

## Hypoxic neuropathy: relevance to human diabetic neuropathy

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**Summary.** Clinical and neurophysiological studies were conducted in 47 patients with chronic obstructive airways disease and compared with 46 age-matched control subjects. Symptomatic neuropathy was reported in 13% and ankle jerks were absent in 45% of hypoxic patients. Peroneal and median nerve conduction velocities and median and sural sensory nerve amplitudes were significantly reduced in hypoxic patients ( $p < 0.01$ ). Six hypoxic patients underwent biopsy of the sural nerve, soleus muscle and overlying skin. Nerve glucose, sorbitol, fructose and *myo*-inositol concentrations were normal. Detailed light and electronmicroscopy revealed both nerve fibre and microvascular pathology. Segmental demyelination (32%) and unmyelinated fibre degeneration were found to be prominent lesions. The sural nerve perineu-

rium was thickened due to an increase in the number of perineurial lamellae and an increase in intraperineurial space. Basement membrane thickening was observed in capillaries of nerve, muscle and skin. Endothelial cell hyperplasia and hypertrophy were observed in nerve and muscle capillaries but not in skin capillaries. In conclusion, this study has provided neurological, neurophysiological and neuropathological evidence of a neuropathy in hypoxic patients with chronic obstructive airways disease. These findings may be of relevance to some aspects of the aetiology of human diabetic neuropathy.

**Key words:** Hypoxia, diabetes, neuropathy, microangiopathy.

The pathogenesis of human diabetic neuropathy remains unclear and multiple mechanisms have been postulated [1]. Metabolic [2] and hypoxic [3] mechanisms appear to play a key role in the aetiology of human diabetic neuropathy. Studies on patients with chronic obstructive airways disease may provide relevant information for studying the effects of systemic hypoxia on human peripheral nerve structure and function.

A peripheral neuropathy in such patients was first reported by Appenzeller et al. in 1968 [4]. A number of clinical [5], neurophysiology [6–8] and pathology [4, 8] studies have attempted to define the incidence and characteristics of this peripheral neuropathy. Symptoms range from lower limb paraesthesia [5] to distal sock hypoaesthesia with subsequent motor impairment related to increased severity of disease [9]. Reduced ankle jerks have been reported in patients with minor features of a neuropathy [9] whilst intact ankle jerks have been reported by others in patients with severe airways disease and neuropathy [4]. Neurophysiology studies have demonstrated a reduction in the sensory potential amplitude and distal sensory conduction velocity; with normal [9], slightly abnormal [8] or markedly abnormal [4] motor nerve conduction veloc-

ities. Pathology studies have revealed considerable large myelinated fibre loss, axonal degeneration [4, 8] and Schwann cell proliferation [4]. Recently, thickening of the basal lamina in both endoneurial and endomysial capillaries has also been reported [8]. Axonal degeneration has also been reported in severely hypoxic patients treated with the respiratory stimulant Almitrine [10, 11]. In recent studies, we have demonstrated that diabetic nerve is hypoxic *in vivo* [12] and that extensive microangiopathy with reduced microvascular oxygen diffusing capacity is frequently observed in sural nerve biopsies from diabetic patients [13]. As hypoxia may represent a major contributory factor to the aetiology of human diabetic neuropathy [3, 14], we studied non-diabetic hypoxic patients and demonstrated that one of the cardinal features of diabetic neuropathy, resistance to ischaemic conduction failure [14], is hypoxia induced [15].

It therefore appears that previous studies of a peripheral neuropathy in patients with chronic obstructive airways disease have produced somewhat disparate and even contradictory results.

We have conducted a detailed clinical neurophysiological, biochemical and pathological investigation in a large

**Table 1.** Standard electrophysiological measures in control subjects and hypoxic patients. (Mean  $\pm$  SD)

	Age (years) mean [range]	Median nerve		Peroneal nerve MNCV (m/s)	Sural nerve SNAP ( $\mu$ v)	Vibration perception threshold (volts)	Thermal discrimination threshold ( $^{\circ}$ C)
		MNCV (m/s)	SNAP ( $\mu$ v)				
Control subjects ( <i>n</i> = 46)	58 [36–73]	55 $\pm$ 3.1	13.8 $\pm$ 5.6	46.9 $\pm$ 4.6	6.8 $\pm$ 3.9	12.9 $\pm$ 2.2	0.7 $\pm$ 0.55
Hypoxic patients ( <i>n</i> = 47)	62 [31–73]	50 $\pm$ 3.6 <sup>b</sup>	9.7 $\pm$ 4.9 <sup>a</sup>	42.5 $\pm$ 5.4 <sup>b</sup>	3.4 $\pm$ 3.6 <sup>b</sup>	24.9 $\pm$ 14.0 <sup>b</sup>	2.9 $\pm$ 5.4 <sup>a</sup>

