Polyneuropathy in critically ill patients

CHARLES F BOLTON, JOSEPH J GILBERT, ANGELIKA F HAHN, WILLIAM J SIBBALD

From Departments of Clinical Neurological Sciences, Pathology and Medicine, and The Critical Care/Trauma Unit, Victoria Hospital, University of Western Ontario, London, Ontario, Canada

SUMMARY Five patients developed a severe motor and sensory polyneuropathy at the peak of critical illness (sepsis and multiorgan dysfunction complicating a variety of primary illnesses). Difficulties in weaning from the ventilator as the critical illness subsided and the development of flaccid and areflexic limbs were early clinical signs. However, electrophysiological studies, especially needle electrode examination of skeletal muscle, provided the definite evidence of polyneuropathy. The cause is uncertain, but the electrophysiological and morphological features indicate a primary axonal polyneuropathy with sparing of the central nervous system. Nutritional factors may have played a role, since the polyneuropathy improved in all five patients after total parenteral nutrition had been started, including the three patients who later died of unrelated causes. The features allow diagnosis during life, and encourage continued intensive management since recovery from the polyneuropathy may occur.

During a four year period five patients developed a severe polyneuropathy within one month of admission to a critical care unit. Although two patients gradually recovered from the polyneuropathy, three later died of unrelated causes. Systematic analysis of clinical data, and neuropathological studies of both central and peripheral nervous systems, failed to reveal a cause. Nonetheless, we suggest the features of this unusual polyneuropathy form a distinctive pattern which allows diagnosis during life. It is our purpose, therefore, to document the clinical, electrophysiological and morphological characteristics, discuss possible causes and suggest future approaches to management.

Methods

Because of their unusual nature, the five patients were recalled from the many seen in the Victoria Hospital critical care unit between 1977 and 1981. This unit has 18

beds, admits 1,300 patients a year, is located in an 860 bed teaching hospital, and has a referral base of 1·2 million persons. The voluminous charts were reviewed, particularly regarding events in the first month, since these might theoretically have been of aetiological significance in the development of the polyneuropathy. Day 1 was designated as the first day of admission to the critical care units of either Victoria Hospital or the referring hospital (the first 18 and 16 days of patients 2 and 3, respectively.)

Initially, all patients received standard intravenous solutions to ensure haemodynamic stability. Tube feeding (Ensure, Ross (Abbott) Laboratories, Montreal, Canada) was given at varying times and rates. When provided, the total parenteral nutrition formula was: 10% Travasol, 250 ml/l; 13·5% dextrose, 750 ml/l; Na 40, K 20, Mg 2·5, Ca 5·0, Cl 30 and acetate 37·5 mg/l; and a 10 ampule of multivitamins: vit C—1000 mgm, vit A—10,000 IU, vit D—1000 IU/UI, vit E—10 IU/UI, thiamine HCL—45 mg, riboflavin—10 mg, niacinamide—100 mg, pyradoxine—12 mg, and d pantothenic acid—26 mg. Supplements were: folate 5 mg, vit K—10 mg, vit B12—100 mg twice weekly; trace elements (zn—2 mg, Mn—1 mg, Cu—1 mg, Cr—2 μg, I—120 μg) once weekly; intralipid 10%, 500 ml thrice weekly, and albumin hydroxine gel alternating with magnesium and aluminium hydroxide 30 ml every two hours, maxeran 10 mg every eight hours by nasogastic tube, and cimetidine 300 mgm every six hours IV as required to maintain gastric pH >5·0.

All patients had full neurological examination, initially and in follow-up. Electrophysiological studies were performed on patients 1 to 4, using surface electrodes for nerve conduction studies and concentric needle electrodes for electromyography;[1-3] isolation procedures prevented such studies in patient 5. Phrenic nerve conduction[4] was studied in patient 3.

Table 1   *Cerebrospinal fluid results*

Patient	Week*	WBC/mm³	RBC/mm³	Protein (mg/dl)	Sugar (mg/dl)
1	3	0	0	10	78
2	4	0	0	38	78
	9	0	0	80	112
3	5	1	8	31	56
4	2	90	11000	23	117
	6	0	64	25	110
5	4	1	16	64	67
Normal		<4	0	15–45	—

*In Critical Care Unit.

Neuropathological studies of the central and peripheral nervous system were performed on patients 3, 4 and 5. Brain, spinal cord, muscle and nerve were fixed with 10% buffered formaldehyde, processed and embedded in paraffin, according to standard techniques. Sections were stained with haematoxilin and eosin, solochrome R and Bodian's stain for axis cylinders. Samples of nerve roots, peripheral nerves and muscle, obtained by surgical biopsy or necropsy, were fixed in buffered glutaraldehyde, processed and embedded in epon according to standard procedures. Semithin sections were stained with toluidine blue; selected thin sections were stained with uranyl acetate and lead citrate and viewed with a Philips 201 electron microscope. Samples of superficial peroneal nerve were teased in glycerine and the different fibre types assessed and classified according to Dyck.[5] Muscle histochemistry was done using haematoxylin and eosin, Gomori's trichrome, periodic-acid-shiff, fat stain, myosin ATPase at pH 4·3, 4·6, 9·3 and oxidative enzyme stains.

