renal failure, and towards lengthening the expectation of life by repeated dialysis in selected patients with chronic renal failure.

Dr. Parsons described the principles of the artificial kidney, emphasizing that haemodialysis was now virtually free from complications. Renal disease requiring this treatment fell into three categories: acute reversible renal failure (tubercle necrosis); acute glomerular disease; and chronic renal failure. In the second category, investigation, including renal biopsy, was often required to determine whether the disease was reversible or irreversible. The third category was subdivided into surgical and medical cases. In the surgical, dialysis might be required prior to operative relief of post-renal obstruction or to prepare a patient with chronic renal failure for operation on a lesion outside the urinary tract. In the medical group the place of dialysis was less clear: perhaps the main indications were very slow deterioration of renal function and sudden deterioration due to infection or gastro-intestinal disease. Dr. Parsons subdivided his patients in whom dialysis for acute reversible renal failure, including acute glomerular disease, was indicated into mild cases (B.U.N. rising at less than 30 mg./100 ml. per day) and severe (B.U.N. rising at more than 30 mg./100 ml. per day). The mild group required dialysis only when clinical deterioration occurred—this was usually associated with a B.U.N. of 180–200 mg./100 ml. The severe group required dialysis even in the absence of clinical deterioration when the B.U.N. reached 120–150 mg./100 ml. With smaller machines than his at Leeds, the critical level of B.U.N. might be 100–110 mg./100 ml.

Dr. J. P. Merrill (Boston, Mass.), in the discussion, said it was essential for an artificial-kidney team to be skilled in conservative methods of treatment. Of 900 patients with acute renal failure admitted to his unit, 500 had been treated conservatively. He approved of earlier prophylactic dialysis, which had the important advantage of increasing the patient's resistance to infection.

Dr. A. C. Kennedy (Glasgow) described a patient who had died apparently without cause after successful dialysis, and the panel agreed that, with the bigger machines especially, there was a risk of too efficient dialysis being fatal owing to sudden biochemical changes.

Mr. Band, Dr. Parsons, and Mr. Arthur Jacobs (Glasgow) discussed the problem of prostatic obstruction...
with long-standing chronic uremia. Catheterization was often effective, but dialysis rapidly improved the general condition and led to earlier prostatectomy; the risk of infection was diminished. Mr. Band warned against too early operation when the bladder was atomic. Dr. Robson introduced the mechanism of anuria and the subsequent diuretic phase in acute renal failure. Was anuria the result of acidosis causing vasocostriction? Dr. Merrill thought that, despite a relatively normal renal blood flow, there was patchy ischaemia resulting in interstitial oedema which compressed the tubules; the diuretic phase began when the intratubular pressure overcame the increased intra-tubular pressure.

Nephrotic Syndrome

Dr. Mary K. Macdonald (Edinburgh) spoke on the microscopy of the kidney. She presented the renal biopsy findings in 34 adult cases of proteinuria in which there was no clinically recognizable cause. On light microscopy a high incidence (6 cases) of normal glomerular histology was found; in each instance electron microscopy revealed abnormalities in the glomerulus consisting of patchy slight thickening of the capillary basement membrane and "swelling" of the foot-processes of the epithelial cells. These were beautifully illustrated by electron micrographs. In 8 cases features of membranous glomerulonephritis were found on light microscopy, and it was possible on electron microscopy to divide this group into two distinct types. In the first the changes in the basement membrane and epithelial cells were similar to those observed in the group with normal histology and differed only in severity. In the second there was gross irregularity in both the thickness and the structure of the basement membrane, and the surface projections of this membrane frequently interdigitated with smeared epithelium. In one case of postural proteinuria electron microscopy revealed very slight patchy thickening of the basement membrane and some of the epithelial-cell foot-processes were abnormally thick and rounded. The effect of steroid therapy was illustrated in a case with normal glomerular histology where clinical cure was associated with the resolution of the abnormalities in the fine structure of the glomerulus. A similar result was obtained in a patient with early membranous glomerulonephritis, but it was followed by relapse when steroids were withdrawn. The resumption of steroid therapy was again associated with clinical cure and the disappearance of the basement membrane and epithelial cell abnormalities.