Motor nerve conduction velocity (MNCV) in metres per second (m/s), Sensory nerve action potential amplitude (SNAP) in microvolts ( $\mu$ v).  
<sup>a</sup> = *p* < 0.005; <sup>b</sup> = *p* < 0.001

**Table 2.** Incidence of isolated teased fibre abnormalities (%) in chronic hypoxic patients and control subjects. (Mean  $\pm$  SEM)

Patient group	Normal fibres	Paranodal abnormalities	Segmental demyelination	Segmental remyelination	Axonal degeneration	Axonal regeneration	Total ab- normal fibres
Control subjects ( <i>n</i> = 5)	93.60 $\pm$ 2.29	1.2 $\pm$ 0.74	1.00 $\pm$ 0.32	1.6 $\pm$ 0.51	1.2 $\pm$ 0.58	1.6 $\pm$ 0.68	4.58 $\pm$ 1.57
Chronic hypoxic patients ( <i>n</i> = 5)	62.1 $\pm$ 6.02	8.9 $\pm$ 2.31	16.74 $\pm$ 5.89	6.36 $\pm$ 1.17	2.2 $\pm$ 0.74	3.68 $\pm$ 1.77	37.9 $\pm$ 6.15

number of hypoxic patients to define the incidence and characteristics of their neuropathy when compared with age-matched control subjects. Such an evaluation may provide further understanding of the possible role of hypoxia in the pathogenesis of human diabetic neuropathy.

## Patients and methods

### Patients

Forty-seven patients (30 males, 17 females) with chronic hypoxia (previously documented PaO<sub>2</sub>  $\leq$  60 mm Hg (8 KPa)) secondary to obstructive airways disease (chronic bronchitis or emphysema) were studied. All patients had PaCO<sub>2</sub>  $\leq$  56 mm Hg (7.5 KPa), arterial pH was normal without respiratory acidosis and at steady state during the study. Detailed examination revealed normal fasting blood glucose and glycosylated haemoglobin levels, negative serology for syphilis, normal serum B<sub>12</sub>, liver function tests and serum creatinine; no history of exposure to neurotoxic chemicals or drugs, no evidence of malignant disease or other causes of neuropathy. Although all these patients had a considerable reduction in exercise tolerance, all were ambulant and none was confined to bed or chair. None of the hypoxic patients had clinical evidence of malnutrition or recent large weight loss. Although some patients were on diuretic therapy, none had significant peripheral oedema, and none had uncontrolled cardiac failure. Control data was obtained from 46 age-matched control subjects who were either healthy volunteers or hospital patients with no history of neurological or respiratory disease.

### Neurophysiology

In addition to standard neurological history and examination, motor nerve conduction velocities were measured in the median and peroneal nerves using surface electrodes and a Medelec MS92A electrophysiological system (Medelec Ltd., Old Woking, UK). Sensory nerve conduction and amplitude were also assessed in the median and sural sensory nerves. The Medelec system employs normalised computer averaging with automatic artefact rejection. The maximum display sensitivity is 0.1 microvolts/division. A maximum of 32 sweeps was used for data acquisition of sensory action potentials. Vibration perception threshold was assessed over the great toe using a biothesiometer [16] (Bio-Medical Instrument Company, Ohio, U.S.A.) employing a length calibrated instrument. Thermal (warming) perception threshold were measured on the flexor surface of the

wrist and on the dorsum of the foot using a thermo-aesthesiometer (Free University, Amsterdam, The Netherlands). A forced choice method was used [17]. All neurophysiological assessments were carried out after patients were made comfortable in a warm environment and skin temperatures were maintained above 30 $^{\circ}$ C.

Minimal criteria for peripheral neuropathy were defined as two or more electrophysiological abnormalities (relative to laboratory normal range), plus either absent ankle reflexes, or diminished vibration perception [18].

