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Poststreptococcal glomerulonephritis

Chronic glomerulonephritis is the most common cause of renal failure in patients suitable for dialysis and transplantation.[1] Few of them, however, can remember an episode of acute glomerulonephritis; and how often acute poststreptococcal glomerulonephritis has long-term sequelae (renal failure or raised blood pressure) remains uncertain.

In attempting to classify glomerulonephritis pathologists and physicians have struggled to find common ground, and many varieties have been identified and others reclassified. Acute poststreptococcal glomerulonephritis has survived this process to remain a definable and usually easily recognisable disease. It has a reasonably consistent clinical picture, a known cause, and—if textbooks are to be believed—a predictable and in most cases a benign natural history. A few patients can be recognised early on to have adverse features on clinical grounds, and in these the probability of a poor prognosis may be supported by examination of a renal biopsy specimen.

In 1977 the belief that most patients with poststreptococcal glomerulonephritis have a good prognosis was challenged by Baldwin and his colleagues in New York.[2] They observed that patients who had shown a complete clinical recovery, with no proteinuria, no abnormality in the urine deposit, and no hypertension, could present later with sclerosed kidneys and renal failure or hypertension—but with no sign of active glomerulonephritis in biopsy specimens. The New York study suggested that after acute poststreptococcal glomerulonephritis less than half of all patients would have normal renal histology and renal function if followed up over several decades despite, in some, a period of clinical normality. Their experience, though more extensive than most other series, may have been distorted by an initial selection of the more severe cases and also by loss from follow-up of over half their patients, perhaps mostly those with milder disease. There is also the possibility (as in most such studies) that either the "seed" or the "soil" was atypical and unusually conducive to a poor long-term prognosis. The New York patients were of mixed ethnic origin—less than half Caucasian, and many came from underprivileged sections of the community. They had acute glomerulonephritis between 1959 and 1972, and the streptococci present at that time may have had a greater potential for causing chronic illness than at other times or in other places.

A report this year from Woodville, South Australia, by Lien *et al*,[3] conflicts with Baldwin's gloomy predictions and provides support for the more traditional views on prognosis. The study was based on adults with poststreptococcal glomerulonephritis admitted to a single hospital. Few patients were lost during follow-up; and a late renal biopsy was carried out whenever possible, even if no clinical features suggested continued activity. No epidemic occurred during the decade of study, but the average of six adult cases of poststreptococcal glomerulonephritis seen each year is more than the referral rate to most British nephrology units (which almost certainly look after a larger population than the Australian hospital reporting this series). This implies either that the illness is more common in the Woodville community or that referral for nephrological assessment and biopsy is more frequent. Certainly in Britain many patients with haematuria—who may well have glomerulonephritis—are evaluated in urology units, some of which have a low index of suspicion for medical causes of haematuria.[4] In England, too, many patients may be looked after by general physicians and family doctors reassured by the popular concept that the illness has a benign prognosis. The renal biopsies on the Australian and American patients would not be performed as a routine in many British units, where biopsy is often reserved for those patients who are slow to recover or who present with severe renal failure, nephrotic syndrome, or other atypical features.

Information from the initial biopsy done as a routine and from a late follow-up biopsy in over half of the patients makes the Australian report a useful contribution to understanding the illness. Renal biopsy at the time of diagnosis did not allow an absolute prediction of prognosis in individual cases. Abnormalities in renal function and in late biopsy appearances were found in some patients with all grades of severity at their initial presentation. There were signs of incomplete resolution in six of 18 biopsies performed after more than five years' follow-up—but all these patients still had some clinically detectable abnormalities such as haematuria, hypertension, proteinuria, or raised serum creatinine concentrations—a useful reassurance for physicians who assume normality of the kidney when such measurements are normal. On the other hand, some attempt to assess the referral criteria of local doctors would have improved the report. Assessment of the local incidence of the disease would also have been

helped by statements on the size of the population "at risk," and on whether the unit was providing primary, secondary, or tertiary care (or a combination of these). There was also some uncertainty about whether all cases were poststreptococcal: low serum complement activity was accepted as an alternative to a raised antistreptolysin titre in 14% of patients and other unknown provoking agents could have caused the glomerulonephritis in these cases. Despite these limitations this Australian survey is among the best studies reported.

Nevertheless, some uncertainties remain. Most patients are not Australians, and in some ethnic groups the natural history may be different. Prognosis may also differ with different streptococci: the late results of patients followed after an epidemic in Trinidad showed that only 1·4% of 722 patients had clinical evidence of chronic renal disease 7-12 years later,[5] and in Venezuela[6] the results were intermediate between the series so far discussed. The age of the patient may also be important: most of Baldwin's and all of the Australian patients were adult. In children the prognosis is more generally agreed to be benign if urinary abnormalities do not persist.[7 8] The Australian series is, however, consistent with European experience—where only a few cases of chronic renal failure are caused by an earlier attack of clinically recognisable poststreptococcal glomerulonephritis and few cases of acute poststreptococcal glomerulonephritis proceed to renal failure. A bad prognosis can be suspected clinically by the severity of the presenting illness or by the continuation of clinical features. Nevertheless, some patients may continue with detectable clinical abnormalities and yet still have a good long-term prognosis. Possibly this could be detected by serial analysis of serum creatinine concentrations.[9] A benign course would be associated with stable concentrations, while continuing loss of nephrons causes a progressive rise, initially within the normal range.