Case reports

Patient 1
A 56-year-old hypersensitive and mildly diabetic woman experienced epigastric pain, vomiting, generalised weakness and a 20 lb (10 kg) weight loss. She was mildly confused and feverish. Treatment in the critical care unit for phenformin-induced lactic acidosis, dehydration, transient renal failure and pneumonia due to *Staphylococcus aureus* and *Klebseilla pneumoniae* was successful; cephalolithin sodium and gentamycin were given. At 3 weeks she could not be weaned from the respirator and complained of numbness, tingling and burning of the hands and feet. Swallowing, tongue protrusion and biting were strong, but neck, chest wall, abdomen and limb muscles were very weak. All deep tendon reflexes were absent. Position sense and vibration sense were distally impaired, but pinprick was preserved. The CSF was unremarkable. (table 1). Electrophysiology (table 2) indicated a severe axonal degeneration of motor and sensory fibres, electromyography revealing numerous fibrillation potentials and positive waves and absent voluntary unit activity in proximal and distal limb muscles. Aetiological investigations of the polyneuropathy were negative (see below). After total parenteral nutrition was started at 3 weeks, gradual recovery occurred. She left hospital in a wheelchair at four and one half months, was still confined to a wheelchair at six months, but her limbs were now moderately strong. The deep tendon reflexes were still absent. Vibration and position sense were normal, but pain and temperature were impaired distally. Two-point discrimination was absent in the feet. Electrophysiology confirmed improvement (table 2); abnormal spontaneous activity in muscle had almost disappeared and voluntary motor unit activity had returned, several units being highly polyphasic, indicating reinnervation. At two years, she could walk independently but still had residual signs of polyneuropathy.

Table 2   *Nerve conduction studies*

Patient	Month*	Conduction velocities (m/s)†				Cap distal latencies (ms)				Cap amplitudes			F response latencies (ms)‡	
		Median motor	Median sensory	Peroneal motor	Sural sensory	Thenar muscle	Digital nerve	EDB muscle	Thenar muscle (mv)	Digital nerve (µv)	EDB muscle (mv)	Sural nerve (µv)	Median nerve	Peroneal nerve
1	1	—	—	45·5	—	3·9	0	3·8	0·8	0	1·4	0	28·5	—
	6	52·6	—	41·8	—	4·3	3·2	4·9	6·0	4	2·4	0	28·1	53·3
2	1	64·6	72·9	46·7	46·4	3·6	2·7	3·6	0·1	6	0·9	3	—	—
	2	53·2	57·9	39·4	41·9	5·7	3·2	3·9	0·7	7	1·2	6	33·4	46·3
	3	51·9	48·4	39·1	40·8	5·1	2·5	4·2	1·5	12	1·1	6	32·1	53·5
3	1	48·0	55·2	—	—	3·3	2·5	—	2·8	16	0	0	32·4	—
	3	51·4	53·1	38·7	42·7	3·6	2·6	5·1	6·0	24	0·2	3	31·2	—
4	1	56·7	61·7	50·0	—	4·9	3·0	3·5	0·4	10	0·2	0	—	—
	3	—	—	—	34·7	—	—	—	—	—	0	5	—	—
Normal														
Mean		57·4	62·3	48·6	45·6	3·7	2·6	4·7	11·0	43	7·0	15	27·7	47·7
2SD		49·4	53·2	41·0	37·4	4·5	3·2	6·3	5·2	8	1·4	0	33·4	58·7

*In Critical Care Unit.
†Conduction velocity nerve segments: median—elbow to wrist, peroneal—knee to ankle, sural—midcalf to ankle.
‡F response stimulation sites: median—wrist, peroneal—ankle.
Cap means compound action potential. EDB means extensor digitorum brevis muscle. SD means standard deviation.
— means not measured.

Patient 2

A 56-year-old housewife was admitted to the critical care unit for treatment of oesophagopleural fistula and empyema complicating hiatus hernia surgery. *Klebseilla pneumonia* and *Streptococcus* were cultured and antibiotics given (table 4). For two weeks, there was moderate, generalised oedema and she was mildly confused. She improved generally, but could not be weaned from the ventilator. Both abdominal and chest wall respiratory movements were weak. Face, tongue and limb muscle fasciculated, the face being mildly weak and the limbs moderately weak. The deep tendon reflexes were reduced, moderately in arms and severely in legs. The plantar responses were flexor. She responded to pinprick in all areas. Electrophysiology (table 2), including electromyography of proximal and distal muscles, indicated a severe and widespread axonal degeneration of peripheral nerves. EEG and CSF (table 1) were unremarkable. Aetiological tests were negative (see below). Total parenteral nutrition was started on day 18. All antibiotics were discontinued but her temperature persisted. Cultures revealed *Klebsiella pneumoniae* and *E coli* in chest drainage, *Straphylococcus aureus* in blood and *Candida albicans* in urine. Intravenous gentamycin was given. Rectal biopsy revealed *Pseudomonas enterocolitis* but *Clostridium difficile* was not isolated from the stool. At five weeks, her spleen was removed and the stomach disconnected from the oesophagus. Despite the persisting medical and surgical complications, the polyneuropathy progressively improved (fig 1). At three months, strength in the face was normal. The fasciculations had disappeared. She still required full ventilatory assistance but proximal limb muscles were only mildly weak and distal limb muscles were moderately weak. The deep tendon reflexes were mildly reduced in the arms but still absent in the legs. All sensory modalities were normal, except for decreased pinprick below the ankles. Electrophysiology showed progressive improvement (table 2), abnormal spontaneous activity disappearing, and motor unit potentials returning, indicating considerable reinnervation muscle. At seven months, the oesophagus was re-attached to the stomach. She was discharged at ten months, still draining from the right-sided bronchopleural fistula and still requiring a tracheostomy tube, but able to breathe and walk independently.

