PART II

EDITORIAL  URAEMIC NEUROPATHY

Chairs: U Binswanger
       A Fournier
Uraemic Neuropathy

P K THOMAS
Royal Free Hospital, London, England

Uraemic neuropathy was largely unrecognised until the introduction of chronic haemodialysis. Reports of symptoms suggestive of peripheral neuropathy in the earlier literature are difficult to evaluate because of inadequate documentation. Even as late as 1961, Marin and Tyler reported two cases of neuropathy in association with 'hereditary interstitial nephritis', but were uncertain as to whether the neuropathy was due to the uraemic state or whether it was related to the underlying hereditary disorder. The initial accounts of peripheral neuropathy occurring in patients under treatment with haemodialysis for chronic renal failure were those of Hegstrom et al (1961, 1962). At this stage, the possibility that the neuropathy was caused by the dialysis had to be entertained.

The first substantial description of uraemic neuropathy was that of Asbury, Victor and Adams (1963) who documented four cases of a mixed motor and sensory polyneuropathy occurring in association with severe chronic renal failure. None had been treated by haemodialysis. As the causation of the renal failure was diverse, it was concluded that renal failure itself, being the common denominator, had been responsible for the neuropathy. Hegstrom et al (1962) and Konotey-Ahulu et al (1965) demonstrated that the neuropathy could be improved by haemodialysis and a later study by Jebson, Tenckhoff and Honet (1967) clearly related the onset of peripheral neuropathy in nondialysed cases to deteriorating renal function. A number of studies have established that the development of neuropathy correlates with a reduced glomerular filtration rate but poorly with the blood urea and creatinine levels.

The incidence of peripheral neuropathy in chronic renal failure is difficult to assess and has varied considerably between various series. The reasons for this are multiple and include differences in the definition of neuropathy and in case selection. Most of the series have been on patients accepted for inclusion in
chronic dialysis programmes. Studies on series of cases treated conservatively, such as that of Nielsen (1971) have yielded a frequency of clinical neuropathy in the region of 50 per cent. In patients accepted for dialysis programmes, the incidence has fallen as the criteria for inclusion have matured. In the initial 20 cases accepted at the Royal Free Hospital, the incidence was 75 per cent (Konotey-Ahulu et al, 1965). As an example of the current situation, the status of cases at the time of initiation of treatment in the renal dialysis unit at St Leonard’s Hospital, London, are shown in Table I. Approximately 20 per cent had symptoms of neuropathy.

<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>Final</th>
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<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>85 (79)</td>
<td>67 (88)</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>3 (3)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Sensory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>numbnss</td>
<td>10 (9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>paraesthesiae</td>
<td>6 (6)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>‘restless legs’</td>
<td>6 (6)</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Total</td>
<td>107 (100)</td>
<td>76 (100)</td>
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</table>

The clinical features of uraemic polyneuropathy display no particularly distinctive features. Sensory symptoms predominate. Muscle cramps have not been included; these are encountered in many patients, most commonly in relation to dialysis itself and show little obvious relationship to the occurrence of clinical neuropathy. Since cramps are not generally a feature of other neuropathies, it is likely that they are related to fluid and electrolyte disturbances. The sensory symptoms consist of feelings of numbness and tingling paraesthesiae, usually in the feet, less commonly also in the hands. The occurrence of ‘restless legs’ as a symptom of uraemic neuropathy was first noted by Callaghan (1966) and was later commented upon by Thomas et al (1971). On the other hand, Neilsen (1971) was less impressed. In his material he found that ‘restless legs’ occurred as a symptom with equal frequency in cases with and without evidence of neuropathy. In the present series of cases from St Leonard’s Hospital under treatment by chronic haemodialysis, if those patients who reported ‘restless legs’ as a symptom at the time of their initial assessment are taken together with those who reported it during later assessments, it occurred in 13 individuals, nine of whom had collateral evidence of neuropathy, either in the form of symptoms or signs, or in the form of abnormalities of nerve conduction. Although this suggests a relationship to neuropathy, the numbers are small, and a $\chi^2$ test is not significant. From these observations, there is therefore no statistical confirma-
tion that ‘restless legs’ are related to neuropathy rather than being due to some independent effect of the metabolic derangements. They are, for instance, a symptom of hypercapnic states, where there is no associated evidence of neuropathy (Spillane, 1970).