More patients will need to be followed over several decades before Baldwin's conclusions can be considered to apply only to his particular population. Total reassurance for those patients who have poststreptococcal glomerulonephritis and who have no persisting clinical features will not be possible until such studies establish that the benign prognosis, observed over ten years by Lien and colleagues,[3] will persist over many decades.

No evidence in any of these series suggests that after the attack of acute glomerulonephritis antibiotic prophylaxis has anything to offer. Antibiotics probably do not influence prognosis in the acute phase of glomerulonephritis either, but penicillin should be given to eliminate the streptococcus. An adequate course is 10 days at a dose of 250 mg, six hourly, of penicillin V or an equivalent oral penicillin, or a "single shot" of benzathine penicillin 2·4 megaunits.

Poststreptococcal glomerulonephritis is not a common disease and, like other poststreptococcal syndromes, its incidence was probably decreasing even before antibiotics. When the diagnosis is made, however, there is an urgent need to allay (when possible) the fears of the patients and relatives that result from increased public awareness of the lethal nature of some kidney conditions.

[1] Jacobs, C, *et al*, *Proceedings of the European Dialysis and Transplant Association*, 1977, **14**, 4.
[2] Baldwin, D S, *American Journal of Medicine*, 1977, **62**, 1.
[3] Lien, J W K, Mathew, T H, and Meadows, R, *Quarterly Journal of Medicine*, 1979, **189**, 99.
[4] Turner, A G, *et al*, *British Medical Journal*, 1977, **2**, 29.
[5] Nissenson, A R, *et al*, *American Journal of Medicine*, 1979, 67, 255.
[6] Rodriguez-Hurbe, B, *et al*, *Clinical Nephrology*, 1976, **5**, 197.
[7] Dodge, W F, *et al*, *Medicine, Baltimore*, 1968, **47**, 227.
[8] Travis, L B, *et al*, *Clinical Nephrology*, 1973, **1**, 169.
[9] Rutherford, W E, *et al*, *Kidney International*, 1977, **11**, 62.

Randomised controlled trials?

Bernard Shaw is alleged to have attributed his vigour to controversy; Popper[1] has said that theories justify our preference for them only if they can weather attempted refutations. Cranberg's defence of methods other than randomised controlled trials for resolving problems in medicine (p 1265) should be considered in this spirit.

The problems most often studied by randomised controlled trials fall into two broad categories. Firstly, such trials are used to examine broad topics such as prevention of a second myocardial infarction and the treatment of mild hypertension. Many workers believe that because multiple, possibly interrelated, factors influence the outcome there is no alternative to the randomised controlled trial in these circumstances—yet it may be just this profusion of detail that weakens the method. As Black[2] has argued, where there are many factors effective randomisation becomes impossibly complex and the design of a trial insufferably so. In such cases we may doubt whether the randomised trial ever settled a problem. Almost all reports of trials on these broad clinical issues were seen initially as apparently conclusive but later became the subject of debate—though they often highlighted difficulties and drew attention to factors previously underestimated.

The second type of problem for which randomised trials are usually required is assessing drug treatments. The phases through which a new drug passes have been described, conveniently briefly, by Dollery.[3] Phase 1 poses the question "Has the new drug a pharmacological action that may be useful in treatment?" and necessarily requires a small open trial. If the results are hopeful, what then? Publication at this point, as Cranberg says, citing a BMA panel, greatly increases the difficulty of setting up a controlled trial. The alternative to suppress publication and start a trial—is both selfish and counterproductive: the sooner a wide audience is made aware of a possible advance the sooner will the work be assessed; and, equally important, any spin-offs can be thought about and explored. Our current insistence on randomised controlled trials has undoubtedly had a salutary effect on loose thinking, but more than once this has been at the expense of progress.

In the second phase of assessment there is a shift in emphasis from "Does the drug work?" to "How does it compare with other treatments in efficacy and safety?" At first sight a randomised controlled trial seems the obvious way to answer that question. But apart from the difficulty of ensuring homogeneity in the groups there are other problems. Whether or not we use a placebo for comparison is perhaps a side-issue; but many clinicians believe it to be unethical with certain classes of drug (though the Empire Rheumatism Council trial[4] that finally sanctified gold as a treatment for rheumatoid arthritis is an example of a good trial, its use of placebo does seem questionable). Clinicians may be deterred by the laborious nature of a randomised controlled trial, which requires substantial back-up facilities not available everywhere. Furthermore, anyone who has conducted such a trial and has tried to explain the objectives to patients will know how it alters the relationship between doctor and patient. The knowledge that treatment is not to be determined by the doctor cannot enhance trust.

Even if we suppose that these difficulties can be circumvented the methods used in randomised controlled trials are often imprecise. As one example, measurement of