INTRODUCTION

There are essentially two types of nerve fibre degeneration. In so-called axonal degeneration the myelin does not show important changes unless the axons lose their continuity. Slowing of conduction remains limited to 10 or 20% of the normal value (Kaeser, 1965). Conduction is impossible once the axons are interrupted. The second type of nerve fibre degeneration is primarily a disease of Schwann cells. These cells envelop the axons and contain the myelin sheath. Schwann cell degeneration therefore leads to demyelination. The process of the so-called segmental demyelination has been studied carefully in the last decade (Weller, 1965). Demyelinated axons are still able to conduct; conduction velocity is, however, considerably decreased (Kaeser, 1965). Demyelination has to be considered in any neuropathy in which a loss of 40% or more of the normal conduction velocity occurs (Gilliatt, 1966).

Slowing of conduction is a well known feature of uraemic polyneuropathy (Jebsen et al, 1967). In an attempt to discover whether this is due to Schwann cell degeneration we tried to assess to what extent conduction may be slowed in uraemic neuropathy. In addition we studied peripheral nerves of four patients with severe renal insufficiency, three of whom had physical signs of neuropathy.

a. MOTOR CONDUCTION VELOCITY OF THE PERONEAL NERVE

Twenty-one healthy, adult volunteers and 50 patients with severe, irreversible renal insufficiency were examined. Serum creatinine levels were continuously higher than 100 mg/l in every patient. Patients with other causes for polyneuropathy than renal insufficiency were excluded from this investigation. At the time of examination treatment with intermittent dialysis — if indicated — had not yet started.
Patients were divided into three groups. Patients in the first group had no physical signs of neuropathy though a few of them complained of cramps, restless legs, pain or paraesthesia. In the second group physical signs of neuropathy were limited to abolished tendon reflexes, disturbance of vibratory sensibility and muscular atrophy; most patients in this group had symptoms of neuropathy. Patients in the third group had many symptoms and signs of neuropathy including a neurogenic paresis.

The conduction velocity of the fastest conducting motor nerve fibres (MCV) of the peroneal nerve was determined in the usual way. The temperature gradient along the lower limbs was not corrected. However, the temperature in the extensor digitorum brevis muscle or the difference in temperature 1 cm subcutaneously between knee and ankle was recorded.

RESULTS

The mean value for MCV in our 21 healthy volunteers was 52 m/sec ± 6 (Table I). In the first group of patients the mean value for MCV was 44.4 m/sec ± 7. This is significantly less than in healthy volunteers (Student's t-test, p = 0.0004). In the second group conduction had slowed further to a

<table>
<thead>
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<th>serum creatinine</th>
<th>signs of neuropathy</th>
<th>number of patients</th>
<th>mean MCV m/sec</th>
<th>standard deviation</th>
<th>lowest value</th>
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<td>26</td>
<td>52.3</td>
<td>6</td>
<td>42.8</td>
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<tr>
<td>&gt;100 mg/l</td>
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<td>14*</td>
<td>44.4</td>
<td>7</td>
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<tr>
<td></td>
<td>paresis</td>
<td>6**</td>
<td>37.8 oo</td>
<td>3</td>
<td>30.9</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>26.3 oo oo</td>
<td>5</td>
<td>20.3</td>
</tr>
</tbody>
</table>

*0 lower than normal, Student's t-test, p = 0.0004

**0 lower than in patients without signs of neuropathy, Student's t-test, p = 0.002

***0 lower than in patients with only few signs of neuropathy, Student's t-test, p ≈ 0

*not measurable in 1 other patient

**not measurable in 3 other patients

mean value of 37.8 m/sec ± 3. This is significantly less than in the first group (Student's t-test, p = 0.002). In the third group the mean MCV had fallen to 26.3 m/sec ± 5. This is again significantly less than in the second group (Student's t-test, p ≈ 0) and only about 50% of the mean value for MCV in healthy volunteers. The lowest value in the third group was also about 50% of the lowest normal value (20.3 and 42.3 m/sec). Examination of MCV was impossible in four patients due to atrophy of the extensor digitorum
brevis muscles.

The mean temperature in the extensor digitorum brevis muscle was lower in the ambulant volunteers than in the, mostly bedridden, patients (28.9 and 30.8 centigrades respectively). The mean age of the volunteers was lower than the mean age of the patients (27 and 38 years respectively). The difference in mean age and in mean temperatures between volunteers and patients had a reverse effect on MCV. It did not seem probable that the factors age and temperature together had a considerable influence on the difference for the mean values of MCV between volunteers and patients.

b. MICROSCOPICAL EXAMINATION OF PERIPHERAL NERVES

MATERIAL AND METHODS

The peripheral nerves of the lower limbs of three patients who had had a severe, irreversible renal insufficiency were examined. Two of these patients had shown symptoms and signs of neuropathy. A sural nerve biopsy was studied from one patient who developed physical signs of neuropathy during treatment with intermittent dialysis.

Samples of these nerves were fixed in formol saline. Paraffin and frozen sections were cut and stained with haematoxylin-azophloxine and oil red o. Other sections were stained according to the methods of Klüver Barrera, Holmes, Klüver Barrera and Holmes, and Van Gieson. Isolated nerve fibres were teased after post fixation in 1% osmium tetroxide and maceration in 60% glycerine (Vizoso & Young, 1948).

RESULTS

The pattern of degeneration appeared to be identical in all the examined nerves. The degree of degeneration varied according to the location of the nerve and the severity of the physical signs of neuropathy. We will describe here only the findings in one peripheral nerve in each of the two patients with the most severe neuropathy.

