PERIPHERAL NERVE CHANGES IN AMYLOID NEUROPATHY

BY

P. K. THOMAS AND R. H. M. KING

(From the Department of Neurology, the Royal Free Hospital, London WC1)

The initial description of the pathological changes in the peripheral nervous system in amyloidosis was given by De Navasquez and Treble (1938), although the case reported by De Bruyn and Stern (1929) as an example of hypertrophic neuropathy was probably the same condition. De Navasquez and Treble found extensive involvement of the dorsal root and sympathetic ganglia in their case. The fat cells around the ganglia were delimited by a thin layer of amyloid, and deposits were present in the walls of small arteries. There were nodular extracellular deposits within the ganglia, and the ganglion cells were surrounded and appeared compressed by masses of amyloid. Deposits, which radiated out from the arteries, were present in the peripheral nerve trunks. Nerve fibres were seen to be distorted by deposits in the connective tissues. Similar changes were recorded by Götze and Krücke (1941) and in the hereditary Portuguese cases (Andrade, 1952; Horta and Trincão, 1963). Krücke (1959, 1963), in particular, has studied the peripheral nerves in amyloidosis, and is of the opinion that the dorsal root ganglia represent the site of most severe involvement.

The median nerves may be indirectly affected by compression in the carpal tunnel because of infiltration of the flexor retinaculum with amyloid. This occurs in the Indiana form of hereditary amyloidosis (Rukavina et al., 1956) and in the similar family from Maryland (Mahloudji et al., 1969). It is also encountered in amyloidosis related to myelomatosis (Dayan, Urich and Gardener-Thorpe, 1971).

Observations on the ultrastructural changes in amyloid neuropathy have so far been limited. Dyck and Lambert (1969) reported findings obtained in sural nerve biopsies from two dominantly inherited cases. Unmyelinated axons were "virtually absent" and groups of Schwann cell processes without such axons were abundant. Evidence of degeneration of myelinated axons was observed and the characteristic amyloid fibrils were seen associated with collagen fibrils. A probable increase in the number of mast cells was also noted.

A further ultrastructural study was reported by Coimbra and Andrade (1971a, b) from observations on sural nerve biopsies in 5 cases of the Portuguese type of inherited amyloidosis. Degenerative changes were found in myelinated nerve fibres with Büngner band formation. Degeneration of unmyelinated axons was considered
to be less obvious and regenerative activity was little in evidence. Deposits of amyloid fibrils were prominent in the advanced cases but sparse in the earlier cases. They were mainly endoneurial in distribution and were either interstitial or perivascular. A relationship to collagen fibrils and fine fibrillar material in the endoneurium was noted and occasionally the amyloid fibrils fused with Schwann cell basal laminae and were even considered to invade the Schwann cell cytoplasm. The changes in the nerve fibres were believed to antedate the amyloid and it was suggested that its deposition was a secondary event.

The present report describes the ultrastructural observations obtained in nerve biopsies from 4 cases of amyloid neuropathy, 3 of which were sporadic and in one of which there was a family history of similar disorder. The clinical features were in general similar to those of the Portuguese variety of the disease. A preliminary account of the findings was given by Thomas and King (1972).

**CASE REPORTS**

**Case 1** (Maida Vale Hospital No. 65495). In 1963, when he was aged 57, the patient insidiously developed numbness and tingling in his feet which gradually spread up as far as his knees. This was accompanied by spontaneous aching and stabbing pains in both legs. A year after the onset of these symptoms, he became impotent. In 1966, he noticed weakness in both legs and tingling and weakness in both hands. He was admitted to Ipswich and East Suffolk Hospital (Dr. John Hughes). Examination showed generalized weakness and wasting of both legs, and wasting of the forearm and hand muscles. The tendon reflexes were absent in the legs and the plantar responses were unobtainable. Appreciation of light touch, pin-prick and vibration was absent below the knees. His haemoglobin was 65 per cent and the ESR 14 mm at one hour. The CSF was normal except for a protein content of 120 mg/dl. A chest X-ray showed no abnormality and myelography was negative. The fasting blood sugar level was normal, as was vitamin B₁₂ absorption (Schilling test). A barium meal revealed a small hiatus hernia.

