THE TREATMENT OF ACUTE RHEUMATIC FEVER AND ACUTE GLOMERULO-NEPHRITIS WITH PENICILLIN

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The main purpose of this paper is to draw attention to an article from an American centre, distinguished for the contributions of its staff to the subject of streptococcal infections, which indicates a new approach to the treatment of acute rheumatic fever and new thinking about its pathogenesis. It will be suggested that this new approach could be applied also to the problem of acute glomerulo-nephritis, and the results in four cases of this disease will be given in outline.

The article (Mortimer et al., 1959) reports a controlled study of the effect of penicillin given in large doses* over six weeks to patients admitted to hospital with acute rheumatic fever; the authors found a definite reduction in the incidence of valvular disease of the heart a year later in those cases in which evidence of a "fixed" valvular lesion was not already present on admission. Penicillin, in this series, did not appear to have any effect on the symptoms and signs of the acute phase of the illness, but other authors are quoted who have, in contrast, reported that it did considerably influence the acute illness.

As the authors point out, the usual theory of the causation of rheumatic fever supposes that some substance produced by the streptococcus during the acute respiratory illness initiates the chain of events leading to rheumatic fever, and that, after the respiratory infection, the continued presence of the organism is not essential. Support for this view comes from the fact that few or no streptococci may be found in the throat of patients with rheumatic fever, and previous reports that penicillin does not influence the course of the disease.

Mortimer and his colleagues quote evidence which suggests that streptococci do persist, though in small numbers, in the oro-

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*500,000 units four-hourly for ten days, followed by procaine penicillin 600,000 units twice a day for eleven days, followed by one injection of benzathine penicillin, 1,200,000 units.

pharynx after infection with an epidemic strain for many months and that this persistent colonization is important in relation to rheumatic fever. Several studies indicate that it is the persistence of Group A streptococci in the oropharynx or elsewhere that may be responsible for this disease, and that penicillin given for long enough, and in a dosage adequate to eradicate the organism, favourably influences its course. In this investigation, penicillin was found to have an effect upon the valvular lesion, suggesting that the streptococcus continues to participate in the rheumatic reaction even after acute symptoms appear; the organism was recovered from the oropharynx in only 15 per cent of these cases so that it is possible (though it is specifically disclaimed that their data demonstrate this) that penicillin exerted its antibacterial effect at the site of the lesion the progress of which it had seemed to influence, namely the cardiac valves. Several previous workers have reported that they were able to culture haemolytic streptococci from the cardiac valves of patients who had died from acute rheumatic fever. The administration of penicillin, therefore, may be the most important part of the treatment of rheumatic fever. As it influenced the development of valvular disease without affecting the acute symptoms and signs, they suggest that the pathogenesis of each may be different.

This important paper is one of a number which indicate that rethinking about rheumatic fever is going on; there is a definite tendency to move away from theories based on immunological reactions continuing long after the streptococcus has disappeared, towards the view that in some way the living streptococcus is responsible for the manifestations seen. Clearly, if this new view is confirmed, and it becomes possible to treat rheumatic fever when it has already appeared, then it is no longer necessary to treat the acute respiratory illness with antibiotics solely to prevent the development of that complication, as many have felt it necessary to do in the light of evidence presented by Cantanzaro et al. (1954), Denny et al. (1949), and others. It follows also that if penicillin will prevent serious damage when given soon enough in rheumatic fever, there is a pressing need for early diagnosis; this imposes a special obligation on the general practitioner.

All this must surely make one think again about the problem of acute glomerulo-nephritis. In this disease, also, the evidence for an immunological reaction, initiated by the streptococcus during the acute respiratory episode, which then proceeds independently of that organism, is no more convincing than in the case of rheumatic fever. This theory was first put forward to explain the latent interval that was so often observed to occur between scarlet fever and the subsequent appearance of acute nephritis; a similar interval
occurs in serum sickness and it was suggested, therefore, that a similar mechanism underlay both. What was thus no more than a speculation about the nature of the process leading to acute diffuse nephritis was taken up so eagerly that it became inexpedient to diagnose that disorder unless a latent period could be demonstrated. The need to explain those cases that appeared too soon after the respiratory infection to be acceptable was met by the label of "focal nephritis" and the many inconsistencies that have flowed from this were well reviewed by Rudebeck (1946).