It is of interest that pain and hyperaesthesiae were totally absent from this series. The significance of this in relation to the pattern of nerve fibre loss has been considered by Thomas (1974). Unpleasant dysaesthesiae such as ‘burning feet’ are occasionally encountered in cases of severe neuropathy. Muscle weakness related to neuropathy is less common. In two of the patients in the present series, there was an almost pure motor neuropathy, in one of whom it was severe.

The incidence of abnormal signs at the time of the initial assessment is shown in Table II. Slightly more patients than had symptoms, 21 as compared with 15, exhibited abnormalities on examination. A proportion of patients, therefore, have an asymptomatic neuropathy. The commonest abnormalities are depression or loss of the ankle jerks and impairment of vibration sense in the feet. Cutaneous sensory loss is less frequent, as is loss of postural sensibility. Loss of joint position sense can, at times, be severe. In one patient from the Royal Free Hospital with severe sensory loss, but with relative preservation of motor power, the postural loss resulted in a marked sensory ataxia and such severe pseudobulbar palsy that an extrapyramidal disturbance was initially considered to be present.

### Table II  Incidence of signs of neuropathy in chronic dialysis cases at time of initial assessment and at most recent follow-up examination

<table>
<thead>
<tr>
<th></th>
<th>Initial %</th>
<th>Final %</th>
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<tbody>
<tr>
<td>No abnormal signs</td>
<td>79 (74)</td>
<td>52 (68)</td>
</tr>
<tr>
<td>Muscle weakness ± wasting</td>
<td>4 (4)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Tendon reflex depression or loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>knee jerks</td>
<td>8 (8)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>ankle jerks</td>
<td>16 (15)</td>
<td>14 (18)</td>
</tr>
<tr>
<td>Sensory loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>light touch</td>
<td>4 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>pin prick</td>
<td>4 (4)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>vibration</td>
<td>12 (11)</td>
<td>10 (13)</td>
</tr>
<tr>
<td>joint position</td>
<td>4 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>107 (100)</td>
<td>76 (100)</td>
</tr>
</tbody>
</table>

As has been noted by Nielsen (1971) isolated peripheral nerve lesions may be superimposed upon a generalised polyneuropathy. This was also true of a number of cases in the present series, the peroneal nerve being the most commonly affected. Such lesions tend to occur at the common sites for external pressure on nerves and suggest that the peripheral nerves in uraemic neuropathy, as in certain
other peripheral neuropathies such as that related to diabetes, are abnormally vulnerable to pressure. The reason for this is so far obscure.

Tyler (1965) originally pointed out that uraemic neuropathy apparently occurs more commonly in males. This was also the experience of Nielsen (1971) who found evidence of neuropathy in 62 per cent of males as against 32 per cent of females. The present series is unusual in that the incidence of clinical neuropathy was identical in males and females, being 32 per cent in the former and 33 per cent in the latter. If cases with defects of nerve conduction alone are also included, the proportions rise to 56 per cent in males as against 44 in females. In this series, which totals 107 cases, this difference does not reach statistical significance. The mean age of the males and females was identical, being 37.8 in the males and 37.4 in the females.