Over the following two years his condition deteriorated slowly. He was readmitted in May 1968 because of a small hæmatemesis considered to be due to his hiatus hernia, which was confirmed by a further barium meal. Xylose absorption was impaired. Serum folic acid and vitamin B₁₂ concentrations were normal.

The patient was admitted to Maida Vale Hospital for further investigation in September 1968. He then also gave a history of troublesome constipation over the preceding year and of faintness on standing up suddenly for two years. He denied any disturbance of micturition. There was no family history of similar disorder. Examination showed bilateral cataracts and mild bilateral ptosis. The right pupil was unreactive to light on direct or consensual stimulation; the left responded sluggishly. Neither pupil constricted on convergence. Otherwise the cranial nerves were normal. In the limbs, there was symmetrical distal weakness and wasting, more marked in the legs. The tendon reflexes were present in the arms but absent in the legs; the plantar responses were unobtainable. There was distal loss of all forms of sensation in the arms and legs and healed ulcers over the left ankle and right shin. The peripheral nerves were not thickened. His blood pressure fell from 160/90 when lying to 125/75 on standing; examination of the cardiovascular system was otherwise normal. The liver and spleen were not palpable.

His haemoglobin was 10·7 g/dl, WBC 4,500/μl and ESR 17 mm at one hour. Routine urine testing was normal with no proteinuria. A glucose tolerance curve was normal, as were the plasma electrolytes; the blood urea was 57 mg/dl. The serum proteins were normal, with a normal electrophoretic pattern. Apart from a protein level of 80 mg/dl, the CSF was normal. A chest X-ray showed slight cardiac enlargement; an ECG and IVP were normal. Electromyography of
affected muscles showed chronic partial denervation. Motor nerve conduction velocity in the left median nerve was normal (51 m/sec); a reduced value was obtained in the left ulnar nerve (24 m/sec). No median or ulnar sensory action potentials were obtained on stimulation of the left index and fifth fingers with percutaneous recording at the wrist.

A radial nerve biopsy was performed in September 1968.

Case 2 (Royal Free Hospital No. 1B 167). In 1967, at the age of 55, the patient became anorexic and began to lose weight. In the following year mild proteinuria and a greatly enlarged liver were discovered. He was admitted to the Royal Free Hospital for investigation in June 1968 when he gave a three-month history of aching pain in both lower legs. A full blood count was normal. The ESR was 48 mm at one hour. Serum protein electrophoresis revealed elevated alpha one and gamma fractions. Liver function tests demonstrated slightly elevated serum alkaline phosphatase and 5-nucleotidase activities; liver biopsy revealed the presence of amyloid, as did a rectal biopsy. A chest X-ray was normal. There was no glycosuria, but a glucose tolerance curve showed a mildly diabetic response. Renal function tests were normal, but there was proteinuria (1·1 g per twenty-four hours). Intravenous pyelography was normal. The serum cholesterol level was elevated (590 mg/dl).

The patient was readmitted in October 1969 for investigation of peripheral neuropathy. The pains in his legs had continued and were described as a constant aching in his feet and lower legs, followed later by burning sensations in the soles of the feet. Subsequently he noticed that he was unable to appreciate temperature with his feet and that his feet did not sweat. He was unaware of any weakness in his legs and had no symptoms in his hands. He reported feelings of dizziness and dimming of his vision on rising from a lying or sitting position, especially in the mornings. He complained of constipation, but had no difficulty with micturition. There was no family history of similar disorder.

