Ellis, H.A. and Peart, Kathleen M.: Renal osteodystrophy with particular reference to the effects of chronic intermittent haemodialysis.

To define the nature of the bone changes associated with dialysis, bone obtained by iliac crest biopsy (50 samples) and at necropsy (63 cases) has been examined in 96 patients with chronic renal failure including 55 treated for periods of 1 month to 5 years by intermittent haemodialysis. The proportions of total bone, mineralised bone and osteoid were estimated in undecalcified sections of iliac crest using a point-counting technique. For comparison 75 control samples of iliac crest were obtained at necropsy. The severity of osteitis fibrosa in decalcified sections was graded on a scale 0 to 5.

Osteomalacia occurred in non-dialysed (54.5%) and dialysed (49.1%) subjects, became progressively more marked after prolonged periods of dialysis and was present in all cases after 2 years.

Total bone in individual non-dialysed patients was normal or elevated and in the group as a whole was significantly elevated. In the dialysed patients total bone was variably low, normal or high irrespective of the duration of dialysis.

The proportion of mineralised bone in the non-dialysed group was not significantly altered whereas in the dialysed group a characteristic feature was the significant and progressive reduction in mineralised bone as the period of dialysis increased.

Osteitis fibrosa was less conspicuous in the dialysed subjects, only 11% having grade 3 changes compared with 35% of non-dialysed patients with grade 3, 4 and 5 changes.

It is concluded the bone changes after prolonged haemodialysis differ quantitatively from those in chronic renal failure.

Progressive loss of mineralised bone, increase in osteoid and change in the character of osteitis fibrosa leads to the formation of cancellous traveculae with irregularly thinned mineralised central portions surrounded by osteoid and with relatively few sites of active osteoclasia and marrow fibrosis.


Chronic nephritis has been produced in young male rats weighing 150 g by repeated injection of anti-rat kidney rabbit serum. The natural history of the disorder has been studied by serial determinations of blood calcium and urea levels and histological examination of the bones at death or sacrifice of the animals. Metaphyseal changes have been produced in the animals which are identical to those described by Morrison [1962], namely, distortion of the cartilage, infiltration by osteoclasts and bone marrow, widened osteoid seams and general disorganisation of the bone spicules. The shafts of the bones showed the presence of osteitis fibrosa cystica.

These changes appear to be independent of the serum calcium, phosphorus and blood urea levels and in 2 animals out of 10 severe metaphyseal changes were present despite normal blood urea concentrations. The implications of these findings are discussed.
Brocklebank, T.: Peritoneal dialysis and the use of heparin in the management of haemolytic uraemic syndrome.

In the past 6 months 10 children with haemolytic uraemic syndrome have been treated at the RVI Newcastle and the West Cumberland Hospital, Whitehaven. Peritoneal dialysis was necessary for 7 children and 4 died. Clinical and epidemiological details are given and the place of peritoneal dialysis and the use of heparin in the management of this condition is discussed.

Wardle, E.N. and Wright, N.: The role of endotoxin in the production of acute renal failure in association with obstructive jaundice.

A single dose of endotoxin given to rats with obstructive jaundice produced death due to a Shwartzman reaction with intravascular coagulation and fibrin deposition in the renal vasculature. This effect was found to be due to delayed clearance of endotoxin from the circulation in the presence of obstructive jaundice. The finding is relevant to ‘hepato-renal failure’ which can be caused by bacter-aemia after biliary tract operations.

Glasgow, E.F. and White, R.H.R.: ‘Not so minimal’.

A recent review of renal biopsy specimens obtained from 145 children with an acquired nephrotic syndrome disclosed focal and segmental lesions, in which proliferation was absent or inconspicuous, in 12 instances [White et al., 1970]. We now describe the histological and clinical features in 17 cases.

The basic lesion consists of a localised increase of mesangial fibrillar material without cellular proliferation. When fully developed it is characterised by partly and completely sclerosed as well as normal glomeruli, accompanied by focal tubular atrophy and interstitial fibrosis. Electron microscopy confirms the mesangial appearance and in advanced cases reveals the deposition of collagen. The capillary basement membrane shows both thickening and thinning with occasional localised splitting, while ‘bridges’ of basement membrane cross some capillary lumens. We have designated the condition, briefly ‘focal glomerulosclerosis’. The differentiation of early lesions from ‘minimal changes’ may be very difficult.

13 patients were girls. The age of onset ranged from 2 months to 14½ years. 13 presented with a nephrotic syndrome, 2 had symptomless proteinuria and 2 had a mixed nephritic-nephrotic presentation. Haematuria was observed in 12 children, microscopically in 2, while 7 were hypertensive, 5 of them at onset. Proteinuria selectivity was impaired in 14 out of 16 cases, while serum C3 levels ranged from 99 to 187 mg/100 ml (normal), except in one child with a single reading of 64 mg/100 ml.

Only one child out of 15 responded to steroid therapy. Eleven were treated with cyclophosphamide and 4 with azathioprine, but none responded. Three children have died, one is on dialysis and 2 have early chronic renal failure. Ten patients have persistent proteinuria with or without episodes of oedema, leaving only one in remission. The rate of deterioration varies widely but the histological severity affords a rough guide to prognosis.