With respect to the course of uraemic neuropathy, conservative measures of treatment such as dietary protein restriction, or peritoneal dialysis performed only sufficiently often to maintain life, fail to arrest the progress of the neuropathy (but see Dyck et al, 1975). As has already been mentioned, early studies showed that the neuropathy can be improved by adequate periodic haemodialysis. Table I gives more recent findings from the cases at St Leonard's Hospital, where the proportion of asymptomatic cases increased in the dialysed cases as compared with their initial status. Table II shows that the same is true for the findings on examination. The follow-up period ranged from one to nine years. Of those who retained abnormal signs, it is evident that depression of the ankle jerks and impaired vibration sense again stand out as the salient findings. Nielsen (1971) and Bolton, Baltzan and Baltzan (1971), together with earlier workers, have established that recovery is substantially better after successful renal transplantation. Dobbelstein et al (1968) and Nielsen (1971) have drawn attention to a biphasic course of the clinical recovery: sensory symptoms and signs disappear with a time course of days or weeks; motor recovery takes considerably longer. Nielsen has suggested that the early rapid phase may indicate the resolution of a toxic effect of a retained metabolite on axolemmal function, with the delayed recovery indicating regeneration from a structural lesion of the axons.

Asbury, Victor and Adams (1963) demonstrated at necropsy in their four cases that there was a distal degeneration of nerve fibres in the limb, which was accompanied by chromatolysis in the anterior horn cells. A predominant loss of large myelinated fibres was demonstrated by Dyck et al (1971) and Thomas et al (1971) and the former authors confirmed that the degeneration was maximal distally. This suggests that uraemic neuropathy may be of 'dying-back' type, in which a progressive centrifugal degeneration takes place (Cavanagh, 1964).

Neuropathies can in general be subdivided into those in which there is primary damage to the myelin sheath with relative preservation of the axons, and those in which there is degeneration of the axons with consequent myelin breakdown, as occurs during Wallerian degeneration (Gilliatt, 1966). The most satisfactory way of detecting selective demyelination is to examine teased single nerve fibres.
Despite the fact that other workers such as Dinn and Crane (1970) and Dayan et al. (1976) claimed that uraemic neuropathy was primarily demyelinative in type, both Dyck et al. (1971) and Thomas et al. (1971) found the opposite, namely that there was relatively little evidence of selective demyelination. The two latter studies confirmed the earlier observation by Jennekens et al. (1969) that regions of paranodal demyelination and remyelination tend to occur repeatedly along the length of certain individual nerve fibres, with other fibres totally spared. This suggests that the demyelination is secondary to some abnormality affecting particular axons.

Nerve conduction velocity has emerged as one of the most useful parameters of peripheral nerve function, although there are others that can be utilised. In general, in neuropathies that give rise primarily to axonal destruction, conduction velocity is relatively mildly affected; values do not usually fall below 35 ms\(^{-1}\) in the upper limbs and 30 ms\(^{-1}\) in the lower. In demyelinating neuropathies, substantially lower values may be encountered. Until recently, alterations in conduction velocity have usually been related to structural changes in nerve (Thomas, 1971). However, there is now evidence that in experimental diabetes in rats, conduction velocity may be appreciably reduced in the absence of detectable morphological change (Sharma and Thomas, 1974). The mean value for motor conduction velocity in the peroneal nerve at the time of the initial assessment in patients with clinical neuropathy was 30.4 ± 6.1 ms\(^{-1}\), as compared with a control value of 49.7 ± 7.1 ms\(^{-1}\). Cases accepted for haemodialysis without symptoms or signs of neuropathy had an intermediate value of 41.1 ± 3.8 ms\(^{-1}\). This degree of reduction is consistent with the expectation for a neuropathy that gives rise predominantly to axonal degeneration, although the possibility of a direct metabolic effect on conduction unrelated to structural change has to be borne in mind. Recovery from the latter type of disturbance could be responsible for the initial rapid phase of improvement after successful renal transplantation. It could also account for the interesting observation by Nielsen (1971) that conduction in uraemic neuropathy may be decremental, that is, the degree of slowing of conduction increases with distance of propagation.