Patient 3

A 66-year-old retired schoolteacher was admitted to the critical care unit for acute respiratory failure superimposed on chronic obstructive lung disease. Despite intravenous fluids, nasogastric feedings, intravenous steroids and antibiotics (table 4), weak respiratory movements necessitated full ventilatory support. Neurological examination was initially negative. *Proteus mirabilis* and *E coli* were cultured from urine and *Enterobacter* from blood. At three weeks, all limbs were first noted to be moderately weak proximally and distally. Total parenteral nutrition was started. At five weeks, there was mild weakness of facial muscles, severe weakness of limb muscles and absence of all deep tendon reflexes. He responded to pinprick in all areas. Electrophysiology indicated a severe motor and sensory polyneuropathy due to axonal degeneration (table 2). Bilateral phrenic nerve studies[4] disclosed an absent
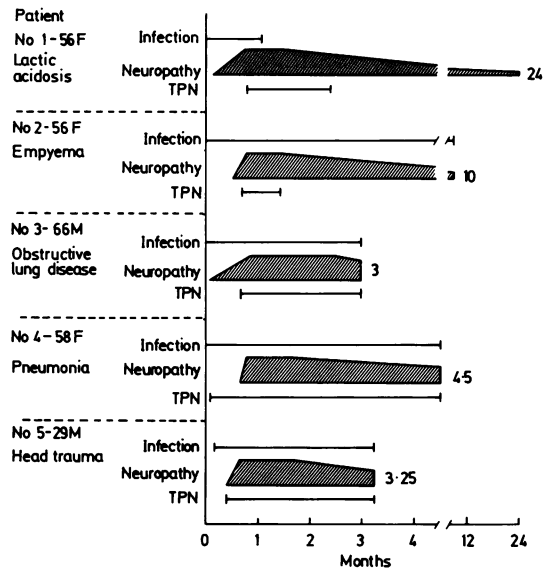

Fig 1 *The course of the polyneuropathy in relationship to infection and total parenteral nutrition (TPN). The polyneuropathy developed soon after admission to the critical care unit and the onset of infection, and it improved despite persisting infection and only after TPN had been started. (The primary diagnoses are listed on the left; months refers to time following admission to the critical care unit; the height of the polygons depict the magnitude of the polyneuropathy, which was ultimately severe in each patient; the number after each polygon indicates the time in months of the last examination (before death in the last three patients)).*

response from both leaves of the diaphragm. Needle electrode examination indicated widespread denervation of muscle, including external oblique and intercostal muscles. Excessive polyphasic units were recorded in the facial muscles. CSF was unremarkable (table 1). Aetiological investigation proved negative (see below). At seven weeks, fascicular biopsies of the superficial and deep peroneal nerves at the ankles showed mild loss of myelinated fibres and ongoing axonal degeneration. Some fibres were thinly myelinated, indicating either remyelination or regeneration. There was no active demyelination (table 3) nor

Table 3 *Results of superficial peroneal nerve teased fibre preparations**

Patient	A & B	C	D	E	F	n
3	83·7			4·5	11·8	110
4	75			22·1	2·9	140
5	4·9	0·9		94·4		144

*A & B—normal fibres.
C—paranodal demyelination.
D—segmental demyelination.
E—axonal degeneration.
F—segmental remyelination.
Expressed as percentage of total number (n) of teased fibres.[5]

endoneurial inflammation. The extensor hallucis longus, right quadriceps and intercostal muscles showed moderate denervation atrophy, variability in muscle fibre size and cytoarchitectural disorganisation, suggesting an associated primary myopathy, with no evidence of acid maltase deficiency. Electrophysiology and clinical examination at ten weeks suggested improvement (table 2, fig 1). Needle electrode studies indicated partial reinnervation. However, he died of a cardiac arrest at three months.

Necropsy revealed multifocal organising pneumonia, emphysema, chronic bronchitis, moderate coronary atherosclerosis and bilateral organising haemorrhagic necrosis of the adrenal cortex. The temporalis, deltoid, triceps, biceps, intercostal, diaphragm, quadriceps and peroneus longus muscles from both sides demonstrated denervation atrophy. The spinal cord and nerve roots were normal at multiple levels. Ongoing axonal degeneration was evident in the common peroneal, vagus and phrenic nerves and cervical sympathetic trunks, occasional cluster of mononuclear inflammatory cells being seen. The brainstem, cranial nerves, cerebellum and cerebral hemispheres were normal. It was concluded that he had suffered from a chronic axonal motor and sensory polyneuropathy.

Patient 4
A 50-year-old housewife was admitted to the critical care unit because of bilateral lobar pneumonia. The temperature was 36·5°C. Generalised petechiae and oedema were present. The neurological examination was initially normal. Antibiotics (table 4) and full ventilatory assistance were given. Several water and electrolyte disturbances were corrected. On day 4, she received total parenteral nutrition. Cultures at multiple sites, including biopsied lung, were negative. A screen for disseminating intravascular coagulation, tests for cold agglutinins and antinuclear antibody were negative, but her platelets fell to 53,000/mm.³ The liver biopsy revealed mild amyloid infiltration. Moderate transient renal failure was managed conservatively. On day 10, she developed signs of a severe encephalopathy with right hemiplegia and generalised and multifocal seizures. The EEG revealed continuous multifocal epileptiform activity, but the CT brain scan was normal. A lumbar puncture revealed findings consistent with subarachnoid haemorrhage (table 1). Acute and convalescent serum revealed no evidence of viral infection (see Aetiological Investigations). The encephalopathy gradually improved following treatment with antibiotics, steroids, phenobarbital and phenytoin sodium. However,

while she was able to trigger the respirator, open her eyes and move her head from side to side, the limbs remained totally flaccid and areflexic. She would grimace to painful stimulation of the upper limbs but not of the lower limbs. Electrophysiology at one month (table 2) indicated a severe motor and sensory polyneuropathy of the type in which there was predominantly an axonal degeneration. Needle electrode examination disclosed numerous fibrillation potentials and positive sharp waves in muscles of the face, and of proximal and distal limbs. Voluntary motor unit activity was absent in limb and minimal in facial muscles. Serum creatinine kinase, magnesium and phosphate were all normal. Repeat needle electrode studies at 11 weeks showed evidence of early reinnervation of facial, arm and leg muscles. She had spontaneous flexion movements of the hips, knees and left shoulder, but severe distal muscle atrophy and areflexia remained. Despite the neurological improvement, signs of pulmonary sepsis continued. A left lung abscess was surgically drained at 2 months, but she expired on the operating table later, at 4 months, when an attempt was made to excise this abscess.

