sophisticated tools are needed and one such is the growing Cochrane Collaboration around the world.

You only have to read a recent review of treatment of membranous nephropathy in adults[5] to realise how a single reviewer writing an invited article over the space of a few months is biased and selective of the studies included. The more systematic approach is to engage in a collaborative group. This is not a strait-jacket to restrict clinical freedom but a helpful way of making the best knowledge available for the benefit of our patients.

There are few randomised trials in nephrology. These have been gathered together by Denis Fouque and colleagues.[6] There is growing recognition that we need a Renal Review group to pull together the systematic reviews of randomised control led trials and other data that can be used to inform our clinical judgement. Meetings in Lyon, at the EDTA in Madrid and at the American Society of Nephrology (ASN) in San Diego have demonstrated that there is a small but willing band prepared to consider the daunting task of writing systematic reviews in renal disease. This is a movement which will grow and hopefully many of you will feel motivated to take part. Many hands make light work, especially in the arduous task of hand searching journals for randomised clinical trials. I urge you to follow the development of the Review Group and, if you would like to participate, to contact Denis Fouque in Lyon or me in Edinburgh.

As an example of the usefulness of this approach, there is a recent ASN abstract.[7] Here is an analysis of the randomised, controlled trials of low protein diets in renal disease, all relatively small, and including the USA modification of diet in renal disease trial which was inconclusive. A meta-analysis of all of these trials demonstrates that a low protein diet is useful in slowing the progress of renal failure, particularly for patients with glomerulonephritis. This is important. It is data that does not just affect our clinical practice but also justifies the use of scarce resources, for example dietitians.

REFERENCES


[1] Taylor JE, Henderson IS, Mactier RA, Stewart WK. Effects of withdrawing erythropoietin. *Br Med J* 1991; **302:** 272–3.

[2] Renal Association Standard Subcommittee. Treatment of adult patients with renal failure. *Royal College of Physicians* 1995.

[3] Klahr S. Anaemia, dialysis and dollars. *N Engl J Med* 1996; **334:** 461–3.

[4] Anti-platelet Trialist's Collaboration. Collaborative overview of randomised trials for anti-platelet therapy-II. Maintenance of vascular graft or arterial patency by anti-platelet therapy. *Br Med J* 1994; **308:** 159–68.

[5] Stageman CA, de Zeeuw D, de Jong PE. Treatment of idiopathic membranous nephropathy: the dilemma of who, when and how. *Nephrol Dial Transplant* 1995; **10:** 1982–4.

[6] Fouque D, Laville M, Haugh M, Boissel JP, Liberati A. The Cochrane Collaboration (CC) and systematic reviews in nephrology. [Abstract] *J Am Soc Nephrol* 1995; **6:** 387.

[7] Fouque D, Laville M, Haugh M, Boissel JP. Meta-analysis of low protein diet treatment effects in chronic renal failure. [Abstract] *J Am Soc Nephrol* 1995; **6:** 404.


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# LESSONS FROM A SYMPOSIUM ON RENAL MEDICINE HELD IN THE COLLEGE ON 20 SEPTEMBER 1995★

*W. D. Plant, Department of Renal Medicine, Royal Infirmary of Edinburgh*

This Symposium addressed several major issues in renal medicine, focusing upon the current state of clinical practice and upon experimental work in the pathogenesis of disease. A theme running through all presentations was the ongoing difficulty in generating evidence-based recommendations because of the dearth of large well executed clinical trials, the heterogeneity of renal disease and the difficulties in extrapolating from experimental models to human clinical disease. There has been impressive progress in certain areas; the key messages that struck this reviewer are detailed below.

## ACUTE RENAL FAILURE (ARF)

This is still associated with high mortality (c. 50 per cent of cases) despite advances in general supportive care and in the technologies of renal replacement therapy. Over the past 30 years there has been a shift in the pattern of diseases associated with ARF and requiring dialysis. Obstetric causes are now extremely uncommon, whereas ARF associated with complex severe medical diseases has increased dramatically. The case-mix now features a much more elderly population, many of whom have associated significant reno-vascular, cardiac or liver disease. The increase in complex cardiac, vascular and hepato-biliary surgical procedures has also produced more difficult cases of ARF.