Reference

The effect of chlorpropamide in 7 patients with diabetes insipidus, 7 normal controls and one patient with acute renal failure in the polyuric phase has been studied. Chlorpropamide (500 mg/day) was given orally for 4 days. No salt restriction was instituted.

In all patients with diabetes insipidus urine volume decreased significantly falling from a mean value of 7.371-2.430 ml/day. SG rose from 1,001 to 1,011 and Uosm showed a significant rise from 115 to 351 mosm/l. Ch2o fell significantly from 5.2 to 2.2 ml/min and GFR showed a significant decrease from 202 to 116 ml/min. There were no significant changes of V, Uosm, C\textsubscript{\textdegree}20, SG, GFR and Cosm in hydrated and non-hydrated controls and in the one patient with acute renal failure.

These results indicate that the decrease in urine volume produced by chlorpropamide in patients with diabetes insipidus is due to a reduction of free water clearance with the formation of Tc\textsubscript{\textdegree}20m some of the cases. It suggested that chlorpropamide has an ADH-like activity.

Renal Association
(February 3, 1971)


There appear to be two major ways in which immunologic events may cause glomerular injury. The first results from formation by the host of antibodies capable of reacting with the glomerular capillary basement membrane (GBM) and is responsible for about 10-20% of glomerulonephritis. The anti-GBM antibodies in the circulation react with the GBM probably via endothelial pores. The second results from the formation of antibodies to circulating antigens, either endogenous or exogenous, and is involved in 80-90% of glomerulonephritis. The antibodies combine with circulating antigens and probably complement-forming macromolecular complexes which may become trapped in the glomeruli. This trapping first is seen in hyperplastic mesangi and later along the subepithelial aspect of the GBM. Either mechanism serves to concentrate an antibody reaction within the glomerular capillary wall. These two types of immunologic reactions then produce glomerular injury by similar sequences of events involving complement, the kinins, leukocytes and platelets. The severity of the disease appears dependent upon the amount of antibody and antigen reacting.

Lachmann, P.J.: Mechanisms of complement mediated tissue damage.

During the complement reaction sequence, 3 types of phenomenon occur to account for the biological effects observed.

Components are bound at the reaction site, often in substantial amounts.

Fragments of components which may have biological activity are liberated from the reaction site.

The terminal complement factors produce lesions in phospholipid membranes that cause them to leak. These lesions are normally found at the reaction site but in certain circumstances can occur elsewhere.

In the kidney complement fixation may result from antibodies reacting with glomerular basement membrane antigens, from the localisation in the kidney of circulating immune complexes and possibly from complement activation in the fluid phase. The role of these mechanisms in tissue damage is to be discussed.

Varia

Holborow, E.J.: Specific uptake of immune complexes by lymphoid tissues.

Although soluble immune complexes are implicated in pathogenetic mechanisms, they play a physiological role in antibody production, and in immune animals are responsible for localisation of antigen in germinal centres of lymphoid tissue. We have found that heat-aggregated IgG
(HGG) injected intradermally or intravenously into guinea-pigs or mice localises within a few hours in germinal centres in the draining lymph node or in the spleen. The dendritic pattern of localisation in the germinal centres mimics the pattern of binding of autologous IgG in normal mouse lymphoid tissue, and the pattern obtained when soluble immune complexes are similarly injected. Aggregated HGG thus serves as a model for studying the physiological handling of soluble complexes by lymphoid tissues. We have now found various conditions under which germinal centre localisation of complexes is impaired, namely, (1) in mice treated with anti-mouse-lymphocyte globulin, (2) inNZBmice and in NZB × NZW hybrid mice before onset of autoimmune disease, (3) in mice during the immunosuppressed phase of acute malaria.

The indications are that soluble complexes are transported into germinal centres by lymphoid cells which have surface receptors for altered Ig; and preliminary experiments with membrane immunofluorescence show that some lymphocytes from the blood and lymphoid tissues can take up aggregated HGG at their surfaces.

Steward, M.W.: Reaction kinetics of antibodies in nephritis-prone inbred strains of mice. Development of progressive nephritis following chronic antigen administration in rabbits is related to the pattern of antibody response of the rabbit [Dixon et al., 1961; Pincus et al., 1968]. LCM virus infection in mice is known sometimes to be associated with nephritis, and Oldstone and Dixon [1969, 1970] showed that this occurred in some inbred strains but not in others. Mice of these strains were immunized with human serum albumin and human transferrin. The kinetics of the interaction of the antibodies produced with radioactive antigen were studied and the equilibrium constants, K, determined. The effect of sex, age at first immunization, dose of antigen, and adjuvant upon the affinity of the antibodies produced was also investigated. It was found that those strains which develop nephritis after LCM infection produced antibodies to all the antigens studied of significantly lower affinity than those mouse strains which do not develop the disease. The implications of these findings in the pathogenesis of nephritis and the possibility of prevention or treatment by immunisation will be discussed.