### Tissue biopsy

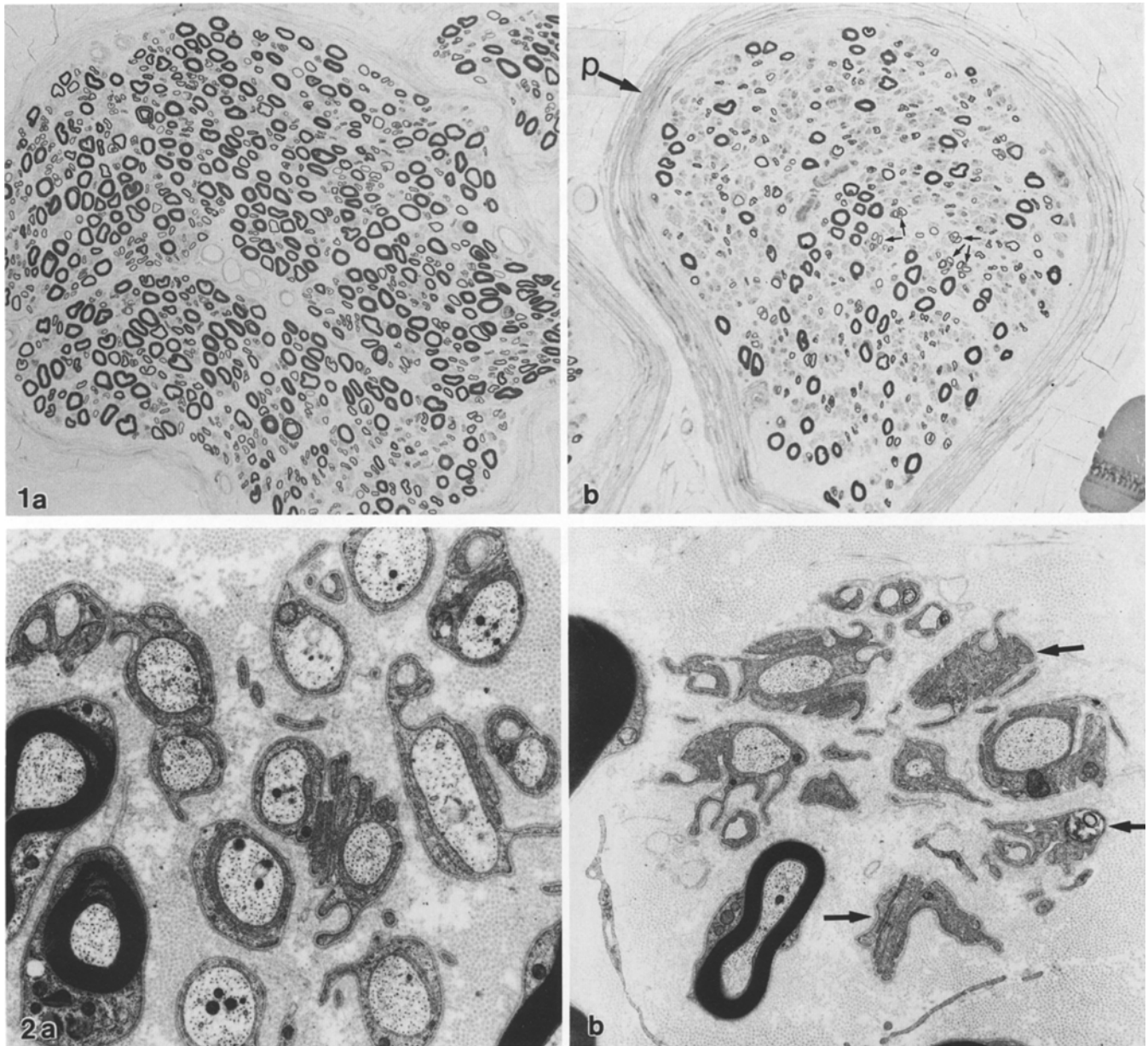
Six unselected hypoxic patients with abnormalities of electrophysiological and sensory tests underwent biopsy of the sural nerve, soleus muscle and overlying skin under local anaesthesia (lignocaine 2%) after approval from the Central Manchester Hospitals Ethical Committee. The nerve segment was immediately divided into two, a portion being frozen in liquid nitrogen and subsequently stored at  $-70^{\circ}$ C for biochemical analysis and the other was fixed and dehydrated through immersion for light and electronmicroscopy, including teased fibre preparations according to previously described standardized techniques [19]. The muscle and skin specimens were also immediately fixed and processed for light and electronmicroscopy using previously described methods [13] and compared with control biopsies obtained from brain dead transplant donors and traumatic amputees; in whom electrophysiological and other investigations were not feasible at the time of biopsy.

### Biochemical methods

The concentrations of glucose, sorbitol, fructose and *myo*-inositol were assayed by gas liquid chromatography of their trimethylsilyl derivatives according to previously described methods [20]. Samples were run on a Shimadzu GC-8A gas chromatograph (Shimadzu Analytical instruments, Kyoto, Japan) fitted with a 25  $\mu$ m fused silica capillary column 25 m in length (J and W Scientific Inc., Rancho Cordova, Calif., USA) using alpha-methyl-D-Mannoside as an internal standard.