Yet it is debatable to what extent a latent period is a constant feature of either glomerulo-nephritis or rheumatic fever. A detailed study of 12 out of 15 patients with rheumatic fever, who had been followed from the time of the acute respiratory infection, revealed little evidence of a latent interval in 9 of them; lassitude, anorexia, loss of weight and a raised E.S.R. were to be found from 14 to 40 days before the appearance of fever and arthritis, and in 3 of the 4 persons in whom a definite latent period was observed activation of the disease process may have been induced by re-infection with a different streptococcal type (Rantz 1945). The early observations on post-scarlatinal nephritis took little account of this possibility and it was not realized how often it occurred. An analysis of routine laboratory work in American Air Force camps touches upon 36 patients with streptococcal infections who subsequently developed rheumatic fever; in 28 instances a different streptococcal type was found at that time and in 4 other cases no streptococcus was cultured at all (Ravenswaay, 1944). Moreover, the latent interval would seem often to have been the gap between the acute infection and the time that clinical signs of acute nephritis were first noted and it is not known how long the kidney might have been affected. Often the diagnosis would first be made on the appearance of oedema; the favourite explanation for this phenomenon has been a generalized capillary damage but recent evidence suggests that the oedema fluid is a transudate and that renal retention of salt and water is more important (Earle and Seegal, 1957). If this is so, then it is more likely that the necessary reduction in renal function preceded, by some time, the appearance of oedema than that the two coincided. There is, indeed, some evidence that the kidney is involved in some way quite early on; an early haematuria following streptococcal infections was found to be especially common in those who subsequently developed nephritis (Rammelkamp, 1956). Even in the reports of early writers on this subject it is clear that nephritis often followed immediately on scarlet fever without any latent interval (Turner, 1894; McCrae, 1913). The considerable confusion in the literature on this point, and on the related subject of the classification of acute nephritis, presents an opportunity to those who see
these cases early in their course and are sometimes, indeed, the only ones to see them.

The two main difficulties about accepting any theory of the causation of acute nephritis that would implicate the streptococcus directly are the inconstancy of the recovery of the organism from the throat or nose and the rarity of finding it in the urine. It has been shown that it is common to find Group A streptococci in excised tonsils when pre-operative swabbing has failed to isolate them (Rantz, 1941; Nelson, 1948), and, while there are, indeed, some early reports, such as those referred to by Ophuls (1917), and Turner (1894), in which streptococci are said to have been demonstrated in the urine or kidneys of these patients, it is now, in any case, realized that the absence of an organism from the urine does not necessarily imply that it is not present in the kidney; the work that has been done on biopsy of the kidney shows that in some cases of renal infection the organism may only be cultured from material obtained in this way (Muehrcke, 1955).

The pathology of acute diffuse nephritis also appears distinct from that seen in other states in which infection is believed to play the major or only role, such as pyelonephritis and some cases of subacute bacterial endocarditis. Whether it is therefore necessary to postulate two completely different causative mechanisms is not clear and it may be relevant to consider that the two groups differ in the nature of the infecting, or responsible, organism, in the acuteness of the disease process and in the point of time at which the kidney is likely to be available for examination.

In this uncertain situation the experience of two clinicians is interesting; Sen (1946), reporting from India, and Razzaz (1949), from Jordan, claimed that penicillin produced a striking improvement in acute nephritis in children. It would certainly seem worthwhile, in the light of all these considerations, and on the assumption that it is still present in the body and responsible for the manifestations of acute nephritis as well as those of rheumatic fever, to try and eradicate the streptococcus from wherever it may be. The evidence from the literature is that at least 10 days of penicillin in high doses are necessary to achieve this.

For the past year this practice of six partners, looking after 16,000 patients, and in close co-operation with the Public Health Laboratory at Stafford, have been following the urines of patients after streptococcal sore throat. In May, 1959, Mrs B., aged 29, was seen with a sore throat from which a Group A streptococcus (subsequently shown to be type 4) was cultured; two days later she was worse and was put on oral penicillin. Urine was collected on this day but did not arrive at the surgery till two days after and,
although this specimen showed the typical features of the urinary syndrome of acute nephritis, the next specimen, two days after the commencement of penicillin, showed only a few leucocytes. Subsequent urines were normal.

The experience of this case and the reports from the related field of rheumatic fever suggested that penicillin was worth trying in cases of acute nephritis, and four such cases, and one case of rheumatic fever, have since been treated by the author with 10 to 17 days of penicillin; so impressive have been the results that it is considered justifiable to make this preliminary communication of them. The number of cases is obviously far too small to be significant and, moreover, all were children, but, as it is likely to be impossible for any one doctor—or even a partnership—to collect enough cases to be able to present a significant experience, and as no specific therapy is available for acute nephritis, the results in even so small a series are perhaps worth presenting so that others may be encouraged to try the effects in their own cases or to put forward their own views.