References
Denman, A.M.: Immuno-supression in New Zealand black mice

Anti-lymphocytic globulin (ALG) provokes complex nephritis in normal mouse strains but this can only be detected by histopathological examination of the kidney. (NZB × NZW) F1 (BW) mice, destined to develop spontaneous glomerulonephritis, succumb to an accelerated form of complex nephritis after receiving ALG, despite the concomitant ablation of cell-mediated immunity. However, in moderate dosage ALG not only fails to provoke immediate renal disease in BW mice made tolerant to this heterologous protein, but also retards the subsequent development of spontaneous disease. Nevertheless, ALG given intensively or to recipients thymectomised as adults (a procedure which potentiates the effect of this agent) precipitates renal disease even in tolerant recipients. The disease in such mice is characterised by proliferative changes in the glomeruli rather than by the features of complex nephritis typical of the natural disease. This provocative
effect can be counteracted by restoration with lymphoid cells. It is postulated that ALG delays the onset of renal disease in tolerant animals by eliminating cells which would otherwise become sensitised to the provoking agent, but that more widespread ablation of lymphoid cells encourages the proliferation of auto-antibody cells or even of cells in the glomeruli themselves.


Evidence that glomerular fibrin deposition plays an important pathogenic role in renal disease has been obtained from the study of experimental (immuno-logically induced) glomerulonephritis.

Fibrin deposition is also seen in various human renal diseases and fibrin derivatives are found in the serum and urine of patients with glomerulonephritis. The deposition of fibrin on the vascular endothelium is also thought to be responsible for anaemia in the haemolytic uraemic syndrome – microangiopathic haemolytic anaemia. Fibrinogen turnover, measured using iodine-labelled fibrinogen, may be greatly accelerated in this condition. Microangiopathic haemolytic anaemia is also a feature of malignant hypertension and occurs in the patients with post partum renal failure [Robson et al., 1968]. In both these conditions extensive vascular lesions, with fibrinoid necrosis of the renal arterioles are seen. Fibrinoid necrosis in small vessels and capillary microthrombi are also a feature of some types of renal allograft rejection. Such changes have lead to the use of anticoagulants in these conditions.

Reference

Two main mechanisms are responsible for the morphological and functional changes that are seen in the rejection of renal grafts. These processes may operate separately or in conjunction.

Cellular mechanism. This occurs in fairly pure form in the early stages of acute rejection of untreated allogeneic kidneys transplanted into normal recipients. It is characterised by infiltration of the graft by lymphoid cells and is not associated with complement depression or platelet uptake by the transplant. Damage is produced in the peritubular capillaries and vasoconstriction is induced in the small arteries and arterioles of the graft.

Humoral mechanism. This is characterised by deposition of circulating host antibodies on the graft vasculature including the glomerular capillaries. These antibodies may be formed before the kidney is transplanted, as in the rejection of renal xenografts between disparate species or they may be formed after transplantation. In both instances, platelet aggregation may be a complication leading to either acute renal failure or later impairment of function due to obliterative vascular lesions following organisation of the aggregates.

A mixture of the two mechanisms is seen in the later stages of the rejection of untreated allografts in normal recipients and in allogeneic kidneys that are transplanted into incompletely immunosuppressed recipients.


August x AS hybrid or August homozygous kidneys transplanted to AS rats which were injected with AS anti-August antiserum show prolonged survival due to immunological enhancement. One factor which affects the degree of enhancement obtained is the amount of graft incompatibility present. A homozygous incompatibility shows only limited enhancement, whereas kidneys with a heterozygous incompatibility showed indefinite survival. The indefinite
survival of heterozygous grafts in serumtreated recipients is believed to be due to the induction of a state of auto-enhancement. The possibility that tolerance may play a role in the prolonged survival has been studied. Rats bearing enhanced kidneys are capable of showing both humoral and cell-mediated immune responses against donor antigens. The potential value of enhancement in human kidney transplantation will be discussed.

Book Review-Livre nouveau
Dans cet excellent travail d’investigation clinique chez l’homme, G.A. Glazer a étudié la volémie, le débit cardiaque (mesuré par les courbes de dilution du bleu Evans) et le débit sanguin rénal dans différents types d’hypertension artérielle.
Parmi ses constatations les plus originales, on retiendra (a) l’augmentation nette de la volémie et de l’index cardiaque dans la sténose de l’isthme aortique, (b) le fait que, dans le syndrome de Takayashu, l’augmentation de la volémie et de l’index cardiaque qui existent en l’absence de sténose artérielle rénale font place à une diminution de l’index cardiaque avec augmentation des résistances périphériques lorsqu’il y a une sténose artérielle rénale, (c) une corrélation statistiquement significative entre secretion d’aldostérone et résistances périphériques, et (d) le caractère tardif de la diminution du débit sanguin rénal.
L’influence du traitement hypotenseur fait apparaître, sous Guanéthidine, une augmentation de la volémie que l’auteur rapporte à une insuffisance cardiaque. On ne peut que regretter que cet excellent travail, écrit entièrement en russe, ne comporte même pas de résumé anglais, car il aurait mérité une audience Internationale. P.Y. Hatt