stimulant for cattle and sheep. It may move against the Searle Company for allegedly withholding data on metronidazole and spironolactone, and has raised questions about the data on naproxen. While valuable drugs such as minoxidil, cimetidine, and newer beta-adrenergic blockers remain unapproved, the agency has become trapped in a pointless legal tangle about the useless cancer remedy Laetrile. Several courts have recently overruled the FDA ban on this compound, allowed

several patients to use it, and ordered the agency to compile a public record and hold public hearings—which may provide a precedent for other legal actions by drug manufacturers. And, finally, the agency has banned the use of Red No 4 dye for causing bladder polyps in dogs, so that henceforth Maraschino cherries will have a dirty orange color—an unappetising though not necessarily bitter prospect for the aesthetically inclined non-canine Manhattan fancier.

Today's Treatment

Diseases of the urinary system

Treatment of glomerulonephritis by drugs—II

J S CAMERON

British Medical Journal, 1977, 1, 1520-1522

Lupus nephritis

One form of nephritis is worth separate consideration, because the prognosis has improved so much over the past 25 years—even if we are unsure exactly why (fig 1). The prognosis in the absence of steroids was 20% at five years; the introduction of antibiotics does not seem to have made much impact in the nephritis of systemic lupus erythematosus. During the next decade corticosteroids were employed to suppress the clinical manifestations of the disease, and during this period survival improved. Higher doses of corticosteroids were used in most patients with lupus nephritis over the next decade, with some investigators using immunosuppressive drugs in addition. Over the past seven years the combination of lower doses of steroids plus immunosuppressive agents has become common. During all this period survival increased.

To what extent can we attribute this improvement in survival to the drug treatment? Diagnosis of milder forms of the disease might contribute to the improvement overall, but lupus nephritis—especially the severe diffuse forms of nephritis when the patient is usually uraemic, nephrotic, or both—has shown a similar improvement. It is difficult to believe that these patients were being missed four times out of five in the early 1950s. The infective complications of lupus have, if anything, been made worse by immunosuppressive treatment, so that a non-specific effect on mortality from infection cannot be considered responsible. It seems likely that the improvement in prognosis has accompanied immunosuppressive treatment, although no controlled trials of no treatment versus corticosteroids were ever performed. Why should this be so when, in other forms of nephritis, no benefit seems to be seen? It may be that the florid B-cell overactivity found in systemic lupus erythematosus, with antibodies produced in great excess against various endo-

FIG 1—Survival of patients with systemic lupus, 1953-77. Actuarially calculated five-year survivals of published series.¹ Upper line represents data for all patients with lupus; second line, patients with lupus nephritis—that is, a subset of the first group; and lowest line survival of patients with biopsy evidence of severe diffuse lupus glomerulonephritis. Data for 1955 for all lupus are at four years and for 1957 for severe diffuse lupus nephritis two years (in brackets). From 1948 to 1953, corticosteroids were little used. From 1953 to 1964, corticosteroids in moderate doses (10-30 mg/day prednisone equivalent) were used in most units for short periods. From 1964 to 1970, higher doses (60 mg prednisone/day) were used for periods of six months or longer. From 1970 most units employed prednisone in lower doses and an immunosuppressant agent, either cyclophosphamide or azathioprine. Reproduced from *Renal Disease*,² with permission of the publishers, which see for detailed references.

genous and exogenous antigens, may be the dominant feature of the disease, even if a deficiency of suppressor T lymphocytes may be a more fundamental event in the pathogenesis.

Even so, we need to know whether the addition of immunosuppressive agents to the corticosteroid regimen has contributed anything. Is the further improvement in prognosis over the past five years attributable merely to more careful use of corticosteroids and avoidance of side effects? Analysis of causes of death in series of cases of lupus nephritis seems to show little change in pattern, apart from possibly more deaths from

cerebrovascular lupus in long-term survivors. If anything, death from renal failure in lupus has become a rarity, and the relative numbers dying from complications of immunosuppression has increased.

Nevertheless, several controlled clinical trials, all of them open to criticism, have failed to show any clear advantage of combined treatment with corticosteroids alone, at least up to three years or so. There are some indications, however, that the addition of immunosuppression—even for a relatively short period—reduces the number of patients going into renal failure subsequently. On corticosteroid treatment alone, deaths from renal failure are rare in any case up to five years, and it may prove difficult to show that this has been reduced still further. Our current policy is to use corticosteroids and azathioprine routinely in all patients with severe forms of lupus nephritis; some of the patients judged to have milder renal disease on histological examination are managed on corticosteroid treatment alone.