As ARF is now frequently seen in the context of multi-organ failure, much of the renal replacement therapy (RRT) now takes place in the intensive therapy unit (ITU) rather than on renal wards. Standard haemodialysis is not always appropriate in the setting of significant haemodynamic instability and modalities of continuous renal replacement therapy (CRRT) are increasingly used. These include continuous veno-venous haemofiltration (CVVH), continuous arterio-venous haemodialfiltration (CAVHD) and slow continuous haemodialysis. These techniques utilise more biocompatible membranes and pharmaceutically purer replacement fluids, and consequently are less likely to cause haemodynamic instability. The care of such patients is now a multi-disciplinary endeavour, which requires a different approach to previous mono-speciality practice.

In the Royal Infirmary of Edinburgh about 200–250 cases of severe ARF are seen each year, with about 50 per cent of these requiring RRT. The mean total cost of an in-patient event for renal patients not requiring ITU is about £5,500; a patient treated with CVVH (mean stay 7·4 days) has a cost of £7,500; one surviving to have CVVH and haemodialysis in the ITU (mean stay 19·3 days) costs more than £20,000.

The understanding of the pathogenesis of ARF in different contexts has advanced dramatically particularly in the setting of acute sepsis, where acute derangements in cardiovascular function and the role of inflammatory mediators

★A list of speakers and the titles of their papers presented at this symposium is recorded in *Proceedings* Vol. 25 p. 717.

have been defined in experimental and clinical studies. The role of non steroidal anti-inflammatory drugs (NSAID's) in the pathogenesis of ARF is increasingly recognised. These agents act by interfering with the prostaglandin mediated regulation of afferent arteriolar blood flow: this effect can be demonstrated by measuring urinary prostaglandin excretion, even in normal subjects. In patients with prostaglandin dependent afferent arteriolar autoregulation (such as those with chronic renal, cardiac and hepatic failure and those with sepsis) the effect of administered NSAID's on renal function can be catastrophic.

## RANGE OF RENAL VASCULITIS

The vasculitides have a wide range of clinical presentations depending upon the size of the vessels involved in the inflammatory process and upon the organ systems affected. These differences have been employed in the categorisation of 'syndromes' of vasculitis. Nosology remains a contentious issue but there has recently been a move towards a new framework of classification with the publication of the Chapel Hill Consensus in 1994; it is now felt that these diseases should be classified on the basis of aetiology, pathogenesis, morphology and clinical syndrome.

The development of tests for antineutrophil cytoplasmic antibodies (ANCA) has enhanced the ability to diagnose the small vessel vasculitides, Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA) with high sensitivity and specificity. The antigens against which c-ANCA (Proteinase-3) and p-ANCA (myeloperoxidase) antibodies are directed have been identified. These diseases are now recorded with an annual incidence of approximately 15 cases per million of population which is probably a true rise in incidence, rather than an increase in recognition. Certain environmental factors are known to trigger these diseases e.g. a vasculitic illness with antibodies directed against myeloperoxidase has been reported in patients treated by penicillamine and hydrallazine.

There is broad agreement on the objectives of therapy, but some uncertainty as to how these are best achieved. Combined initial therapy with steroids (either oral prednisolone or intravenous (iv) methylprednisolone) and cyclophosphamide (either orally or iv) is now standard. The additional benefit of plasma exchange, other than in patients who are requiring dialysis at presentation, is uncertain. Maintenance therapy is usually with steroids and cyclophosphamide (replaced by azathioprine or methotrexate in certain regimens); the best means of using cyclophosphamide is the subject of a number of trials. Monoclonal antibodies directed against specific T-cell antigens and intravenous immunoglobulin therapy with anti-idiotype activity are ongoing developments.