### Histological and morphometric procedures

Single teased fibres were isolated in unpolymerised Epon and mounted on glass slides in catalysed Epon for assessment of abnormalities using previously described criteria [21]. Semithin and ultra-



**Fig.1 a, b.** **a** Transverse section of normal sural nerve  $\times 300$ ; **b** Transverse section of sural nerve from a hypoxic patient  $\times 300$  showing thickening of the perineurial sheath (*p*), reduction of myelinated fibre density and regenerative clusters (*arrows*)

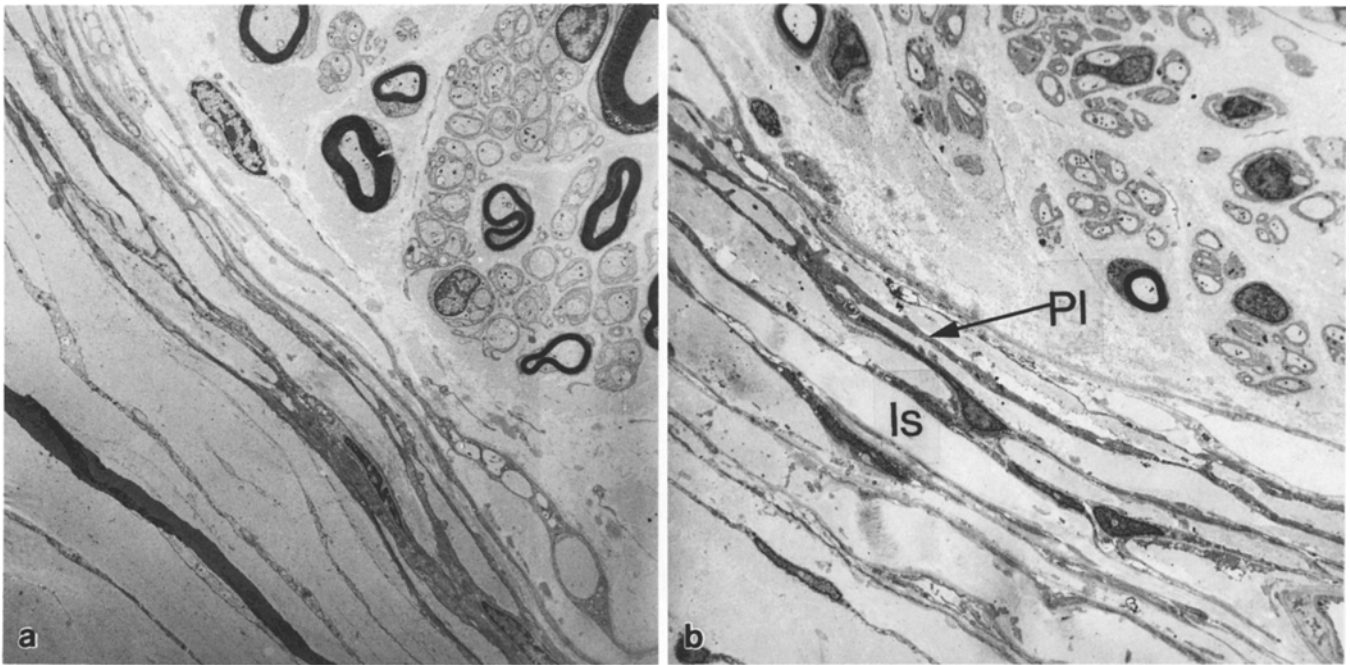
**Fig.2 a, b.** **a** Electronmicrograph of normal sural nerve showing dense population of unmyelinated fibres ( $\times 6000$ ); **b** Electronmicrograph of sural nerve from a hypoxic patient showing Schwann cell processes without axons (*arrows*) ( $\times 6000$ )

thin sections were cut on a Reichert OMU4 ultracut ultramicrotome and stained with thionin and acradine orange and methanolic uranyl acetate/lead citrate respectively. Myelinated fibre density and fascicular area were derived from montages of all fascicles in the sural nerve using a camera lucida and a direct count. A systematic random sampling procedure was employed to produce electronmicrographs of myelinated fibres ( $\times 4000$ ) unmyelinated fibres ( $\times 10000$ ) and perineurium ( $\times 3000$ ,  $\times 18000$ ). Myelinated fibre and axon diameters, and unmyelinated fibre axon diameter were

assessed from electronmicrographs using a magnetostrictive digitizer interfaced to a BBC microcomputer system. The unmyelinated fibre density and the number of axons per Schwann cell profile were counted directly from electronmicrographs ( $\times 10000$ ). Detailed microvascular pathology was assessed from electronmicrographs of all capillaries in view from nerve ( $\times 8000$ ) skin ( $\times 8000$ ) and muscle ( $\times 12000$ ) using previously described rationale to differentiate capillaries, and stereological methods to assess quantitative microvascular pathology [13]. Perineurial pathology was assessed from random intercept lengths for the perineurial sheath (outer border of perineurium to inner border of perineurium), perineurial cell (outer border of perineurial cell to inner border of perineurial cell) and basement membrane (outer free border of basement membrane to perineurial cell membrane) were digitized employing a magnetostrictive digitizer interfaced to a BBC microcomputer system. The number of perineurial cell lamellae were counted directly from each electronmicrograph. The intraperineurial space (*Ips*) was derived from the formula:

$$Ips = (Tpt) - ((Pct \times 1) + (bmt \times ((1 - 1) \times 2)))$$

Where *Tpt* represents the mean perineurial sheath thickness, *Pct* is



**Fig. 3 a, b.** **a** Electronmicrograph of normal sural nerve showing perineurial sheath ( $\times 2000$ ); **b** Electronmicrograph of sural nerve from a hypoxic patient showing thickening of the perineurial sheath and an increase in the number of perineurial lamellae (PI) and intra-perineurial space (Is) ( $\times 2000$ )

the mean perineurial cell thickness, bmt is the mean perineurial cell basement membrane thickness and 1 is the mean number of perineurial cell lamellae in the perineurial sheath.

### Statistical analysis

All neurophysiological data were compared using the two-tailed Mann-Whitney U-test employing the Amstat statistical package for Amstrad computers (S. C. Coleman Ltd., Ashby-de-la-Zouch, Leics, UK). Pathological results were compared using the two-tailed Mann-Whitney U-test employing the Minitab statistical package on the University of Aberdeen Honeywell-Bull DPS8770 mainframe computer system.

## Results

### Clinical

Symptoms typical of peripheral neuropathy (eg. paraesthesia, dysaesthesia, burning pain) were reported in 13% of hypoxic subjects and ankle jerks were absent in 45% of these patients. A reduction or absence of fine touch and vibration sensation was observed in 41% of hypoxic patients. The control subjects had no symptoms or signs of peripheral neuropathy.

### Neurophysiological

The patients and control subjects were age-matched, and abnormalities of all principal electrophysiological parameters found are summarised in Table 1. Peroneal and median nerve conduction velocities were significantly re-

duced in hypoxic patients ( $p < 0.001$ ). Median ( $p < 0.005$ ) and sural ( $p < 0.001$ ) nerve sensory amplitudes were also significantly reduced in hypoxic patients. 'Objective' measures of sensory perception revealed abnormalities in the lower limb: vibration ( $p < 0.001$ ) and thermal ( $p < 0.005$ ) perception thresholds at the hallux were significantly higher in hypoxic patients compared with control subjects.

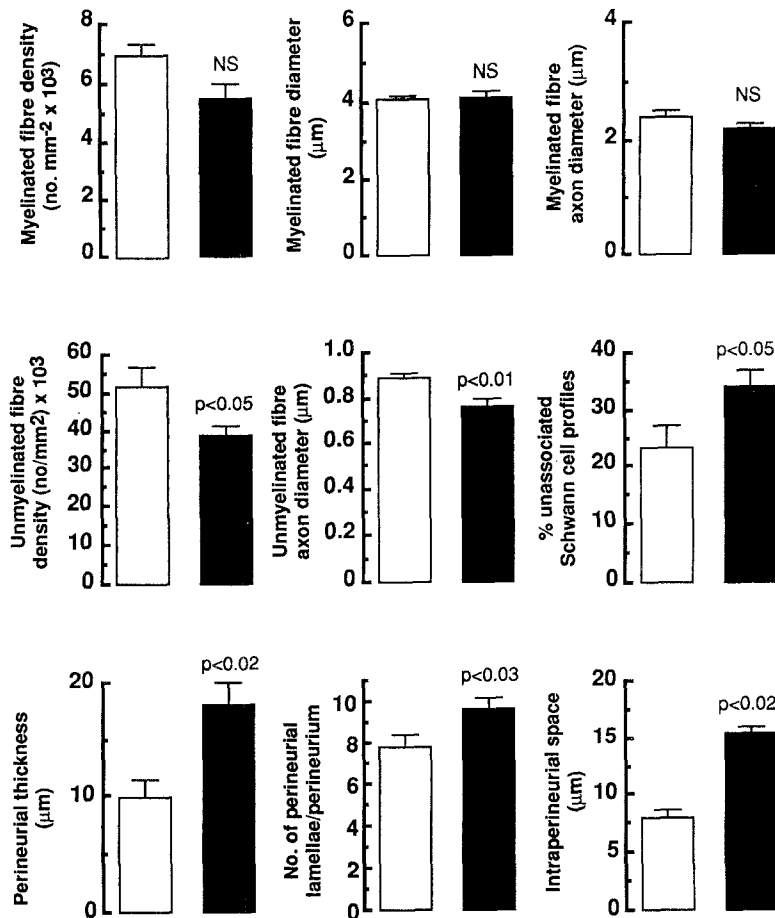
### Biopsy findings

The mean age of control biopsy subjects was  $56.5 \pm 9.9$  (Mean  $\pm$  SEM) years compared with  $64.6 \pm 2.15$  (Mean  $\pm$  SEM) years for the biopsied hypoxic patients.