Dr. G. C. Arneil (Glasgow) discussed steroid therapy of the nephrotic syndrome in childhood. His data, collected over a period of 28 years, showed a marked improvement in prognosis after the introduction of steroid therapy. This could not be attributed to the advances made in the treatment of infection. He had found prednisolone the most satisfactory steroid and he recommended large doses initially. Side-effects of treatment included Cushingoid features and arrested body growth. Additional measures in treatment were a low-sodium, isocaloric diet, chlorothiazide in steroid-resistant cases, and antibiotics when infection occurred. In successful steroid therapy the diuresis occurred before an increase in the serum albumin level could be detected, and it had been found that the onset of the diuresis and the red cell in proteinuria occurred simultaneously. A diuresis induced by chlorothiazide was not associated with a decrease in proteinuria.

Dr. E. Lovell Becker (New York) briefly reviewed immune mechanisms in the nephrotic syndrome. Renal biopsy material from patients with membranous glomerulonephritis, demonstrated by fluorescein microscopy, showed the deposition of gamma-globulin in proteinuria occurred simultaneously. A diuresis induced by chlorothiazide was not associated with a decrease in proteinuria.

Renal Transplantation

Dr. J. P. Merrill gave the second Sydney Watson Smith lecture, on the subject of renal transplantation. He first discussed some general problems of tissue grafting. A piece of skin grafted from person A on to person B began to be rejected after 6 days. Antigens from the graft reached the regional lymph nodes and the sensitized lymphocytes assumed destructive properties. A second skin graft was rejected even more rapidly (accelerated reaction). The accelerated reaction was not organ-specific—an important point, since a kidney would be rejected more rapidly as a result of previous skin grafting. In an animal made hypersensitive by foot-grafts, the last rejected graft showed remarkably little histological change (white graft reaction). Instead there was perivascular cellular infiltration and thrombosis of the host's blood-vessels near the graft, leading to ischaemic rejection. This suggested that at least part of the local rejection mechanism took place in the host tissues.

Dr. Merrill then turned to the more specific problem of renal transplantation. In the dog a transplanted kidney ceased to function after 5 days. The most significant histological change in the rejected kidney was infiltration with round cells. The position in humans was different and a little more favourable. In chronically uremic humans rejection was slower and the cellular infiltration was polymorph in nature. The difference was, no doubt, partly a matter of species, but the retarding influence of chronic uremia was also important. Dr. Merrill related his own experience of 23 human transplants (not in identical twins). In 3 the transplanted kidney survived long enough to show some abnormalities. In one instance caused by a series of skin grafts, the last rejected graft showed remarkably little histological change (white graft reaction). Instead there was perivascular cellular infiltration and thrombosis of the host's blood-vessels near the graft, leading to ischaemic rejection. This added to the importance of the local rejection mechanism took place in the host tissues.

Dr. Merrill then discussed the problem of attempting to produce immunological tolerance in a person who had no identical twin. One method was to destroy some of the patient's white blood cells by x-irradiation followed by marrow transfusion. Unfortunately in the human transplused marrow failed to survive for more than a few months, and, in addition, being immunologically competent, produced a graft-versus-host reaction, which might be fatal. It was possible, however, to limit x-irradiation to make the haemopoietic system "sick" and hence, in a sense, immunologically immature. Further
limited x-irradiation could be given at intervals after transplantation, possibly combined with steroid therapy. Radiomimetic agents, such as 6-mercaptopurine, could be used instead of or as a supplement to x-irradiation. Dr. Merrill pointed out that the place of these potentially dangerous procedures was not yet clearly defined and he did not want to paint a rosy picture.

In looking to the future of renal transplantation, Dr. Merrill emphasized that, immunologically, the kidney was a relatively favoured organ. It did not produce a graft-versus-host immunity. Furthermore, renal transplantation was equivalent to giving a large dose of antigen intravenously—a method known to facilitate the establishment of tolerance experimentally. Possible developments lay in new techniques of "matching" tissues, selective injury to lymphopoietic tissue without destruction of bone marrow, and use of anti-serotonin agents to prevent vascular rejection mechanisms.

Discussion on Renal Transplantation

After his lecture Dr. J. P. Merrill was the moderator of a panel discussion on renal transplantation, in which the members of the panel were Dr. J. R. Anderson (Glasgow), Professor R. McWhirter (Edinburgh), Professor M. F. A. Woodruff (Edinburgh), and Dr. J. S. Robson (Edinburgh).