With such therapy as methylprednisolone/plasma exchange and cyclophosphamide, renal function can be initially salvaged in up to 75 per cent of cases, even if significant renal scarring exists. Even in those with creatinine concentrations $>500\,\mu mol/L$, dialysis can be avoided (at least in the short term) in 40–50 per cent of cases. Relapse is common (20–40 per cent in the first year) and is associated with the specificity and persistence of circulating ANCA; it is commoner in those with anti-Proteinase-3 antibodies, and intercurrent illnesses frequently act as triggers for this.

## WT1 GENE AND RENAL DEVELOPMENT

Insight into the developmental biology of the kidney has been gained from basic



science research into the structure and function of the Wilm's tumour suppressor gene (WT1). This gene, which is localised on chromosome 11, encodes a protein that binds to DNA and represses the transcription of many important growth factor genes, such as insulin-like growth factor gene.

During embryonic life, the ureteric bud grows from the mesonephros and induces condensation and differentiation in the loose mesenchyme of the metanephric blastema. There is intense expression of WT1 at this time, possibly protecting the mesenchyme from apoptosis and allowing induction to proceed. It therefore seems to be a critical factor in mesenchyme-to-epithelial transition by the developing kidney and gonads. In postembryonic life WT1 is expressed only by the podocytes.

Study of WT1 has been facilitated by its closeness on chromosome 11 to the PAX6 gene which is abnormal in inherited aniridia. Deletion of one copy of WT1 is associated with mild genital abnormalities only; deletion of the second copy with Wilm's tumour. In the Denys Drash syndrome, gene mutation (arginine to tryptophan changes) leads to impairment of DNA binding and the phenotype expressed has progressive chronic renal failure with shrunken glomerular tufts, hypertrophied podocytes, male pseudohermaphroditism with streak gonads and ambiguous external genitalia and Wilm's tumour.

In a WT1 gene knock-out mouse model, deletion of both copies of the gene leads to complete renal agenesis with apoptosis of the metanephric mesenchyme, streak gonads and cardiac and pulmonary abnormalities. Deletion of one copy of the gene leads to Wilm's tumour. If part of the gene is deleted, then a Denys Drash phenotype is expressed as a result of impaired DNA binding.

## MECHANISMS OF GLOMERULAR INFLAMMATION

Critical to an understanding of how the glomerulus is damaged in renal disease is insight into the mechanisms of glomerular inflammation and scarring; an impressive body of experimental work is now available from non-human models and cell culture studies. The local inflammatory response is the end-point of a complex interaction between pro- and antiproliferative stimuli. Some stimuli derive from soluble, diffusable factors, others from non-soluble, non-diffusable elements such as heparan sulphate, proteoglycans and fibronectin. The cellular elements, i.e. vascular endothelium, mesangial cells and podocytes, which participate in the local inflammatory response, make up a very small proportion of the renal tissue, and normally have a very slow turnover. Mesangial cells rarely divide, endothelial cells do so with some greater frequency and podocytes almost never divide. However, these are the target cells upon which the balance of other factors impact, potentially leading to cell proliferation or to enzyme induction, protein synthesis and secretion of further active factors.

Among the soluble factors promoting cell mitosis in experimental mesangial cell culture systems are platelet-derived growth factor (PDGF), epidermal growth factor (EGF), 5-HT, and endothelin-1. Concomitant administration of transforming growth factor-$\beta$ (TGF-$\beta$) inhibits this response. Studies on the mechanisms whereby PDGF induces proliferation have focused upon its effect on cell cycle kinetics; PDGF administration moves cells from the G0/G1 resting phases into the more active G2/M phases; co-administration of TGF arrests this process by keeping cells in the S phase (between G1 and G2). The mechanism whereby cells move to a more active phase seems to reflect the relative expression of certain

genes. One such gene is early growth response gene (EGR-1). Recognition of the factors which promote mitosis raises the possibility of interfering with the processing of such genes using tools such as anti-sense oligonucleotides: there has been some experimental work carried out with this approach.