Considerable pathology was observed in myelinated fibres (Fig. 1), unmyelinated fibres (Fig. 2) and the perineurium (Fig. 3) of hypoxic patients when compared with control subjects. Both regenerative clusters, indicative of axonal regeneration, and thinly myelinated fibres, indicative of remyelination, were observed qualitatively (Fig. 1 b) in hypoxic patients.

### Myelinated fibres

Teased fibre preparations showed paranodal abnormalities (demyelination and remyelination in the paranodal region with widening of the nodal gap), marked segmental demyelination and remyelination (32%) and slight axonal degeneration and regeneration (5.9%) in the sural nerve of hypoxic patients (Table 2). Mean myelinated fibre density, mean fibre and its axonal diameter were not significantly reduced in hypoxic patients when compared with control subjects (Fig. 4a). The percentage of fibres  $\leq 6 \mu\text{m}$  (78% vs 79.5%) and  $\geq 6 \mu\text{m}$  (22% vs 21.5%) were not different between control and hypoxic nerves respectively. Therefore, there was no selective small or large fibre loss.



**Fig. 4.** Myelinated fibre density and myelinated fibre and axon diameter (upper panel); Unmyelinated axon density and their diameter and percentage of Schwann cell profiles without axons (middle panel); Perineurial sheath thickness, number of perineurial lamellae and the intraperineurial space (lower panel) in the sural nerve of control subjects □ and hypoxic patients ■. (Mean ± SEM)

### Unmyelinated fibres

Unmyelinated fibre degeneration occurred as there was an increase in the percentage of Schwann cell profiles without axons ( $p < 0.05$ ), reduction in axon density ( $p < 0.05$ ) and reduced mean axon diameter ( $p < 0.01$ ) in hypoxic nerves (Fig. 4b). The distribution of the number of axons per Schwann cell profile and the size frequency distributions of unmyelinated axons were no different in hypoxic patients when compared with control subjects (Fig. 5), suggesting a lack of axonal sprouting.

### Perineurium

The sural nerve perineurium was significantly thickened in hypoxic patients ( $p < 0.02$ ). Both the number of perineurial cell lamellae ( $p < 0.03$ ) and the intraperineurial space ( $p < 0.02$ ) were significantly increased in hypoxic patients (Fig. 4c). The thickness of perineurial cells and their basement membrane were not significantly different in hypoxic patients when compared with control subjects.

### Endoneurial capillaries

The mean sural nerve fascicular area in hypoxic patients was not different from control subjects. Endoneurial capillary density and estimated oxygen diffusing capacity were slightly but not significantly reduced in hypoxic nerves.

Endothelial cell profile number ( $p < 0.005$ ) and nuclear number ( $p < 0.03$ ), luminal ( $p < 0.02$ ) and vessel ( $p < 0.02$ ) perimeters; and capillary wall thickness ( $p < 0.03$ ) were significantly increased in hypoxic patients.

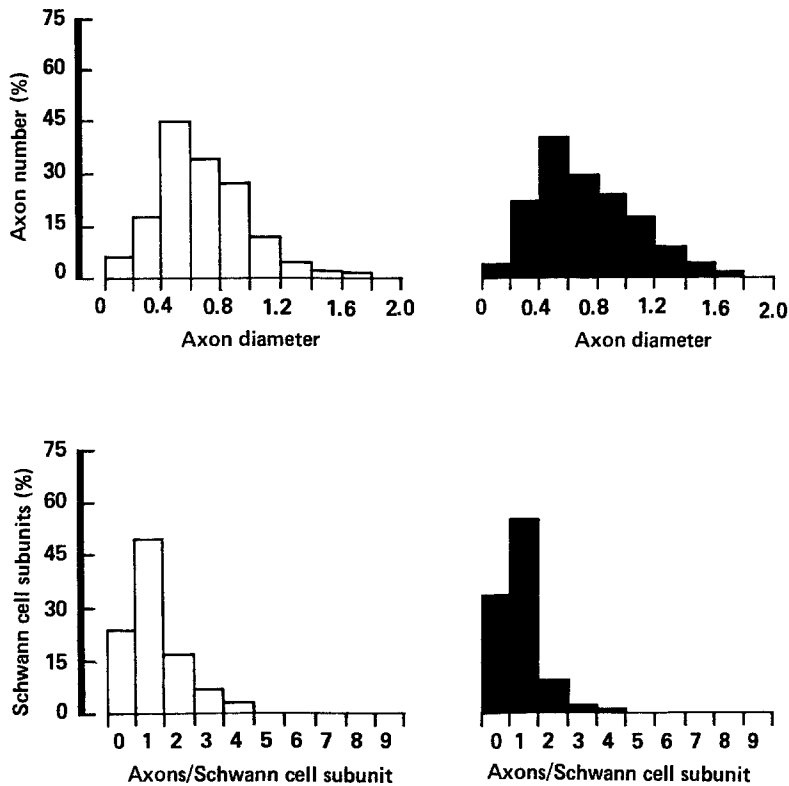
Endothelial cell outer perimeter was not significantly different between hypoxic patients and control subjects. Both endothelial cell thickness and basement membrane thickness were increased but failed to attain a statistically significant difference when compared with control subjects (Table 3).