Dr. Anderson referred to the basic problems in immunology fundamental to renal transplantation. The immune response could be suppressed by modifying (a) the graft, or (b) the host. In the case of the kidney, the closer the donor and recipient were genetically, the weaker would be the immune response. In closely related pairs the number of antigens capable of producing immune response was very small, and in similar twins, antigenically alike, the immune response was absent. The graft, therefore, took successfully.

Methods of producing tolerance were (1) conditioning the foetus, too immature to show immune response, by a graft (a suspension of cells). When the foetus grew to maturity it would have developed specific tolerance to the donor of the original graft, and could accept further grafts successfully. (2) In the adult the immune reaction could be suppressed by irradiation, as had been shown by Merrill and his colleagues, and also by Kus in Paris. When whole-body irradiation had been given it was possible that the graft itself might then react against the host. Dr. Anderson concluded by referring to the possibility that the foetus and the mother might develop mutual partial tolerance during gestation.

Dr. Merrill said that renal transplants between parents and children had been disappointing, but the possibility that infants with icterus neonatorum, who had received large transfusions, might develop tolerance to a specific blood donor should be explored. He referred to a renal homograft which had already survived for more than 18 months in a case of non-identical twins. Tolerance was produced by repeated small doses of whole-body irradiation, and he considered that this technique could perhaps be combined with the use of 6-mercaptopurine.

Professor Woodruff said that, in his experience, compatibility of blood groups was not a sufficient guarantee of success in homotransplantation. The homograft problem had been solved in the laboratory, where a high degree of tolerance to homotransplants could be induced in a mammal by the post-natal injection of donor cells. Nature occasionally produced this result in non-identical ( dizygotic) twins who, on account of admixture of their placental circulations, became erythrocyte chimeras. Such twin chimeras were tolerant of each other’s tissues and could interchange skin grafts.

Dr. Robson, referring to whole-body irradiation, said that a sublethal dose given to a patient to condition him to receive a graft was difficult to estimate. Under 400 r was perhaps the safest, and with supervoltage radiation the dose could be reduced. The risk of leukemia, which was real and was also present with radiomimetic agents, was well justified.

Dr. Robson then spoke of the problem of infection in cases of renal transplantation. He firmly believed that infection in the recipient should be treated when it arose, and not before. The policy of "no prophylactic antibiotics" should be emphatically imposed. Dr. Merrill agreed with that, but prophylactic antibiotics should be given when infection existed in the recipient.

Professor Woodruff considered that the graft-recipient reaction could be limited by broad-spectrum antibiotics, and Dr. Merrill agreed that some of the effects of "secondary disease" could be due to infection. Professor Woodruff also stressed the point that micro-methods of blood analysis to minimize the quantity of blood taken from the patient were desirable. Dr. Merrill said that such methods were being developed successfully.

New Appliances

A SIMPLE CRUTCH

Mr. Denis Burkitt, specialist surgeon, Uganda Medical Services, writes: In underdeveloped countries many people are deprived of effective medical treatment owing to limited hospital accommodation. Yet patients with leg injuries are often retained longer than necessary for lack of a suitable crutch to render them ambulant.

Hospital authorities are naturally reluctant to issue elaborate adjustable crutches which might not be recovered, and the commonly used "T" model is useless for weight-bearing. Moreover, there are many sedentary cripples who, with a means of locomotion, might be converted into ambulant workers.

A search has been made for a crutch pattern combining effectiveness and comfort with simplicity and economy. The pattern illustrated appears to meet these requirements. The only materials required are: (1) iron rods as used by any building contractor (½ in. (1 cm.) diameter for adults, ¼ in. (0.6 cm.) diameter for children); (2) a broom handle; and (3) rubber tubing (that used for garden hose is very satisfactory); its life can be considerably lengthened by using a large piece of tubing which can be moved along the iron rod as the weight-bearing area becomes worn. The hand-grip is placed at one-third of the length of the crutch from the upper end.

A crutch can be shortened by cutting a piece from the ends of the iron rods, and the hand-grip can be raised by threading a short length of piping on to each limb before placing the hand-grip. The rubber tube, when worn, can...