Necropsy revealed severe, bilateral organising pneumonia and a large, left upper lobe abscess (*Pseudomonas aeruginosa* cultured). Microscopic examination of the brain showed multifocal perivascular foci of haemosiderin-laden macrophages and surrounding gliosis throughout the white matter and cortex of the cerebral hemisphere and in the pons. The cerebellum and cranial nerves were normal. Multiple levels of the spinal cord were also normal, except for the occasional chromatolytic anterior horn cell and glial bundle in ventral roots. Dorsal and ventral roots of the cervical and lumbar regions showed a few clusters of regenerated, mylinated axons and a few thinly myelinated fibres. Dorsal root ganglion cells were mildly reduced in number. Median, forearm lateral cutaneous, sciatic, common peroneal, superficial and deep peroneal and sural nerves showed moderate to severe loss of large and small myelinated fibres, mild ongoing axonal degeneration, mild regeneration and a reactive Schwann cell proliferation. There was no segmental demyelination (table 3). Scattered mononuclear cells, mainly macrophages containing lipid debris, were observed in several nerves. The peroneus longus muscle and extensor hallucis longus muscle demonstrated severe, chronic denervation atrophy. It was concluded that lesions of the brain represented healed purpura (Moskovicz syndrome) and the lesions of peripheral nerve represented a severe axonal, motor and sensory polyneuropathy.

Table 4 *Antibiotic Treatment**

Patient	Cephalosporins	Aminoglycosides	Penicillins	Others
1	Cephalolithin	Gentamycin	—	—
2	Cephalexin	Clindamycin	Penicillin G	—
	Cephapirin	Gentamycin		
3	—	Gentamycin	Ampicillin	Rolytetracycline
4	Cephamandole	Tobramycin	Cloxacillin	Mycostatin
				Erythromycin
5	Cephazolin	Tobramycin	Penicillin G	Ticarcillin
	Cefostin			Erythromycin

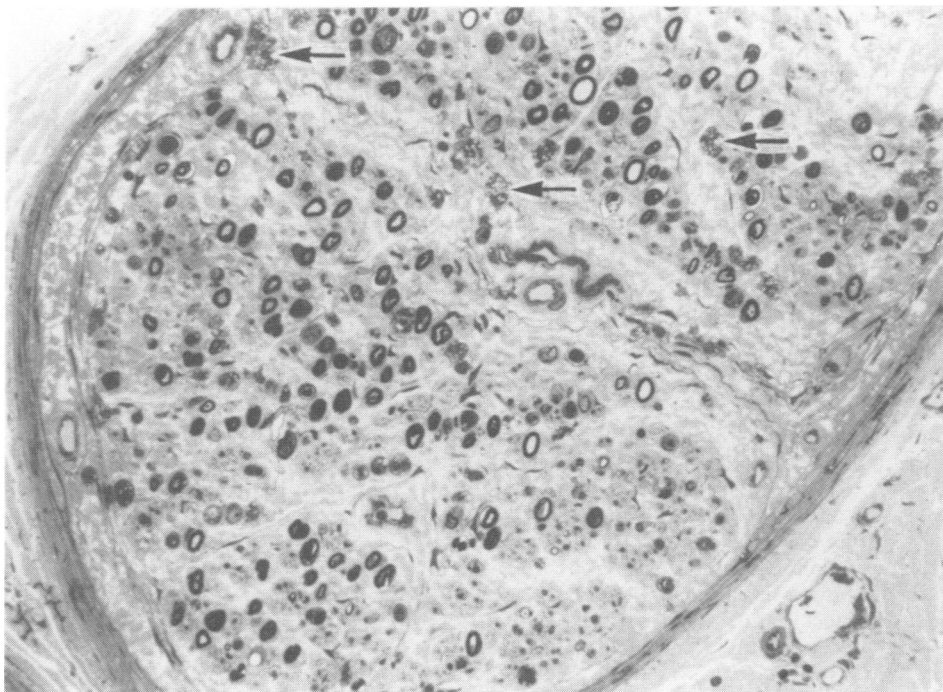*First month in the Critical Care Unit.

Fig 2 *Cross section of superficial peroneal nerve in patient 5 to show severe ongoing axonal degeneration; only a few viable nerve fibres remain. Lipid laden macrophages (↑) are scattered throughout the endoneurium (Toluidine blue stain. Mag × 289).*

Patient 5
A 29-year-old male truck driver was admitted to the critical care unit following a motor vehicle accident. He was unresponsive and had evidence of severe scalp and facial lacerations, facial fractures, destruction of the left eye and a left temporal lobe haematoma. There were occasional, spontaneous flexion movements of the arms, increased tone in the limbs, and moderately reduced deep tendon reflexes. Plantar responses were extensor. He was given intravenous mannitol, pavulon, decadron, antibiotics (table 4) and full ventilatory assistance. Intracranial pressure monitoring revealed increasing oedema and he was given a 9-day course of sodium thiopental to induce barbiturate coma. He became febrile and sputum cultures grew beta haemolytic streptococcus and *Escherichia coli.* At 11 days, when the effects of the barbiturate coma had subsided, he would open his right eye to voice, fixate on the examiner and move that eye in all directions. The right pupil reacted normally. He would grip with his left hand and withdraw all extremities to painful stimulation. At 14 days, painful stimulation evoked only minimal flexion of both arms and no movement in the legs, which remained flaccid, areflexic and immobile. The CSF was unremarkable (table 1). On day 10, total parenteral nutrition was started. At 7 weeks, he began to grip more strongly with

his hands. The deep tendon reflexes in the arms returned and weak flexion movements of the hips appeared during tracheal suctioning. Distal limb movements eventually became severely wasted. Persisting infection prevented transfer to the EMG laboratory for testing. At 3 months, he died of a cardiac arrest following an emergency cholecystectomy.