Examination in October 1969 revealed bilateral ptosis and moderately dilated pupils. The right constricted on illumination, but there was no response on the left; neither reacted on convergence. The remainder of the cranial nerves were normal. There were no abnormal motor signs in the limbs. The tendon reflexes were symmetrical in the arms but absent in the legs; the plantar responses were flexor. No tactile loss was demonstrable but appreciation of pain and temperature was absent distally in both legs; vibration sense was impaired in the feet and tendo-Achillis pain was absent bilaterally. Joint position sense was intact. The peripheral nerves were not thickened. A starch-iodine sweating test showed that sweating occurred over the trunk, but was absent in both legs. His blood pressure fell from 150/95 when lying to 100/80 on standing. Both the liver and spleen were enlarged.

On this admission, a full blood count was again normal, but the blood urea level had risen to 80 mg/dl. The urinary protein content was 4.9 g/twenty-four hours. There was no glycosuria, but a glucose tolerance curve again showed a mildly diabetic response (fasting 85 mg/dl; maximum rise to 195 mg/dl at ninety minutes; 140 mg/dl at two hours). Faecal fat over a three-day period averaged 8.6 g/twenty-four hours. A xylose tolerance test showed defective absorption (urinary excretion of 0.35 g in five hours after 25 g orally).

Motor nerve conduction velocity in the right median and peroneal nerves was reduced (41 and 29 m/sec respectively). On stimulating the digital nerves of the right index finger, a sensory action potential of reduced amplitude (5 μV) was recorded over the median nerve at the wrist.

A sural nerve biopsy was performed in October 1969.

Case 3 (Royal Free Hospital No. 1C 7184). The patient was born in Greece of Greek parents. In 1963, when aged 21, he first noticed weakness and pain in his legs. Shortly after, he developed difficulty with micturition (difficulty in voiding) and impotence. Two years later he observed wasting of his calves and found that he was unable to detect pain and temperature in his feet and lower legs. Subsequently, he developed an atonic bladder with overflow incontinence, and the peripheral weakness and sensory loss in his legs increased. In 1969 he had become aware of wasting of his hand muscles and weakness for fine finger movements. He had suffered from diarrhoea ever since
the onset of his symptoms and by the time he was admitted in August 1970 4-5 motions per twenty-four hours were occurring.

He had three sisters and one half-brother who were healthy, as was his father. His mother had died at the age of 43 from “heart trouble.” She had suffered from weakness of the legs and diarrhea for some years before. Three maternal relatives were known to be similarly affected (fig. 1).

Examination at the time of his admission revealed normal cranial nerve function. There was bilateral weakness and wasting of the small hand muscles and generalized weakness and wasting in the legs, with total paralysis of all muscles below the knees. The tendon reflexes were sluggish in the arms and absent in his legs; the plantar responses were unobtainable. The appreciation of light touch was lost distally in the legs but was preserved in the upper limbs. Pain and temperature sensation was lost over the lower trunk and legs and was impaired distally in the upper limbs. Tendo-calcaneus pressure did not cause pain. Joint position sense was absent in the toes but was preserved in the fingers. Vibration sense was absent in both feet but was retained in the fingers. A starch-iodine test showed absent sweating over the legs. The peroneal nerves at the neck of the fibula and the radial nerves at the wrist were slightly enlarged. His blood pressure fell from 100/70 when lying to 70/40 on standing. The liver and spleen were not enlarged.

A full blood count was normal, as were the serum proteins, blood urea concentration and the plasma electrolytes. The ESR was 5 mm at one hour. A three-day fecal fat collection yielded a fecal fat level of 8.8 g/day. A xylose tolerance test showed slightly impaired absorption (urinary excretion of 3.2 g in five hours after 25 g orally). Chest X-ray was normal. An ECG showed first degree heart block.

Electromyography of the small hand muscles and of the quadriceps, tibialis anterior and extensor digitorum brevis muscles revealed changes of denervation. Motor nerve conduction velocity in the left median and ulnar nerves over the forearm was reduced (41 and 37 m/sec respectively). On stimulation of the digital nerves of the left index finger and percutaneous recording over the median nerve at the wrist, a sensory action potential of low normal amplitude (9 \mu V) was obtained, which had a normal latency to peak (3 msec). No ulnar sensory action potential was detectable.