Dyck et al. (1971) examined nerve conduction in vitro in sural nerve biopsies from two cases of uraemic neuropathy. In their less severely affected case, they were able to demonstrate a gross diminution in the A alpha peak of the compound nerve action potential, with relative preservation of the A delta and C fibre peaks. This correlates well with the predominant loss of large myelinated fibres found histometrically. In their more severely affected case, all three peaks were depressed.

One so far unexplained feature relating to nerve conduction in uraemic patients is an abnormal tolerance to ischaemia, originally established by Christensen and Ørskov (1969). This is also exhibited by certain other metabolic states and was first demonstrated in diabetes. During ischaemia, after an initial phase of hyperexcitability, conduction progressively fails and is accompanied by
the development of muscle paralysis and sensory loss. In the diabetic subject, the excitability phase is prolonged and conduction failure is delayed (Seneviratne and Peiris, 1968). The same is true in uraemia although the changes are less marked. They were analysed by Castaigne et al (1972), who showed that this tendency is increased by dialysis. The interpretation of this interesting phenomenon is unknown, but any coherent description of the pathophysiology of peripheral nerve in uraemia must include an explanation. The conduction block during ischaemia may be related to an excess of potassium ions around the nodes of Ranvier which may accumulate there because of a failure of the metabolically-dependent ionic transfer mechanisms at the nodal axolemma. If the potassium ions diffused away more rapidly from the nodes in diabetes or uraemia, this would exert a protective effect against the action of ischaemia. Seneviratne and Weerasuriya (1974) claimed that the nodal gap substance is defective in diabetes and this might therefore be the explanation. The gap substance is a polyanionic material with a strong cation-binding capacity (Landon and Langley, 1971). The nodal gap substance has not so far been examined in uraemia, but Sharma and Thomas (1974) failed to confirm the observation by Seneviratne and Weerasuriya in diabetes.

The central problem concerning uraemic neuropathy is its causation. Initially suggestions were advanced that the neuropathy was related to vitamin deficiency, either because of the poor nutritional state of the patient or because water soluble vitamins were removed by dialysis. This suggestion was discarded when vitamin supplementation failed to improve the neuropathy, despite the fact that the clinical features and pathology possess similarities to those of nutritional neuropathy. In this connection, it is of interest that Loneran et al (1971) and Sterzel et al (1971) have demonstrated that red cell transketolase, a thiamine-dependent enzyme, is depressed in uraemia. They suggested that the transketolase depression could underly the development of neuropathy. However, it is not known what role transketolase plays in peripheral nerve metabolism. Moreover, Pryse-Phillips and Roberts (see Thomas et al, 1971) found no correlation between the red cell transketolase level and the presence or absence of neuropathy, either in chronically uraemic non-dialysed patients, or in patients receiving regular dialysis.

Another early suggestion brought up the possible influence of magnesium. Stewart et al (1967) found that in patients with uraemic neuropathy, nerve conduction velocity could be improved by reducing the plasma magnesium concentration by dialysis against a magnesium-free fluid. They extrapolated from this the prediction that reduction of hypermagnesaemia might protect against neuropathy. Conversely, Posen and Kaye (1967) suggested, on somewhat tenuous grounds, that hypermagnesaemia might protect against neuropathy. Hollinrake et al (1970) failed to find any significant difference between the mean predialysis plasma magnesium levels in patients undergoing chronic haemodialysis and a control group, or between patients with and without neuropathy. Furthermore,
in a group of cases, some of whom had clinical neuropathy, who were dialysed over a four month period with a magnesium-free dialysis fluid, no alteration in neurological signs or in nerve conduction were observed. No relationship between magnesium and neuropathy was therefore detected.

The improvement of the neuropathy with dialysis suggests that a retained metabolite may be responsible for the neuropathy. A variety of substances have been suggested, such as certain guanidine derivatives (Giovanetti et al, 1969), but none has been validated. In view of the clinical variability in the features of the neuropathy, more than one substance may be involved.