Necropsy revealed mild organising subdural haematomas and subarachnoid haemorrhage over the cerebral hemispheres and spinal cord. There were contusions of the left temporal lobe and diffuse, resolving, petechial haemorrhages and axonal retraction balls throughout the brain. The corticospinal tract had undergone mild, bilateral degeneration. The spinal cord and ventral and dorsal nerve roots were normal. The common peroneal, and superficial and deep peroneal nerves showed severe loss of myelinated fibres and ongoing axonal degeneration (fig 2). The majority of the fibres were undergoing Wallerian degeneration (table 3). There was denervation atrophy, mild in the intercostal psoas and paraspinal muscles, moderate in the deltoid muscle, and severe in peroneus longus, gastrocnemius, tibialis anterior and quadriceps muscles. It was concluded the patient had suffered a severe, primary axonal, motor and sensory polyneuropathy of undetermined aetiology.

Results

1 The Clinical setting

The initial primary illnesses were diverse (fig 1), but each patient soon developed one of several forms of severe pulmonary disease: adult respiratory distress syndrome;[6] empyema complicating surgical procedures for hiatus hernia; obstructive lung disease; bilateral lobar pneumonia; and multiple lung abscesses, respectively. Full ventilatory support and transfer to the critical care unit were necessary within five days of admission to hospital, a tracheostomy was ultimately required and blood gases were thereby well controlled. But signs of sepsis were soon evident and cultures grew a variety of organisms (see Case Reports). Antibiotics were prescribed in different combinations, depending upon antibiotic sensitivities (table 4); all patients received aminoglycosides. Chronic diarrhaea, likely induced by antibiotics and antacids, ensued in each patient; and while *Clostridium difficile* was not cultured from stool, pseudomembranous enterocolitis[7] was diagnosed by rectal biopsy in patients 2 and 3. All patients had nonspecific nutritional deficiency; the mean (range) of serum albumin and blood lymphocytes were: initially 2·8 (1·9–3·4) and 870 (420–1,240) and at one month 2·8 (2·7–2·9) and 740 (330–2,050), normal ranges 3·5–5·0 g/dl. and 1,500–3,500 per mm,[3] respectively. Transient, diffuse oedema of the body, suggesting the "sick cell syndrome"[8] invariably developed. A variety of water and electrolyte disturbances occurred and were corrected appropriately. Patient 1 had transient renal failure and patient 4 had transient liver and renal failure. Thus, systemic illness with evidence of sepsis and multiorgan dysfunction dominated the clinical picture of all five patients during their prolonged stay in the critical care unit.

Cerebral manifestations—transient metabolic encephalopathy in patient 1, multifocal petechial haemorrhages due to thrombotic thrombocytopenic purpura (with recovery) in patient 4, and severe head trauma as a primary event in patient 5—seemed, except for the former, aetiologically unrelated to the polyneuropathy.

2 Clinical features of the polyneuropathy

This complication was evident within one month of admission to the critical care unit. Clinical evaluation of patients in this setting is often difficult because of the severe systemic illness and because methods of ventilatory support and other equipment attached to patients prevent effective history-taking and physical examination. As noted below, electrophysiological examination provided early and definitive evidence of polyneuropathy. However,

certain clinical signs strongly suggested the diagnosis. Spontaneous limb movements became increasingly weak and the muscles were flaccid on passive limb movement. Painful stimulation of the limbs produced weak grimacing of facial muscles but the expected flexion movements of the limbs were inappropriately weak, both proximally and distally. Finally, the deep tendon reflexes that had previously been present became absent. The distribution of the clinical signs suggested involvement of cranial nerves and nerve roots, as well as peripheral nerves, in a polyradiculoneuropathy pattern. Autonomic dysfunction was not evident clinically.

The cerebrospinal fluid was unremarkable (table 1). The protein was only mildly elevated in patients 2 and 5, and the cells were increased only in patient 4 due to purpura.

Patients 1 and 2 recovered gradually over a matter of months, but there was still evidence of a mild polyneuropathy in patient 1 after two years, and a moderate polyneuropathy in patient 2 at 10 months. The remaining three patients died of causes unrelated to the polyneuropathy, but beforehand had clinical and electrophysiological evidence of beginning recovery. In patients 2, 3, 4 and 5, the onset of recovery followed the institution of total parenteral nutrition, and was maintained despite recurring infection and antibiotic therapy (fig 1).

3 Electrophysiological features

Studies in the electromyography laboratory provided an early and clear indication of polyneuropathy. Impulse conduction of motor and sensory fibres was normal or minimally prolonged in proximal and distal segments as measured by F wave latencies, conduction velocities and distal latencies. However, the amplitude of compound muscle and sensory nerve action potentials was severely reduced (table 2). In comparing amplitudes on proximal and distal stimulation, conduction block was not evident. Concentric needle electrode studies revealed numerous fibrillation potentials and positive waves, and marked reduction in numbers of motor unit potentials in proximal and distal limb muscles. The facial muscles showed similar, less severe abnormalities in patients 2 and 4. In patient 3, phrenic nerve conduction[4] failed to evoke responses from either leaf of the diaphragm and needle electrode study of intercostal muscles indicated severe denervation.