A sural nerve biopsy was performed in August 1970.

**Case 4 (Maida Vale Hospital No. 75162).** In 1969, at the age of 61, the patient developed a feeling of coldness in his fingers and feet which slowly spread proximally as far as the wrists and knees. About two years later he became aware that he was unable to appreciate the temperature of bath

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**Fig. 1.—Pedigree of Case 3.** Propositus indicated by arrow; individuals considered to be affected from history are represented by half-filled symbols; line through symbol indicates death. Age when known, or age at death, given below symbols.
water with his feet. At about the same time he began to experience occasional stabbing pains in the legs and a little later a persistent aching in both lower legs. He became impotent and constipated, and on a few occasions had felt faint on standing up abruptly. He had no definite urinary symptoms. He also slowly became aware of wasting of his legs and of unsteadiness in walking. Apart from a myocardial infarct in 1961, his previous health had been good, and there was no family history of similar disorder.

He was admitted for investigation in November 1972. Examination showed small unequal pupils; the response to light was absent on the left and reduced on the right; they constricted normally on convergence. There was slight generalized wasting in the arms, with focal wasting of the small hand muscles. The small hand muscles were weak bilaterally, as were the finger and wrist extensors. There was generalized wasting and weakness in the legs, maximal distally. The right triceps and both ankle-jerks were absent; the other tendon reflexes were obtainable on reinforcement. The plantar responses were absent. The appreciation of light touch was lost in the hands and below both knees. Pain and temperature sensation was lost over a similar distribution. Joint position sense was impaired in the toes but preserved in the fingers. Vibration sense was lost in the feet but retained in the hands. The peripheral nerves were not thickened. A sweating test showed absent sweating over the trunk and limbs except in the axillae. Intradermal histamine failed to produce a flare in the legs, but did so on the forearm and on the abdominal wall. His blood pressure fell from 140/90 when lying to 90/70 on standing. The liver and spleen were not enlarged.

A full blood count was normal and the ESR was 8 mm at one hour. A bone-marrow biopsy was normal, as was a glucose tolerance test. The blood urea concentration was 23 mg/dl and the creatinine clearance was 109 ml/min. A three-day fecal fat collection yielded 3.5 g/day. Chest X-ray was normal. The CSF showed no pleocytosis but the protein content was 240 mg/dl.

Motor nerve conduction velocity in the right median and peroneal nerves was 46 and 31 m/sec respectively. No sensory action potentials were detectable on percutaneous recording at the wrist on stimulation of the digital nerves of the index and fifth fingers.

A sural nerve biopsy was performed in November 1972.

METHODS

Light microscopy.—Portions of nerve were processed in three ways. Transverse paraffin sections from material fixed in Flemming’s solution were stained with Kultschitsky’s haematoxylin (Gutmann and Sanders, 1943), counterstained with van Gieson’s stain, for the examination of the myelin sheaths. Others from material fixed in Heidenhain’s “Susa” solution were stained with haematoxylin and eosin, haematoxylin-van Gieson, Congo red, methyl violet, and Alcian blue. Finally, portions fixed in 10 per cent formol-saline were stained in block with one per cent osmium tetroxide for the examination of isolated nerve fibres by the method described by Lascelles and Thomas (1966).

Electron microscopy.—The specimens from Cases 1 and 2 were fixed by immersion in cold buffered osmium tetroxide. Those from Cases 3 and 4 were fixed by immersion consecutively in 2.5 per cent glutaraldehyde in phosphate buffer at pH 7.4 and one per cent phosphate buffered osmium tetroxide with 7 per cent sucrose. All specimens were dehydrated in graded concentrations of ethanol and, following transfer to propylene oxide, were embedded in Araldite.