The Seattle workers have developed the view that a retained metabolite of middle molecular weight may be responsible (Scribner, 1965; Babb et al, 1971; Christopher et al, 1971). This is based on the fact that substances of such molecular weight traverse dialysis membranes much more slowly than smaller molecules such as creatinine and urea, and the view of these workers that the control and prevention of neuropathy is dependent upon increased hours of dialysis beyond that necessary to achieve chemical correction of uraemia. They were also of the opinion that uraemic neuropathy does not develop in patients under treatment by peritoneal dialysis, which is more effective in removing middle molecules. This has not entirely been the personal experience of the writer, who has seen neuropathy appear in patients treated by peritoneal dialysis.

A substance that has attracted attention recently is myo-inositol, although it is a little below this middle molecular weight range. Elevated plasma levels of myo-inositol are present in uraemia and the levels correlate closely with those of urea. De Jesus et al (1974) were able to demonstrate reduced motor nerve conduction velocity in rats on feeding them diets containing 35 per cent myo-inositol. The extrapolation from this to the suggestion by Clements et al (1973) that hypermyo-inositoluraemia may cause uraemic neuropathy, however, is probably an unwarranted step. These were observations on acute experiments in which structural lesions in the nerves were not demonstrated. From all that is known concerning uraemic neuropathy, it is clear that it only develops in chronic uraemia, and also that it is associated with structural changes in the peripheral nerves. It is not therefore surprising that Reznik, Thomas and Salway (1976) recently found no correlation between fasting plasma myo-inositol levels in undialysed patients with severe chronic uraemia and either the occurrence of neuropathy or with motor or sensory conduction. The same was true of a series of patients on chronic haemodialysis, from whom random plasma myo-inositol levels were obtained.

The causation of uraemic neuropathy therefore remains an enigma. Like diabetic neuropathy, it has attracted the attention of those neurologists who are interested in peripheral nerve, as both conditions provide readily accessible examples of neuropathy in which there is some possibility that the underlying mechanisms may be established.
Acknowledgments

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Open Discussion

THAYSEN (Copenhagen) Thank you for a most elegant presentation. As you mentioned, Kamp Nielsen from our group demonstrated the biphasic recovery of nerve conduction velocity after successful renal transplantation and forwarded the hypothesis that the initial fast phase of recovery is due to elimination of a toxic substance with direct action on the axon membrane, whereas the slow phase is due to regeneration of the anatomical derangement of the nerve. The still non-defined toxic substance with direct action on the nerve axon seems to be eliminated very rapidly by a well-functioning kidney and apparently has only a short lasting effect. To my knowledge, neuropathy does not develop in acute renal failure. Perhaps we may, therefore, learn more about uraemic toxins by comparing acute and chronic renal failure. This is also relevant to a symptom such as uraemic pericarditis, which is rare (if it ever occurs) in acute failure, but is not infrequent in chronic failure. Therefore this question: Do you know of good studies on nerve conduction in acute renal failure?

THOMAS I think that is an interesting point. Certainly in acute renal failure one does not see uraemic neuropathy. There have been some histological studies
claiming to have found changes related to acute renal failure, but I personally find these unimpressive. I agree that it may be that one is dealing with a different toxic metabolite that is retained in chronic renal failure. It is also possible that a substance has to be present for a long time before it has any effect. Certainly we find that with myo-inositol there is a lag period of some weeks before one can see an effect in the experimental situation. With regard to this biphasic recovery, Kamp Nielsen has suggested that initially there is an effect on axolemmal function which can recover rapidly and that the slow recovery then implies axonal regeneration and other structural recovery mechanisms. We would like to know whether there is any relationship between these two or whether they are independant effects. There are still many problems to be solved.

ONEN  (Istanbul)  Just a few comments about acute renal failure in which the findings of neuropathy are not clinically symptomatic: we have some cases of acute renal failure — I suppose about 10 cases — in which we found changes in the nerve conduction velocity.