The observation that PDGF is a much less potent stimulus to mesangial cell proliferation in three dimensional, as opposed to monolayer, cell culture systems, reinforces the notion that there is crosstalk between cells, soluble factors and the background extracellular matrix (which has considerable regulatory potential).

As we learn more about these mechanisms, it becomes clearer that this is an extremely complexly regulated system. Interventions aimed solely at interfering with soluble paracrine factors are unlikely to be sufficient in themselves; therapies will have to be derived to interfere with crosstalk, perhaps by interfering with cell-to-cell adhesion.

## TREATMENT OF IDIOPATHIC NEPHROTIC SYNDROME

Membranous nephropathy excepted, the commoner causes of the idiopathic nephrotic syndrome in adults are Minimal Change Disease (MCD), Focal and Segmental Glomerulosclerosis (FSGS) and, to a lesser extent, Mesangial Proliferative Glomerulonephritis and IgM Nephropathy. Various treatment schedules have been devised and some rigorously evaluated. Ideally, treatment should induce a high rate of remission and maintain a protracted relapse-free interval without causing unacceptable side-effects.

Ninety per cent of children with MCN achieve remission if treated by oral prednisolone (60 mg/m$^2$/day) for 8 weeks. By contrast, less than 60 per cent of adults with MCN achieve remission with a similar regime (1 mg/kg/day) given for 8 weeks. Treatment for 12 weeks does, however, increase the rate of remission to up to 80 per cent. Whereas most patients are steroid-sensitive, a lesser proportion (up to 22 per cent in some series) are steroid-dependent and will relapse immediately upon discounting steroid therapy.

Maintaining remission is often difficult and relapse occurs in 40–60 per cent of patients with MCN, with those classified as 'frequent relapsers' experiencing more than 3 relapses per year. Prolonged steroid therapy may achieve sustained remission but at a considerable cost in side-effects. Schedules employing prednisolone therapy on alternate days or for 3 days per week regimen and the use of methylprednisolone pulse therapy instead of oral therapy have been described, and seem to be more effective with fewer side-effects.

The addition of various alkylating agents (cyclophosphamide, chlorambucil, azathioprine) to treatment schedules extends the duration of the relapse free interval in MCN. Disparate, and occasionally conflicting reports on the varying efficacy of different 'recipes' is explained by the influence on outcome of the patient's age, alkylating agent chosen, duration of therapy and whether or not the patient is steroid-sensitive or steroid-dependent. Thirty-six to 66 per cent of children treated with an alkylating agent remained in remission after 5 years, and up to 60 per cent of adults have been relapse free for 15 years in some series. Treatment schedules of 6–8 weeks duration are reported to achieve a protracted remission in 58 per cent of cases; this rises to 80 per cent with 10–12 weeks' treatment.

Cyclophosphamide has particular toxicity to the testes and ovaries, but also causes haemorrhagic cystitis and is associated with an increased risk of haematological and other neoplasms. Ideally the daily dose should not exceed 2 mg/kg/day in adults or 0·15 mg/kg/day in children. Cumulative exposure of greater than 200–250 mg/kg should also be avoided. Cyclosporin is an effective agent (in up to 80 per cent of cases) in inducing and maintaining remission, especially in patients unresponsive to, or dependent on, steroids. Unfortunately treatment needs to be protracted, with the risk of renal impairment and toxicity. Levamisole remains a controversial agent in adult and childhood MCN. It may be best to reserve it for minor cases.



FSGS is a more serious condition because of the high risk that renal failure will ensue. Patients who are asymptomatic at initial clinical presentation, generally have a good renal outcome without therapy. In the past it was believed that this condition was resistant to steroids—some series reported a remission rate of <10 per cent, when treatment was given for 8 weeks. More recent studies suggest that up to 50 per cent of patients achieve a partial or complete remission if treated continuously for 9 months. Those who show a response are also likely to have the best long-term prognosis for renal function; non-responders have a similar outcome to untreated patients. There is not yet a way of predicting those who will respond.