Ultrathin sections (grey to silver interference colours) were cut with an LKB Ultratome III. The sections were collected on copper mesh grids without carbon support films except those destined for quantitative studies. They were stained with uranyl acetate and lead citrate and examined in a Siemens Elmiskop 101. Preliminary observations were made by light microscopy on 1 μm semi-thin sections stained with methylene blue, or with thionin and acridine orange, for selection of appropriate areas.

Counts of unmyelinated axons were made on prints enlarged ten times from micrographs taken at an initial magnification of ×2,600. Approximately one-quarter of each fascicle was counted, and an estimate made from this of the total fibre density in the fascicle.
RESULTS

Light microscopy.—There was gross depletion in the myelinated nerve fibre population in the biopsy specimens from Cases 1, 3 and 4. Fig. 3A (Plate XX), from Case 1, is representative of the appearances in all three.

The specimen from Case 2 (fig. 3B) showed a moderate depopulation, fibre density being reduced to 2,250 per mm². The mean fibre density for control subjects of this age (40–59) assessed by the same technique is 5,780 per mm² (O'Sullivan and Swallow, 1968). Measurements of myelinated fibre size distribution from Case 2 are shown in fig. 2A. In comparison with a control nerve from the same age group (fig. 2B), a predominant loss of the fibres of small diameter is evident.

![Graph showing fibre diameter distribution](https://academic.oup.com/brain/article-abstract/97/2/395/417549)

**Fig. 2.**—Size-frequency histograms for myelinated fibres in sural nerve. A, Case 2. B, Control subject aged 53 from O'Sullivan and Swallow (1968).

Examination of teased fibres was only possible in Case 2 because of severity of the myelinated fibre loss in the other nerves. This showed a mixed population of fibres. The majority displayed a normal relationship between internodal length and fibre diameter. In some, internodal length was inappropriately and uniformly short suggesting regeneration after axonal degeneration, and in others the appearances were those of remyelination after segmental demyelination, with single or multiple short intercalated internodes of reduced diameter.

In all four nerves, methyl violet or Congo red staining revealed the presence of amyloid deposits. These were most evident around endoneurial blood vessels (figs. 3c and d), but were also observed free in the endoneurium and in the epineurial connective tissues.

Electron microscopy.—The myelinated fibres showed evidence both of degeneration and regeneration. Groups of Schwann cell processes of the type associated with Büngner bands derived from the degeneration of myelinated nerve fibres (Ochoa and Mair, 1969b) were frequent. At times these contained myelin debris and were associated with regenerating axon sprouts (fig. 4A). At other times, clusters of several
myelinated axons were observed, indicative of regenerative activity (Thomas, 1968). In the biopsies from all 4 cases, there were numerous groups of flattened Schwann cell processes (fig. 4b) of the type associated with unmyelinated axons.

The number of unmyelinated axons was grossly reduced in the biopsies from Cases 1, 3 and 4. In each, the density was less than 10 axons per mm². They were more numerous in the biopsy from Case 2, although their density was again reduced. This was 11,000 per mm², which is substantially less than the normal value for this nerve which was found to be 29,000 per mm² for osmium fixed material (Ochoa and Mair, 1969a). A substantially higher density of 47,009 per mm² for glutaraldehyde fixed nerve was reported by Dyck, Lambert and Nichols (1972). In the present series, the biopsies from Cases 1 and 2 were fixed by osmium tetroxide and those from Cases 3 and 4 by glutaraldehyde.

Degenerative and "reactive" changes (Lampert, 1967) were observed in unmyelinated axons. These took the form of accumulation of filamentous material, mitochondria and dense lamellar bodies, or replacement of the axoplasm by finely granular material. Occasionally, axons were filled by branched smooth-walled tubules (fig. 5a).