The electrophysiological abnormalities were consistent with severe axonal degeneration and resulting denervation of skeletal muscle.[9] Follow-up nerve conduction (table 2) and needle electrode studies indicated axonal regeneration of nerve and reinnervation of muscle, substantial in patient 1, and begin-

ning to occur in patients 2, 3 and 4.

4 Morphological features

Samples of anterior and posterior nerve roots, proximal and distal, mixed and cutaneous nerves (patients 3, 4 and 5), were examined by bright field and electron microscopy and teased fibre techniques. They demonstrated in all three patients findings of a moderate to severe, primary, axonal polyneuropathy involving both sensory and motor fibres. Widespread sampling of nerve and muscle suggested that this was most severe distally. In patients 3 and 4, there was evidence of nerve fibre regeneration. In patient 3, muscle biopsies from various sites revealed moderately severe grouped atrophy of type 1 and type 11 fibres. Additional myopathic features and cytoarchitectural disorganisation of muscle fibres were observed. These may have been secondary to the denervation or may represent a primary muscle change.

5 Aetiological investigations

These investigations failed to disclose a cause. Peak blood levels of gentamycin and tobramycin were never in toxic ranges, and trough blood levels only occasionally. Arsenic and lead were not elevated in the urine and blood in patients 2 and 3 and no patient showed clinical signs of arsenic, lead, mercury, thallium or bismuth intoxication.[10] The screening test for urinary porphyrins was absent in cases 1, 2, 3 and 4. Acute and convalescent serum for complement fixing antibodies to influenza A and B, adenovirus, psittacosis, Q fever, *Mycoplasma pneumoniae,* respiratory syncytial virus, mumps V and S, herpes simplex and varicella viruses showed no significant changes in patients 1, 2 and 3. Tissue culture and animal inoculation of cerebrospinal fluid in patient 1 was negative for virus. Serum thyroxine values were normal in patients 1, 2 and 3. The serum phosphate was elevated only in patient 4 in association with transient renal failure. The serum magnesium and creatine kinase values were normal. However, the serum albumin and blood lymphocyte counts (see Clinical Setting) suggested a poor nutritional status. Unfortunately, blood levels of folic acid and vitamin B12 were not measured prior to institution of total parenteral nutrition (except for a normal vitamin B12 level in patient 1).

Discussion

The polyneuropathy in our patients disclosed characteristic features: underlying major systemic illnesses, notably infection and respiratory failure; as these conditions improved, weakness of respiratory muscles, revealed as a difficulty in weaning from the ventilator; then, quickly developing signs of a severe motor and sensory polyneuropathy; unremarkable cerebrospinal fluid; electrophysiological and morphological evidence of a primary, axonal degeneration of peripheral nerves; and gradual, spontaneous improvement.

The aetiology is still uncertain, despite a thorough analysis of clinical records, and complete necropsy studies of three patients. A specific search for a virus in patients 1, 2 and 3 was negative, and there was no evidence of central nervous system inflammation at necropsy. Heavy metal poisoning, porphyria and vasculitis were largely excluded (see *Results*), diabetes mellitus was an associated condition only in patient 1, and evidence for coagulopathy was found only in patient 4. Of the remaining possibilities, three main ones should be considered: a dysimmune disorder, such as Guillain-Barré syndrome, a circulating neurotoxin or a nutritional deficiency.

The predisposing conditions of infection and trauma, the pattern of clinical involvement of cranial, trunk and limb nerves, indicating a polyradiculoneuropathy, and the monophasic course, all favour the diagnosis of Guillain-Barré syndrome.[11] However, we believe this diagnosis is unlikely because of the normal or minor elevation in cerebrospinal fluid protein,[12] the electrophysiological signs of primary axonal degeneration rather than demyelination of peripheral nerves,[9,13,14] and the lack of significant demyelination or inflammation of nerves or nerve roots[15,16] on morphological study. (Note, occasional clusters of mononuclear inflammatory cells were seen at necropsy in the peripheral nerves of patient 3, but not in patients 4 and 5).

The electrophysiological and morphological evidence of a primary axonal degeneration suggests either a toxin or nutritional deficiency[17-19] affecting *only* the peripheral nervous system. Of the various toxins, the most likely endogenous source is bacterial infection, since there was sepsis in all patients; but none of the organisms isolated produce a toxin which is known to affect peripheral nerves; in particular *Cornyebacterium diphtheriae* and *Legionella pneumophilia*[20] were not cultured. Nonetheless, sepsis is known to have widespread[21] and, as yet, poorly understood effects which include accelerated skeletal muscle protein breakdown (patient 3 showed morphological evidence of primary myopathic changes in addition to denervation atrophy)[22,23] but might also include peripheral nerve damage.

Antibiotics are the most obvious source of an exogenous toxin, particularly aminoglycosides, the only group prescribed to all patients. However, while damage to the kidney, eighth cranial nerve

and neuromuscular junction have been well documented complications, polyneuropathy has not.[24-27] The possible exception to this is the recently reported "acute sensory neuronopathy"[28] which was believed by the authors to be a toxic effect of antibiotics or an unusual form of Guillain-Barré syndrome. While differing in its purely sensory involvement, it developed in the same clinical setting as our cases, and it may ultimately be shown to have a similar aetiology.

Nutritional deficiency must be considered.[19 29] Critical illness is known to place excessive demands on nutritional mechanisms,[30] and as in our patients, depress peripheral blood lymphocyte counts and serum albumin. Moreover, after the institution of total parenteral nutrition the polyneuropathy improved (fig 1). Our formula presumably supplied nutrients that were compatible with recovery, and was not deficient in substances such as chromium[31 32] and phosphate,[33] reported to cause polyneuropathy *after* the institution of total parenteral nutrition.