Relapse is less frequent in FSGS than in MCN, but does occur. Alkylating agents and cyclosporin have been used to minimise relapse rates or induce remission in steroid-dependent cases. To date, the outcome is similar to that described for MCN.

## PERITONEAL DIALYSIS

Chronic ambulatory peritoneal dialysis (CAPD) is increasingly used for the treatment for end-stage renal failure. By the end of 1994 there were almost 100,000 patients worldwide maintained on this therapy. Many of the problems which previously caused major difficulties with CAPD have improved. The incidence of peritonitis has declined, largely because of developments in the technology of 'connection'—the widespread use of disconnect systems has had a major impact on a decrease in incidence of coagulase-negative staphylococcal infection. However chronic exit-site infection continues to be a problem.

Newer dialysate solutions have been developed which include solutions with more physiological calcium concentrations, solutions with amino-acids and solutions with glucose polymers. These are, respectively, used in maintaining divalent ion homeostasis, delivering additional protein to malnourished patients and controlling ECF volume in patients whose peritoneal membranes are excessively permeable to glucose. More patients are now being treated with automated peritoneal dialysis (APD), in which some (or all) of the exchanges are done by a machine while the patient sleeps.

CAPD is unlikely to have the same longevity as a treatment modality as haemodialysis and there are a number of reasons for this. It is becoming increasingly clear that the clearance of uraemic 'toxins' varies between patients. Even modest amounts of residual renal function enhances this clearance with CAPD. Heavier patients with no residual renal function may be unable to achieve optimal, or even minimal, levels of solute clearance. Recent observational studies from North America have suggested that there is a relationship between patient survival and the level of solute clearance achieved by peritoneal dialysis and residual renal function. As a consequence, therapy is likely to become more

individualised, and some patients may be deemed more suitable for haemodialysis.

HYPERTENSION, DIABETES AND RENAL DISEASE

Diabetic nephropathy was felt, until recently, to be more prevalent in patients with Type I than Type II diabetes. This is now recognised not to be the case and a significant public health problem looms. The prevalence of Type II diabetes is rising in an ageing population; patients with proteinuria are surviving much longer—to the point of developing end-stage renal disease—and this will undoubtedly place a considerable burden on end-stage renal disease programmes.

The previous view that diabetic nephropathy was less prevalent in Type II diabetes may have been an artifact due to a shorter survival in this group. In Erfurt (formerly in East Germany), 45 per cent of Type II patients died within 4 years of diagnosis. In Heidelberg (formerly in West Germany) the survival has been improving, possibly due to better control of hypertension and correction of other risk factors for vascular disease. Since German re-unification the proportion of Type II diabetic patients accepted onto chronic dialysis has increased dramatically in (former) East Germany, a trend observable also in the rest of Germany, Europe and the USA (where Type II diabetes accounts for between 50 and 80 per cent of all cases of end-stage renal failure).

Renal morphological changes observed in biopsies taken from Type II diabetics with nephropathy are more heterogeneous than in patients with Type I diabetes. In a series of 52 proteinuric patients with Type II diabetes typical changes of diabetic glomerulosclerosis were reported in only 19, with 16 showing chronic non-specific changes and 17 showed glomerular disease superimposed on diabetic glomerulosclerosis. In this series, as in others, changes of chronic ischaemia were prominent. Type I patients are reported as showing increased glomerular size; this is also the case with Type II diabetes in Pima Indians, who have large glomeruli even before the onset of diabetes.