Amyloid fibrils were observed in all four biopsies. These were frequently seen in relation to endoneurial capillaries, sometimes closely associated with reduplicated basal lamina (fig. 5b). Other deposits, often approximately circular in outline, occurred in the endoneurium not in association with blood vessels (figs. 6a and b). These tended to be interspersed with collagen fibrils (fig. 6b). In Cases 1, 2 and 4 they took the form of a felt-work of fibrils (figs. 6a and b). In Case 3, they tended to be organized into interlacing bundles (fig. 7a). The endoneurial deposits were sometimes observed in close relationship to Schwann cells, particularly those associated with unmyelinated axons. Such deposits frequently displaced and distorted the Schwann cells (figs. 6a and b). The amyloid fibrils were noted to invade the Schwann cell basal lamina, which was at times lifted away from the plasmalemma.

Although most of the deposits were intrafascicular, others were observed in the perineurium, where again they were often associated with the basal laminae of the cells. Deposits of various size were also observed scattered throughout the epineurial collagen.

High resolution images of the amyloid deposits demonstrated the characteristic straight unbranched filaments ~7 nm in width with parallel electron dense borders separated by an electron lucent gap (fig. 7c). The filaments were always extracellular in position: no intracellular amyloid was detected, either in Schwann cells or within any other cell type.

Lamellar inclusions (π granules of Reich) were present within Schwann cells associated with myelinated axons. Although no quantitative studies were undertaken, their numbers did not appear to be excessive. Inclusions with a regular crystalline appearance were observed within Schwann cells associated with unmyelinated axons and these were particularly numerous and large in Case 4 (fig. 7b). They were normally circular in outline with a diameter of ~0.5 μm. In
Case 4 they were often oval in outline with a maximal dimension of up to 4 \( \mu m \). They consisted of structures that contained regular arrays of 5 nm filaments in a hexagonal array with a centre-to-centre spacing of 12 nm (fig. 7D). At high resolution these appeared tubular. This material was sometimes subdivided by irregular clefts. In longitudinal section, it appeared lamellated with an apparent spacing of 10 nm. The bodies also occasionally contained clumps of electron dense amorphous or granular material (fig. 7D). They were bounded by an apparent double membrane (fig. 7D), although it was at times difficult to differentiate the inner membrane from the margins of the inclusion material.

**DISCUSSION**

The pattern of the neurological deficit was similar in our three sporadic cases and in Case 3, in which the disorder was probably dominantly inherited. Although histological confirmation has not been obtained in other members of the family, the symptoms in the patient's mother are strongly suggestive of amyloid neuropathy. The clinical features in the patient, who was Greek, corresponded to the pattern of neurological change in the Portuguese variety, as did the two cases of Greek origin reported from America by Dyck and Lambert (1969). The same pattern has previously been described in sporadic cases of primary amyloidosis (e.g. Chambers, Medd and Spencer, 1958). In all the present cases, distal sensory loss with an earlier and greater involvement of pain and temperature appreciation was a salient finding. It is of interest that Case 3 was diagnosed as syringomyelia in the initial stages of his illness. Autonomic involvement was also an early and prominent feature in all 4 cases. This included diarrhoea, bladder atony, impotence, postural hypotension and loss of sweating. Pupillary changes were present in 3 of the cases and were of Argyll Robertson type in Case 4. Distal motor changes in the limbs were a later feature in the development of the neuropathy. Except in Case 2 in which amyloidosis had been diagnosed before the onset of neurological symptoms because of the hepatic involvement, the particular features of the neuropathy in the other 3 cases had led to a presumptive diagnosis of amyloidosis being made before this was confirmed by nerve biopsy.

The ages of onset in the three sporadic cases were 57, 55 and 61. This contrasts with Case 3, in which symptoms began at the age of 21. In hereditary amyloidosis of the Portuguese type, the disease typically begins in the third decade, whereas in sporadic cases the onset is usually between the ages of 50 and 60 (Neundorfer, 1973).