Conversely, specific vitamin deficiency seems unlikely. Acute thiamine deficiency seldom causes an isolated polyneuropathy,[34] but often produces Wernicke's encephalopathy,[35 36] of which our patients had no clinical or necropsy evidence. Deficiency of niacin, pellagra, effects the peripheral nervous system minimally, and the central nervous system maximally.[37] B12 deficiency causes polyneuropathy, but predominantly a subacute combined degeneration of the spinal cord,[38] a condition not present at necropsy in our patients. Pyridoxine deficient polyneuropathy is associated with the use of isoniazid and hydralazine;[19] our patients received neither of these drugs. Vitamin E deficiency causes prominent cerebellar, as well as peripheral nerve signs,[41] again not evident in our patients.

Nonetheless, "nonspecific" nutritional deficiency may cause polyneuropathy. This, and a variety of central nervous systems signs, may complicate gastric stapling for morbid obesity.[40-42] The importance of proper maintenance of the nutritional status in critically ill patients has been recently emphasised.[30 43] As already noted, the effects of undernutrition, or other metabolic disturbances, are currently centred on catabolic changes in skeletal muscle. This contributes to initial respiratory failure and later difficulty in weaning from the ventilator.[44-48] Our observations suggest that polyneuropathy, with a major effect on nerves to respiratory muscles, must be added to the list of causes of neuromuscular respiratory failure in critically ill patients.

We suggest that the nutritional status of patients admitted to critical care units be given close attention. The precise indications for instituting total parenteral nutrition are still being debated, but our observations suggest this treatment should be considered early in the course of critical illness. Potentially neurotoxic substances, notably aminoglycoside antibiotics, should be discontinued, if possible, at the first sign of unexplained respiratory insufficiency, weakness of limb muscles, or reduction of deep tendon reflexes. Appropriate electrophysiological investigation of the peripheral nervous system will detect this polyneuropathy at an early stage. Indeed, subsequent observations have disclosed further cases in our unit,[49] and in a unit at Minneapolis.[50] Intensive, prospective investigation of such patients may disclose the true cause.

References

1 Bolton CF, Baltzan MA, Baltzan RB. Effects of renal transplantation on uremic neuropathy; a clinical and electrophysiologic study. *N Engl J Med* 1971;**284**:1170.

2 Bolton CF, Sawa GM, Carter K. The effects of temperature on human compound action potentials. *J Neurol Neurosurg Psychiatry* 1981;**44**:407-13.

3 Kimura J. F-wave velocity in the central segment of the median and ulnar nerves: A study in normal subjects and in patients with Charcot-Marie-Tooth disease. *Neurology (Minneap)* 1974;**24**:539.

4 Newsome-Davis J. Phrenic nerve conduction in man. *J Neurol Neurosurg Psychiatry* 1967;**30**:420-6.

5 Dyck PJ. Pathologic alterations of the peripheral nervous system of man. In: Dyck PJ, Thomas PK, Lambert EH, eds. *Peripheral Neuropathy*. Philadelphia: WB Saunders 1975:410-23.

6 Hopewell PC, Murray SF. The adult respiratory distress syndrome. *Ann Rev Med* 1976;**27**:343-56.

7 Garrod LP, Lambert HP, O'Grady F. *Antibiotic and Chemotheraphy, 5th ed.* Edinburgh: Churchill Livingstone 1981:346.

8 Flear CT, Bhattacharya SS, Singh CM. Solute and water exchanges between cells and extracellular fluids in health and disturbances after trauma. *J Parenter Enteral Nutr* 1980;**4**:98-119.

9 Bolton CF, Gilbert JJ, Girvin JP, Hahn AF. Nerve and muscle biopsy: electrophysiology and morphology in polyneuropathy. *Neurology (Minneap)* 1979;**29**:354-62.

10 Goldstein NP, McCall JT, Dyck PJ. Metal neuropathy. In: Dyck PJ, Thomas PK, Lambert EH, eds. *Peripheral Neuropathy*. Philadelphia: WB Saunders 1975:1229-62.

11 Arnason BGW. Inflammatory polyradiculo-

neuropathies. In: Dyck PJ, Thomas PK, Lambert EH, eds. *Peripheral Neuropathy*. Philadelphia: WB Saunders 1975:1110–3.

12 Andersson T, Siden A. A clinical study of the Guillain-Barré syndrome. *Acta Neurol Scand* 1982;**66**:316–27.

13 Sumner AJ. Axonal polyneuropathies: In: Sumner AJ, ed. *The Physiology of Peripheral Nerve Disease*. Philadelphia: WB Saunders 1980:340–3.

14 McLeod, JG. Electrophysiological studies in the Guillain-Barré syndrome. *Ann Neurol* 1981; **9(suppl)**:20–7.

15 Asbury AK. Diagnostic considerations in Guillain-Barré syndrome. *Ann Neurol* 1981;**9(suppl)**:1–5.

16 Asbury AK, Arnason BG, Adams RD. The inflammatory lesion in idiopathic polyneuritis. *Medicine* 1969;**48**:173–215.

17 Spencer PS, Schaumburg HH. Pathobiology of neurotoxic axonal degeneration. In: Waxman SC, ed. *Physiology and Pathobiology of Axons*. New York: Raven Press 1978:265–82.

18 Schaumberg HH, Spencer PS. Toxic neuropathies. *Neurology (Minneap)* 1979;**29**:429–31.

19 Erbsloh F, Abel M. Deficiency neuropathies. In: Vinken P, Bruyn GW, eds. *Handbook of Clinical Neurology*. New York: North Holland 1970;**7**:558–663.

20 Holliday PL, Cullis PA, Gilroy J. Motor neuropathy in a patient with Legionnaires' disease. *Ann Neurol* 1982;**12**:4930–40.