We aim to maintain the corticosteroid doses at 10-25 mg prednisone/day, preferably at the lower end of this range, and are usually successful in doing so. We use azathioprine rather than cyclophosphamide, since we have had trouble with cyclophosphamide-induced cystitis, and the risk of bladder malignancy appears to be considerable in treatment lasting years. To date, we have not noted malignancy in any patient treated with azathioprine for systemic lupus erythematosus nephritis, and eight pregnancies have given normal babies in the presence of the drug and corticosteroids. We need longer follow-up to establish the risk of malignancy, which may be higher in patients with lupus in the first place, although the data are not nearly as convincing for man when compared with the information in the animal model, the NZB/NZW mouse. In acutely ill patients with severe crescentic glomerulonephritis we have also used anticoagulants and antiplatelet agents, and, rarely, pulses of methylprednisolone. We have some information that this last treatment removes complexes from the circulation, even when high doses of oral steroids and azathioprine have failed to do so. Plasmapheresis has also been used in acute severe renal lupus, but its role has not been defined.

FIG 2—Period of freedom from relapse in children with minimal change nephrotic syndrome who were corticosteroid-responsive, but underwent multiple relapses with eventual corticosteroid toxicity. Data have been derived from five recent papers using life-table method, "event" in this case being relapse. Dosages of cyclophosphamide were a little different in each series, ranging from 3 mg/kg/day for eight weeks to 3 mg/kg/24 hr for 16 weeks. In two series initial leukopenia was induced with 5 mg/kg 24 hr. Untreated, or given only two weeks' treatment, over 90% of such children will relapse in six months.¹ Reproduced from *Renal Disease*,² with permission of the publishers.

"Minimal-change" disease

One final form of glomerulonephritis remains to be discussed—"minimal-change" disease. This is not, so far as can be judged, a disease arising from the glomerular deposition of soluble immune complexes, such as those forms of nephritis discussed above. The nature of the condition and its cause are obscure; it may not even be an immune disease at all, yet it responds reliably to both corticosteroid and immunosuppressive drugs. Untreated, minimal-change disease remits slowly over a year or two, provided that the patient does not fall to one of the complications of the nephrotic state before remission can occur, particularly thrombosis or infection. Both drugs mentioned will accelerate this tendency towards remission, some 90% of patients being free of proteinuria or oedema within four to six weeks of beginning treatment with corticosteroids, mustard-like drugs, or purine antagonists.

What common effect these drugs have on the disease is completely unknown. The difference lies in the permanence of the remission induced in those patients who, after initial response, relapse persistently, often immediately on withdrawing corticosteroids. The effect of purine antagonists is no more permanent in these patients than that of steroids, whereas mustard-like drugs may convert a persistently-relapsing course into more or less permanent remission, or at least delay its appearance several years. The best studied is cyclophosphamide (fig 2). A two-week course of 3 mg/kg/day does not affect the frequency of relapses, but at doses of 2.5-3 mg/kg/day for six to eight weeks or longer about half of the patients studied had remissions of three to five years, and no further patient from our own series shown as in remission at seven years has relapsed over the next three years. Thus, about one-third of cases appear to achieve permanent remission.

The management of minimal-change disease has now been evaluated in several controlled clinical trials in several parts of the world. There seems little justification for leaving oedematous patients untreated, although some will undoubtedly remit spontaneously if given time. There are no controlled data for children on this point. Nevertheless, if a short course (four to six weeks) of corticosteroids is started at about 60 mg prednisone/day, over 90% will go into remission with few side effects. There are no data to support the use of longer initial courses, which can only induce side effects. Since only half of the patients will subsequently relapse, cyclophosphamide or other drugs not justified as primary treatment except perhaps in the aged, where a nephrotic syndrome is more serious and subsequent gonadal function of less importance.

Corticosteroids may be used for subsequent relapses, as for the first attack, unless side effects or some other event render them unsafe or unsatisfactory. At this point cyclophosphamide in a dose of 3 mg/kg/day for eight weeks may be used. Longer courses may possibly increase slightly the permanence of remission, but gonadal damage occurs with courses of 12 weeks or longer, and this risk does not seem justified at the moment. Some have advocated chlorambucil at this point, but the results in short courses have not been so much better than with cyclophosphamide. Longer courses with higher doses (0.2 mg/kg/day rather than 0.1 mg/kg/day) carry not only the risk of gonadal damage and severe infections but also a risk of leukaemia, which appears to be many times that with cyclophosphamide. For the moment, we have reserved this drug for treating some patients who have relapsed after cyclophosphamide. It is often possible, however, to manage these patients on a lower dose of steroids, with fewer relapses than before cyclophosphamide treatment; it appears that the disease, although not eliminated, has been "softened" in some way, and the tendency to relapse blunted.