In similar fashion to Type I patients, there seem to be a number of factors predicting the onset and progression of diabetic nephropathy. A positive family history of nephropathy or cardiovascular disease increases the risk of developing nephropathy in Type I and Type II patients, as does poor glycaemic control, poor control of blood pressure (BP) and (not well demonstrated until recently) a smoking habit. There seems to be an additional benefit in using ACE inhibitors to control BP in Type II patients as well as in Type I patients, but this benefit seems (at least in some studies) to be more marked when BP is not brought down to low levels.

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# THE NATURAL HISTORY OF AUTOIMMUNE THYROIDITIS: HOW NORMAL IS AUTOIMMUNITY?★

*Colin M. Dayan,† University Department of Medicine Laboratories, Bristol Royal Infirmary*

In 1912 Dr Hakuru Hashimoto described 4 women in whom the thyroid gland appeared to have been transformed into lymphoid tissue, *lymphomatosen veranderung*.[1] Despite the dramatic pathological changes (Fig 1), all 4 women were clinically euthyroid and presented simply with a swelling in the neck. Subtotal thyroidectomies were performed and it appears that all the patients became hypothyroid post-operatively, 'waxing and waning oedema'.[1] This early description of autoimmune thyroiditis raises several questions. What would have happened if Dr Hashimoto had not intervened? Would the women still have become hypothyroid? If not, would the *lymphomatosen veranderung* have ever come to attention had they had not developed visible goitres? And if it is possible to have lymphocytic infiltration of the thyroid without clinical sequelae, in what percentage of the apparently healthy population is this process occurring?

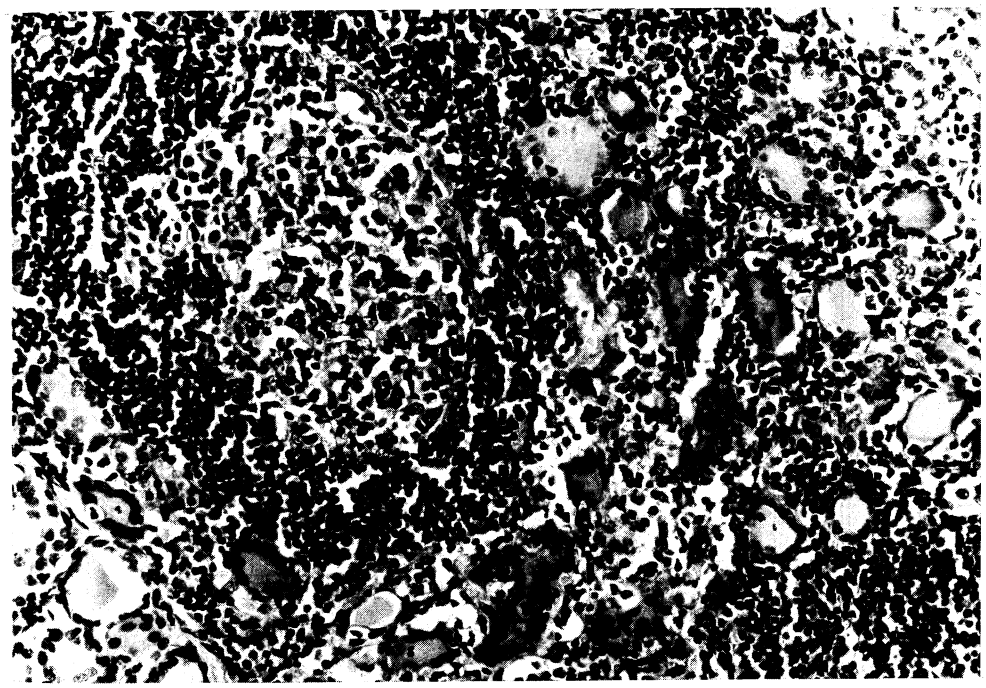

FIGURE 1

Histology of Hashimoto's disease showing dense lymphocytic infiltrate (courtesy of Dr E. Sheffield).

★A Croom Lecture delivered at the Symposium on *Antecedents of Adult Disease: the Paediatric Time Bomb* held in the College on 20 October 1995.

†Consultant Senior Lecturer.