Case 1: This 23 year old man had a chronic renal insufficiency of unknown origin. Intermittent dialysis was started in March 1967. He had at that time neither symptoms nor signs of neuropathy. In August 1967 he complained of burning feet. In September 1967 he developed a stepping gait. Neurological examination revealed weakness and atrophy of the distal muscles of the lower limbs and a disturbance of sensation of both feet. The Achilles tendon reflexes were abolished. Motor conduction velocity in the peroneal nerve could not be determined due to atrophy of the extensor digitorum brevis muscles. A sural nerve biopsy was taken.

NEUROPATHOLOGICAL EXAMINATION

The macroscopic appearance of the sural nerve was normal. On microscopic examination of longitudinal and transverse sections the number of myelinated
Figure 1. Eight nodes of Ranvier of several nerve fibres. The first three nodes are slightly irregular. In the next four nodes myelin seems to have somewhat retracted. There is a beginning demyelination in the last fibre. x 900
nerve fibres was found to be greatly reduced. Many of the remaining fibres showed signs of degeneration. Some axons were varicose, others were twisted. The myelin of some nerve fibres was swollen and had lost its normal structure. Myelin clumps were seen in a number of degenerating fibres. There was a slight increase in intrafascicular nuclei and a moderate endoneural fibrosis. The perineurium was normal. Vascular abnormalities were not seen. There was no accumulation of the abnormal metabolic substance.

Many teased nerve fibres were fragmented or showed myelin changes characteristic of Wallerian degeneration. The nodes of Ranvier in the remaining fibres had an irregular appearance; the myelin often seemed to be retracted from the nodes (Figure 1). Myelin retraction had definitely progressed to demyelination in many fibres (Figure 2). Complete demyelination in a sequence of Schwann cells or even in one Schwann cell was not seen. Frequently there were, however, many short parts of one nerve fibre demyelinated. Remyelinated segments, recognizable by their narrow diameter and small internodal distance, were seen in relatively few nerve fibres.

Transverse sections of the sural nerve were stained according to Kultschitzky-Pal and counterstained according to Van Gieson. Onion bulb formation was not seen.

Case 2: At the age of 42 years renal function of this previously healthy man was found to be diminished. A proliferative glomerulo-nephritis was diagnosed. Renal insufficiency progressed gradually in the next two years. He complained of cramps, restless legs and dysesthesia in March 1967. In June 1967 creatinine clearance

Figure 2. Segmental demyelination at several places in one nerve fibre.
Case 1. x 200
was only 1.5 ml/min. Neurological examination at this time revealed abolished
 tendon reflexes, disturbance of sensibility and muscular weakness distally on
 both lower limbs. Motor conduction velocity in the peroneal nerve was 23 m/
 sec at both sides. He died suddenly two days after this examination.

NEUROPATHOLOGICAL EXAMINATION
The tibial nerve at the height of the internal malleolus showed no macroscopic
 abnormalities. On microscopic examination of longitudinal and transverse
 sections the number of nerve fibres was found to be greatly reduced. The
 majority of the remaining nerve fibres showed degeneration of both axon and
 myelin. In the oil red o stains droplets of neutral fat were seen in degenera-
 ting fibres, but also outside the fibres in macrophages and extracellularly.
 The number of intrafascicular nuclei had slightly increased. Vascular abnor-
 malities were not seen. There was no accumulation of abnormal metabolic
 substances.

Most teased nerve fibres were completely fragmented; many fibres
 showed ellipsoids and ovoids. Most nodes of Ranvier were irregular in form,
 many were slightly widened. Widening of nodes had changed into demyelina-
 tion in some fibres (Figure 3). Completely demyelinated segments were not
 seen. Remyelinated segments were present in relatively few fibres (Figure 3).

Figure 3. a. segmental demyelination. b. remyelination. Case 2. x 800
DISCUSSION

Our nerve conduction studies indicate that at least in patients who were not treated by intermittent dialysis, motor conduction in the peroneal nerve slows down with increasing neuropathy to 50% of the normal value. Slowing of this amount may be explained by demyelination.

Three studies have been published about microscopic investigation of the peripheral nervous system and the spinal cord of cases with uraemic polyneuropathy (Marin & Tyler, 1961; Asbury et al., 1963; Forno & Alston, 1967). Demyelination was suspected but could not be proved. In a short communication Hollinrake and Thomas reported in 1967 a study of teased nerve fibres of two sural nerve biopsies of patients who were treated with intermittent dialysis. In the teased nerve fibres paranodal demyelination and remyelination could easily be recognized; axonal degeneration was also present. Our investigation confirms these findings, not only for patients who were treated with intermittent dialysis but also for patients without this treatment. In all our cases there was a preponderance of axonal degeneration; demyelination was, however, also present in many fibres. Completely demyelinated segments were not seen. There was always some myelin left in the central part of the Schwann cells, around the nuclei. Frequently nerve fibres had many short, demyelinated parts.

Remyelination was present in only a relatively small number of fibres. Schwann cell proliferation was not excessive. Onion bulbs were not seen. More remyelination and more Schwann cell proliferation may perhaps be found in patients who have been treated for longer periods with intermittent dialysis.

SUMMARY

Nerve fibre degeneration in uraemic polyneuropathy is characterized by axonal degeneration and segmental demyelination. Demyelination may explain the slowing of conduction which amounts to 50% of the normal value in the most severe cases of uraemic polyneuropathy.

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