### Muscle capillaries

Muscle capillaries showed increased endothelial cell profile number ( $p < 0.02$ ) and thickness ( $p < 0.01$ ) with increased basement membrane ( $p < 0.01$ ) and capillary wall ( $p < 0.01$ ) thickness (Table 3).

### Skin capillaries

Skin capillaries demonstrated slight but non-significant increases in endothelial cell profile number and endothelial cell thickness in hypoxic patients. Both the basement membrane ( $p < 0.005$ ) and capillary wall ( $p < 0.008$ ) were markedly thickened in hypoxic patients when compared with control subjects (Table 3).



**Fig. 5.** Unmyelinated axon size frequency distribution (upper panel) and distribution of number of axons per Schwann cell subunit (lower panel) in control subjects left side and hypoxic patients right side

### Biochemical

Concentrations of nerve glucose ( $6.81 \pm 0.35$  nmol/mg) and fructose ( $0.36 \pm 0.06$  nmol/mg) were found to be within the normal range [22]. Sorbitol was detected at a very low concentration ( $<0.01$  nmol/mg) and *myo*-inositol levels ( $4.91 \pm 0.18$  nmol/mg) were not reduced [23].

### Discussion

Inappropriate patient selection, differing methods of clinical and neurophysiological assessment, and qualitative rather than quantitative estimates of pathological lesions have produced somewhat contradictory data on the prevalence and characteristics of a peripheral neuropathy in patients with chronic obstructive airways disease.

A distal, symmetrical and predominantly sensory polyneuropathy of the lower limbs with hypoaesthesia, paraesthesia and spontaneous pain has been reported in 14–40% of hypoxic patients [4, 6, 8]. A lower incidence of symptomatic neuropathy (13%) was observed in the present study because it represents the incidence in the general population of hypoxic patients as opposed to selected groups in previous studies [4]. Ankle jerks were absent in 45% of individuals, comparable with most other studies [6, 7, 9]. In the present study, motor and sensory nerve conduction velocities were reduced, together with a reduction in sensory nerve amplitudes, confirming previous observations [6, 8, 9]. However, our findings failed to agree with the observation of preserved nerve conduction and predominant electromyograph and nerve amplitude abnormalities considered to reflect a motor neurone lesion [7].

Neuropathological changes are not clearly established in patients with chronic obstructive airways disease. In the teased fibre preparation, we have demonstrated a significantly greater number of myelinated fibres undergoing segmental demyelination and remyelination. Significant axonal degeneration or myelinated fibre loss was not observed. Appenzeller et al. [4] have reported large myelinated fibre loss, non-specific changes in size frequency distributions and a combination of both axonal degeneration and segmental demyelination in longitudinal sections but not in teased fibre preparations. Recently, Parabelle et al. [8] have reported predominant axonal degeneration and large fibre loss with slight segmental demyelination. This study has also demonstrated unmyelinated fibre degeneration in the form of reduced axon density and size with an increase in the number of Schwann cell profiles without axons. Previous studies have failed to quantify unmyelinated fibre pathology [4, 8]. Appenzeller et al. [4] have reported an increase in the interstitial space, suggestive of endoneurial expansion. This study failed to reveal fascicular expansion. An increase in interstitial space may, therefore, have simply reflected a loss of nerve fibres.

A thickening of muscle and nerve capillary basement membrane has been demonstrated, but it was not assessed quantitatively and was also not compared with control subjects [8]. This study has quantified endothelial cell and basement membrane pathology and has shown significant differences in the capillaries of nerve, muscle and skin from hypoxic patients when compared with control subjects. Endothelial cell hyperplasia, suggestive of a hypoxic basis for endothelial proliferation was demonstrated. A failure of the endoneurial capillaries to increase in size to

**Table 3.** Morphometric measurements ( $\bar{X} \pm \text{SEM}$ ) of capillaries from nerve, muscle and skin in control subjects and hypoxic patients