We should not forget that the impact of diuretics and antibiotics on this group of patients was considerable, with a great reduction in mortality. Nevertheless, it is pleasant to record that a condition that used to carry about 50% mortality over five years now has less than 5% mortality in 10 years. For those of us who have some faith in the application of science to

medicine it is galling, even so, to note that this has been achieved without any knowledge of the nature of the disease or how the drugs act.

References

- ¹ Cameron, J S, in *Perspectives in Clinical Immunology II*, ed J Zabriskie, H Villareal, and E L Becker. New York, John Wiley, 1977. In press.

- ² Cameron, J S, in *Renal Disease*, ed D A K Black, 4th edn. Oxford, Blackwell, in press.

Further reading

- Cameron, J S, in *Glomerulonephritis*, ed R Kluthe and S Batsford, pp 154, 217. Stuttgart, Thieme, 1976.
Cameron, J S, *Proceedings of 6th International Congress of Nephrology, Florence 1975*, p 492. Basel, Karger, 1976.

Medicine in the 'Seventies

Has the Court Report been misunderstood?

An interview with Professor Donald Court

Since its publication in December 1976 *Fit for the Future*, the report of the Committee on Child Health Services, chaired by Professor S D M Court, has been widely debated. Recently, Professor Court discussed with one of the *BMJ* staff some of the criticisms made of the report and his responses to them.

General practitioners, and in particular the GMS committee, have attacked the proposals on the grounds that the introduction of specially trained general practitioner paediatricians (GPPs) would lead to their remaining colleagues losing a vital part of their traditional care for the whole family. Professor Court saw this as a serious misconception. "The committee saw the GPP first and foremost as a general practitioner and a member of a primary health care team," he commented, "and we saw him adding something to general practice which at the moment is undeveloped or underdeveloped—namely, the developmental surveillance of children through childhood to adolescence and then to adult

life. All the partners in the practice would continue to look after the children on their lists, and the GPP would simply be the doctor who would do two essential things by virtue of his special interest and additional training. Firstly, he would be a source for internal referral and consultation about the needs of children; and, secondly, he would ensure (but we emphasised that he or she would not necessarily personally provide) that the children in the practice received proper health surveillance and preventive care, particularly health education. The GPP would also be the named school doctor for one or more schools in the practice neighbourhood."

What, then, was Professor Court's reply to those doctors who feared that the moment one of perhaps three doctors in a practice became labelled the child doctor then all of the child illnesses as well as the developmental examinations would be taken to him? Might not the GPP acquire in time the whole of the child population as his list, while the remaining partners

Vocational training

found themselves dealing only with adults? Professor Court thought that was an understandable fear. "All I can say," he went on, "is that in the limited number of practices where the GPP concept is being applied in greater or lesser degree this has not happened. There may have been some trend along those lines, but much less than might have been expected." It might be, he added, that the risk would be lower if no formal label were attached to the person with the special interest; the important thing was the quality of the training and the experience behind it.

Given that the main role of the GPP would be in developmental assessments, where skills were appreciably lacking at the moment, was there not also in the report an implication that therapeutic skills in paediatrics were also not sufficiently well developed in general practice? The evidence certainly suggested a gap between our increasing knowledge of child development and childhood illnesses and its application in practice. Professor Court thought the answer lay in well-planned vocational training in general practice. This had come late in the field, but it would be mandatory for all principals from 1980 and, he hoped, would contain a universal paediatric component. The committee saw improvement in the standard of therapeutic care of children as coming from the overall vocational training of GPs. True, that would be a very slow process—but so too would be the evolution of the GPP. The whole report had to be seen over a 15-20-year period if it was going to make sense. Furthermore, while vocational training should gradually improve general standards, there was a danger in putting the emphasis too firmly on initial training. The whole problem of rapidly advancing knowledge was that continuing education was needed to keep pace with it. "What will really matter is not only that the GPP has additional training over and above the general paediatric vocational training for general practice but that he maintains it."

The primary care team

Better training in child health for GP and GPP was important in itself but also in developing and strengthening the

Professor S D M Court, Emeritus Professor of Child Health in the University of Newcastle upon Tyne; chairman of the Committee on Child Health Services.