The full details of these four cases of acute nephritis will be published elsewhere as part of a general report on our study here. The most dramatic effect of penicillin was on the temperature which fell in three patients, from 101.8°F., 103.8°F., and 105.4°F. respectively, to normal within 24 hours; the other child, the first to be so treated, had been having intermittent episodes of fever and earache, according to the mother, for four weeks; her temperature took 72 hours to fall from 102.8°F. to normal but she had some difficulty in swallowing the oral penicillin which was first prescribed. The last two patients, both aged 4, were given 600,000 units of procaine penicillin, intramuscularly, daily for 12 and 14 days. The urinary changes returned to normal rather more slowly but followed a continuously favourable course from the first day of treatment so that only a trace of albumin was detectable on the 4th, 5th, 6th, and 9th days respectively. All urines showed numerous red cells and granular or cellular casts, or both, in the early stages.

The case of rheumatic fever also did well; this was a boy of 7 who had been unwell for 15 days after a streptococcal sore throat, treated with aspirin alone, before he developed pain on movement at his left hip, followed two days later by swelling and pain in his left wrist; nose and throat swabs at this stage grew no streptococci, but, on the third day after starting intramuscular penicillin (200,000 units of aqueous, combined with 600,000 units of procaine penicillin) and salicylates, his temperature was normal. The next day the swelling of the wrist had gone and salicylates were stopped on the fifth day without any recurrence of fever or symptoms. His E.S.R.
was normal on the twenty-second day. He was allowed up on the twenty-third day and has been perfectly well ever since. He still receives prophylactic oral penicillin. At no time were cardiac abnormalities detected on clinical examination.

It certainly appeared that in these four cases of acute nephritis and one case of rheumatic fever, all in the early stages, penicillin provided a specific therapy; as there is only one way in which it is known to do so, it seems inescapable that it must have exerted an effect on a sensitive organism present somewhere in the body and the accumulated experience of many authors leaves little room for doubt that this organism was the streptococcus. The serological results that will clarify this point are not yet available; meantime it is interesting to note that Group A streptococci were not isolated from two of the cases of acute nephritis and that, by the time the arthritis appeared in the case of rheumatic fever, the organism could not be shown to be in the nose or pharynx; in this patient the only local evidence of an active disease process was in the joints.

General practitioners have the opportunity of seeing these diseases at an earlier stage than hospital physicians but usually see too few to be able to reach conclusions about the effects of treatment. It would undoubtedly be valuable to collect individual reports from those who have such cases under their care; it would be very interesting to see in what sort of case penicillin was most clearly of benefit, but, even if it were not tried, careful and full case reports, in sufficient numbers, would represent a contribution to this important subject that no-one else is in a position to make. If others are interested, the writer is willing to receive such case reports and to circulate any significant findings. In acute nephritis, reports ought to include, as a minimum, records of accurately taken temperature readings, a nose and throat swab taken before the start of treatment (if the local laboratory knows the swabs are from a case of acute nephritis it is possible to arrange for typing of any streptococcus grown), a laboratory report at least on the initial urine and measurement of the blood pressure in addition to the clinical data.

One other point is of possible interest; it is well known that the manifestations of acute nephritis may first be seen when the scarlet fever patient develops some complication such as otitis media or lymphadenitis and, indeed, that haematuria may coincide with sudden enlargement of the cervical glands (Turner, 1894). In two of the four cases of acute nephritis seen, a swelling of the gland at the angle of the lower jaw on one side preceded the onset of nephritis, by 1 day in one case, and by 5 days in the other; both were seen at this stage and it was observed that on the day that the
nephritis began the glandular swelling greatly increased, being associated in one patient with an enlargement of the tonsil on the same side: but only part of this swelling was due to the gland itself—some was due to a swelling of the surrounding tissues. There was no inflammation of the overlying skin, but it was clear that the degree of swelling was more than could be accounted for by the gland, the size of which could quite easily be assessed. This phenomenon, a swelling of the periglandular tissues, appearing on the same day as the nephritis, so far as can be ascertained, has not been mentioned in the literature, and it would be interesting to know how often it occurs.

Summary

Attention is drawn to recent evidence that the continuing presence of the living streptococcus is responsible, in some way, for acute rheumatic fever and that penicillin has been found by some authors to inhibit the later development of valvular lesions of the heart, and by other to improve the acute symptoms.

Several considerations suggest that penicillin is worth trying in cases of acute glomerulo-nephritis and the wholly favourable results in four such cases, in children, and in one case of rheumatic fever, are described.

In two of these cases of acute nephritis, a swelling of the tissues around an enlarged tonsillar gland on one side was noted to coincide with the onset of nephritis.

It is suggested that it would be valuable to collect case reports of these diseases from general practitioners and the author is willing to receive such reports and to summarize the results for those who are interested.

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