Parameter	Control subjects ( $n = 6$ )	Hypoxic patients ( $n = 6$ )	$p$ value
<b>Nerve</b>			
Mean fascicular area ( $\text{mm}^2$ )	0.08 $\pm$ 0.01	0.08 $\pm$ 0.01	NS
Capillary density no. $\text{mm}^{-2}$	72.86 $\pm$ 4.66	59.81 $\pm$ 5.62	NS
Oxygen diffusing capacity $\text{ml O}_2 \cdot \text{min}^{-1} \cdot \text{Torr}^{-1} \cdot \text{ml tissue}^{-1}$	2.15 $\pm$ 0.15	1.79 $\pm$ 0.21	NS
Luminal perimeter ( $\mu\text{m}$ )	19.44 $\pm$ 0.53	24.72 $\pm$ 1.75	< 0.02
Endothelial cell outer perimeter ( $\mu\text{m}$ )	27.01 $\pm$ 2.38	31.70 $\pm$ 1.63	NS
Vessel perimeter ( $\mu\text{m}$ )	35.68 $\pm$ 1.78	44.35 $\pm$ 2.44	< 0.02
Endothelial cell:			
– nuclear number/capillary	1.29 $\pm$ 0.09	1.58 $\pm$ 0.06	< 0.03
– profile number/capillary	3.77 $\pm$ 0.14	5.43 $\pm$ 0.27	< 0.005
– thickness ( $\mu\text{m}$ )	0.94 $\pm$ 0.09	1.12 $\pm$ 0.12	NS
Basement membrane thickness ( $\mu\text{m}$ )	1.17 $\pm$ 0.09	1.36 $\pm$ 0.11	NS
Capillary wall thickness ( $\mu\text{m}$ )	2.19 $\pm$ 0.23	3.56 $\pm$ 0.20	< 0.03
<b>Muscle</b>			
Endothelial cell:			
– profile number/capillary	2.19 $\pm$ 0.06	2.60 $\pm$ 0.05	< 0.02
– thickness ( $\mu\text{m}$ )	0.34 $\pm$ 0.01	0.48 $\pm$ 0.02	< 0.01
Basement membrane thickness ( $\mu\text{m}$ )	0.19 $\pm$ 0.01	0.56 $\pm$ 0.07	< 0.01
Capillary wall thickness ( $\mu\text{m}$ )	0.68 $\pm$ 0.04	1.22 $\pm$ 0.08	< 0.01
<b>Skin</b>			
Endothelial cell:			
– profile number/capillary	4.04 $\pm$ 0.16	5.00 $\pm$ 0.31	NS (< 0.06)
– thickness ( $\mu\text{m}$ )	1.09 $\pm$ 0.15	1.38 $\pm$ 0.12	NS
Basement membrane thickness ( $\mu\text{m}$ )	0.77 $\pm$ 0.06	1.53 $\pm$ 0.18	< 0.005
Capillary wall thickness ( $\mu\text{m}$ )	2.51 $\pm$ 0.29	4.33 $\pm$ 0.31	< 0.008

accommodate endothelial cell hyperplasia and hypertrophy predisposes such capillaries to luminal occlusion. This study has also established a characteristic thickening of sural nerve perineurium in patients with hypoxic neuropathy which may further impede the transport of nutrients and oxygen and hence alter nerve function and structure [24].

Chronic hypoxia in normal rats has been shown to produce electrophysiological abnormalities similar to those observed in experimental diabetic rats in the absence of hyperglycaemia, nerve sorbitol accumulation and *myo*-inositol reduction [25]. The characterization of neuropathy in hypoxic patients may therefore have relevance and may also provide support for the recent reappraisal of the role of hypoxia in the development of human diabetic neuropathy [3, 13, 14]. The present study has revealed neurophysiological abnormalities similar to those observed in human diabetic neuropathy [16–18]. Morphology studies showed segmental demyelination in hypoxic patients which is also found in asymptomatic neurophysiologically normal diabetic patients [23, 26]. Current evidence indicates an independent effect of the diabetic state on both axon and Schwann cell function and structure [27, 28]. Thus, hypoxia may contribute to the component of the diabetic state which is responsible for segmental demyelination. Unmyelinated fibre degeneration was observed in hypoxic neuropathy and it is a characteristic feature of both early [26] and established human diabetic neuropathy [19, 27]. Microvascular abnormalities, namely, endothelial cell hyperplasia and hypertrophy with basement membrane thickening ultimately predispose the capillaries to luminal narrowing and vascular occlusion producing added hypoxic insult in hypoxic neuropathy. Simi-

lar findings have been reported in human diabetic neuropathy [13, 29, 30].

In conclusion, this study has revealed clinical, neurophysiological and neuropathological evidence of a neuropathy in hypoxic patients. These findings may therefore be of relevance to some aspects of the aetiology of human diabetic neuropathy.

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