21 Beisel WR, Sobocinski PZ. Endogenous mediators of fever-related metabolic and hormonal responses. In: Lipton JM, ed. *Fever*. New York: Raven Press 1980:39–48.

22 Beisel WR. Mediators of fever and muscle proteolysis. *N Engl J Med* 1983;**308**:586–7.

23 Clowes GH, George BC, Villee CA, Saravis CA. Muscle Proteolysis induced by a circulating peptide in patients with sepsis or trauma. *N Engl J Med* 1983;**308**:545–52.

24 Cluff LE, Caranasos GJ, Stewart RB. Clinical problems with drugs. In: Smith LH, ed. *Major Problems in Internal Medicine*. Vol. 5. Philadelphia: WB Saunders 1975:147–8, 184–6.

25 Le Quesne PM. Iatrogenic neuropathies. In: Vinken P, Bruyn GW, eds. *Handbook of Clinical Neurology*. Vol. 7. New York: North Holland 1970;**7**:527–51.

26 Phillips I. Aminoglycosides. *Lancet* 1982;**2**:311–4.

27 Neu HC. Pharmacology of aminoglycosides. In: Whelton A, Neu HC, eds. *The Aminoglycosides*. New York: Marcel Dekker 1982:136.

28 Sterman AB, Schaumberg HH, Asbury AK. The acute sensory neuronopathy syndrome: a distinct clinical entity. *Ann Neurol* 1980;**7**:354–8.

29 Dastur DK, Manghani DK, Osuntokun BO, Sourander P, Kondo K. Neuromuscular and related changes in malnutrition. *J Neurol Sci* 1982;**55**:207–30.

30 Fischer JE. Nutritional management. In: Berk SL, Sampliner JE, Artz SS, *et al. Handbook of Critical Care*. Boston: Little, Brown and Co 1976:4–5.

31 Jeejeebhoy KN, Chu RC, Marliss EB, Greenberg GR, Bruce-Robertson A. Chromium deficiency, glucose intolerance, and neuropathy reversed by chromium supplementation, in a patient receiving long-term

parenteral nutrition. *Am J Clin Nutr* 1977;**30**:531–8.

32 Freund H, Atamian S, Fischer JE. Chromium deficiency during total parenteral nutrition. *JAMA* 1979;**241**:496–8.

33 Weintraub MI. Hypophosphatemia mimicking acute Guillain-Barré-Strohl syndrome. *JAMA* 1976; **235**:1040–1.

34 Erbsloh F, Abel M. Deficiency neuropathies. In: Vinken P, Bruyn GW, eds. *Handbook of Clinical Neurology*. New York: North Holland 1970;**7**:561.

35 Victor M, Adams RD, Collins GH. The Wernicke-Korsakoff syndrome. In: Plum F, McDowell FH, eds. *Contemporary Neurology Series*. Philadelphia: FA Davis Co 1971:1–206.

36 Harper CG. Sudden, unexplained death and Sernicke's encephalopathy: a complication of prolonged intravenous feeding. *Aust NZ J Med* 1980;**10**:230–5.

37 Ishii N, Nishihara Y. Pellagra among chronic alcoholics: clinical and pathological study of 20 necropsy cases. *J Neurol Neurosurg Psychiatry* 1981;**44**:209–15.

38 Erbsloh F, Abel M. Deficiency neuropathies. In: Vinken P, Bruyn GW, eds. *Handbook of Clinical Neurology*. New York: North Holland 1970;**7**:587–94.

39 Harding AE, Muller DP, Thomas PK, Willison HJ. Spinocerebellar degeneration secondary to chronic intestinal malabsorption: a vitamin E deficiency syndrome. *Ann Neurol* 1982;**12**:419–24.

40 Feit H, Glasberg M, Ireton C, Rosenberg RN, Thal E. Peripheral neuropathy and starvation after gastric partitioning for morbid obesity. *Ann Intern Med* 1982;**96**:453–5.

41 Paulson WG, Mojzisik C, Carey L, Martin E. Neurologic complications of gastric stapling for morbid obesity. *Neurology (NY)* 1983;**33 (suppl 2)**:190.

42 McComas CF, Riggs JE, Breen LA *et al*. Neurologic complications following gastric plication. *Neurology (NY)* 1983;**33 (suppl 2)**:191.

43 Larca L, Greenbaum DM. Effectiveness of intensive nutritional regimes in patients who fail to wean from mechanical ventilation. *Crit Care Med* 1982;**10**:297–300.

44 Gertz J, Hedenstierna G, Hellens G, Wahren J. Muscle metabolism in patients with chronic obstructive lung disease and acute respiratory failure. *Clin Sci Mol Med* 1977;**52**:395.

45 Driver AG, LeBrun M. Iatrogenic malnutrition in patients receiving ventilatory support. *JAMA* 1980;**244**:2195–6.

46 Covelli HD, Black JW, Olsen MS, Beekman JF. Respiratory failure precipitated by high carbohydrate loads. *Ann Intern Med* 1981;**95**:579–81.

47 Askanazi J, Nordenstrom J, Rosenbaum SH, *et al*. Nutrition for the patient with respiratory failure. *Anaesthesiology* 1981;**54**:373–7.

48 Roussos C, Macklem PT. The respiratory muscles. *N Engl J Med* 1982;**307**:786–97.

49 Bolton CF, Brown JD, Sibbald W. The electrophysiological investigation of respiratory paralysis in critically ill patients. *Neurology (NY)* 1983;**33 (suppl)**:186.

50 Roelofs RI, Cerra F, Bielka N *et al*. Prolonged respiratory insufficiency due to acute motor neuropathy: a new syndrome? *Neurology (NY)* 1983;**33 (suppl)**:240.