Dyck and Lambert (1969) found that the loss of myelinated fibres in their 2 cases of dominantly inherited amyloidosis predominantly affected those of smaller diameter. This is confirmed for a sporadic case in the present study. Our 4 cases all showed severe loss of unmyelinated axons, and in 3 they were almost absent, again confirming the findings of Dyck and Lambert. They contradict those of Coimbra and Andrade (1971b), who were less impressed with unmyelinated fibre involvement in their series. This pattern of nerve fibre loss, namely a preferential depletion of unmyelinated and small myelinated axons, correlates well with the predominance
of pain and temperature sensory loss and the autonomic changes (Dyck and Lambert, 1969; Dyck, Lambert and Nichols, 1972).

Spontaneous pain, consisting of either lightning pains or constant aching, can be a troublesome aspect of amyloid neuropathy and may be the presenting symptom (Ritama and Björkestén, 1954; Van Allen, Frohlich and Davis, 1969). It was a feature in Cases 1, 2 and 4 in the present series. As has been discussed elsewhere (Thomas, 1974), it is significant that spontaneous pain may occur in a disorder that predominantly affects nerve fibres of small calibre. This would not have been predicted from the dorsal horn gating theory of pain advanced by Melzack and Wall (1965), from which selective large fibre loss would have been anticipated. The observations on amyloid neuropathy serve to redirect attention towards small myelinated and unmyelinated axons as being related to the conduction of impulses that give rise to the sensation of pain. This accords with the studies on peripheral nerve stimulation made in conscious subjects by Collins, Nulsen and Randt (1960). The mechanisms by which damage to these neurons gives rise to the occurrence of spontaneous pain remain to be elucidated.

The causation of the nerve fibre damage in amyloid neuropathy has given rise to discussion. It is generally accepted that this is secondary to the amyloid deposits. Coimbra and Andrade (1971b), from observations on nerve biopsies, reached the reverse conclusion. They considered that the nerve fibre damage preceded the appearance of the amyloid. This cannot be taken as having been conclusively established. Nerve biopsies sample a restricted portion of the peripheral nervous system and it is clearly possible that amyloid deposits in the dorsal root ganglia, or more proximally in the nerve trunks, were present in the early cases in which they found nerve fibre degeneration but little amyloid.

The amyloid deposits are frequently perivascular in distribution. Kernohan and Woltman (1942), in particular, took the view that the peripheral nerve changes are ischaemic in origin. It has been argued (Dyck and Lambert, 1969) that the early loss of unmyelinated axons is against this interpretation as they are relatively resistant to ischaemia. Much of the nerve fibre degeneration in the peripheral nerves, however, is likely to be the consequence of lesions in the dorsal root ganglia. It would be of interest to know whether selective damage to the smaller dorsal root ganglion cells occurs in the initial stages of the disease.

The alternative view to ischaemic damage is that the amyloid deposits exert a direct mechanical effect. There is no doubt that deposits in peripheral nerve can distort nerve fibres. Dyck and Lambert (1969) reported that segmental demyelination of fibres occurred in relation to amyloid masses. A mechanical effect was clearly demonstrated in the present study and it is of interest that a definite tendency was observed for the deposits to occur in relation to Schwann cells associated with unmyelinated axons. The deposits were often closely associated with the basal lamina of these cells. Whether this has consequences other than a direct mechanical effect is not evident from the ultrastructural appearances. Since the capsular cells of the dorsal root ganglia are homologous with Schwann cells, perhaps these cells...
exert a determining effect in relation to the deposition of amyloid around the ganglion cells.

No amyloid was detected within Schwann cells, although this was noted by Coimbra and Andrade (1971a) in their material. Inclusion bodies with a crystalline appearance were observed within Schwann cells associated with unmyelinated axons in all four cases. They were particularly obtrusive in Case 4. They resemble the inclusions described by Fardeau and Engel (1969) in Refsum's disease. They are a non-specific finding in a variety of neuropathies (Lyon and Evrard, 1970), including diabetic neuropathy and dominantly inherited hypertrophic neuropathy (Thomas, 1973), and may be encountered occasionally in normal nerves. Their significance is uncertain. Fardeau and Engel questioned an origin from mitochondria, although definite cristae have not been seen.

SUMMARY

Observations were made on nerve biopsies from 4 cases of amyloid neuropathy, 3 of which were sporadic and in one of which the disorder was probably dominantly inherited. A severe loss of unmyelinated axons was evident in all 4 cases. In 3 there was also severe depletion of myelinated fibres, but in one the loss predominantly affected the smaller fibres. This pattern of fibre loss could be correlated with the impairment of pain and temperature appreciation which was the salient sensory change, and with prominent autonomic symptoms. Spontaneous pain was a feature in 3 of the cases.

The amyloid deposits were mainly intrafascicular and were present around endoneurial capillaries and within the endoneurium where they were observed to distort nerve fibres. There was a tendency for these to be related to Schwann cells associated with unmyelinated axons. Deposits also occurred in the perineurium and epineurium.

The significance of these findings in relation to the pathogenesis of the peripheral nerve changes is discussed.

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LEGENDS FOR PLATES

PLATE XX

FIG. 3A.—Transverse section through radial nerve from Case 1 showing gross loss of myelinated fibres. Kultschitsky's haematoxylin—van Gieson. ×50.

FIG. 3B.—Transverse section through sural nerve from Case 2, showing moderate depopulation of myelinated nerve fibres with a relative preservation of those of larger diameter. Kultschitsky's haematoxylin—van Gieson. ×26.

FIG. 3C.—Transverse section through fascicle from radial nerve from Case 1, showing amyloid deposit surrounding an endoneurial blood vessel. Methyl violet. ×26.

FIG. 3D.—Transverse section through sural nerve from Case 2, showing amyloid deposits around endoneurial vessels. Alcian blue. ×40.

PLATE XXI

FIG. 4A.—Electron micrograph of transverse section through radial nerve from Case 1, showing Schwann cell cluster with which are associated unmyelinated (ax1) and myelinated (ax2) regenerating axon sprouts. A Schwann cell process (Sc) contains myelin debris (md).

FIG. 4B.—Electron micrograph of transverse section through sural nerve from Case 4, showing multiple flattened Schwann cell processes of the type derived from the degeneration of unmyelinated axons.

PLATE XXII

FIG. 5A.—Electron micrograph of transverse section through sural nerve from Case 2, showing Schwann cell processes (Sp) and two unmyelinated axon profiles (ax) filled with branched smooth-walled tubules.

FIG. 5B.—Electron micrograph of transverse section through sural nerve from Case 2, showing endoneurial capillary (cap) surrounded by a zone of amyloid fibrils (af) and reduplicated basal lamina (bl).

PLATE XXIII

FIG. 6A.—Electron micrograph of transverse section through sural nerve from Case 2, showing deposit of amyloid fibrils (af) in endoneurium associated with collagen fibrils (cf), seen as clear areas. Distorted Schwann cell processes (Sp) are present at the margins of the deposit.

FIG. 6B.—Electron micrograph of endoneurial amyloid deposit (af) from Case 2. Distorted Schwann cell processes (Sp) are visible both within and at the margins of the deposit.

PLATE XXIV

FIG. 7A.—Electron micrograph of endoneurial amyloid deposit from Case 3, showing interlacing bundles of amyloid fibrils (af), with which are associated collagen fibrils (cf) seen as clear spaces.

FIG. 7B.—Electron micrograph from sural nerve from Case 4, showing osmiophilic Schwann cell inclusion.

FIG. 7C.—Electron micrograph of endoneurial amyloid fibrils from Case 3, showing unbranched straight double filaments.

FIG. 7D.—Electron micrograph of Schwann cell inclusion from Case 2. This is bounded by a double membrane and contains a regular array of filaments, in this instance sectioned transversely, and a central region of amorphous osmiophilic material.
PLATE XXI

FIG. 4.

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Fig. 5.

To illustrate article by P. K. Thomas and R. H. M. King.
FIG. 6.

To illustrate article by P. K. Thomas and R. H. M. King.
PLATE XXIV

FIG. 7.

To illustrate article by P. K. Thomas and R. H. M. King.