Motor neuropathy associated with abnormal pyruvate metabolism unaffected by thiamine

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The most comprehensive investigation of pyruvate metabolism in peripheral neuropathy is that of Joiner, McArdle, and Thompson (1950). They divided their patients into three groups according to the results of pyruvate metabolism tests (Williams, Mason, Power, and Wilder, 1943). One group (18 cases) contained those with normal blood pyruvate concentrations; in another group (nine cases) were those with abnormal pyruvate values which returned to normal after treatment with either parenteral thiamine for two weeks or intramuscular dimercaproproanol (B.A.L.); and the third group (four cases) comprised those in whom the pyruvate values were abnormally high and in whom treatment with neither thiamine nor B.A.L. produced either clinical benefit or a return to normal of the pyruvate concentrations. This third group is of obvious importance. Subsequently Thompson (1952) proposed a classification of cases of peripheral neuropathy according to the results of pyruvate measurements. Abnormal blood pyruvate values have since been described in patients with a peripheral neuropathy associated with carcinoma (Kremer and Pratt, 1952; Heathfield and Williams, 1954; Henson, Russell, and Wilkinson, 1954) and with multiple myelomatosis (Hutchinson, Leonard, Maudsley, and Yates, 1958).

Pyruvate metabolism tests have been performed on 101 patients with neuropathy, between 1960 and 1964. In 84 of the 101 the results were normal. In 17 patients the results were abnormal: in seven of these they returned to normal on treatment with vitamin B1; four of the patients were diabetic, and two had vitamin B12 deficiency; in both these states, patients may exhibit abnormal pyruvate values (Earl, El Hawary, Thompson, and Webster, 1953; Hornbrook and Marks, 1960; Fry and Butterfield, 1962). There remain four patients with neuropathy who had abnormal pyruvate metabolism tests which were unaffected by treatment with thiamine or vitamin B12. They are described here as in none of them was there evidence of carcinoma or reticulosis.

METHOD

The 'pyruvate metabolism' tests were performed in the morning on patients fasted from 10 p.m. the previous day, but allowed water as desired. After an initial blood sample had been drawn, 50 g. of glucose dissolved in 4 to 1 pint of water was drunk (within 10 min.), and this dose of glucose was repeated 30 min. later. Blood samples were taken 60 and 90 min. after the first glucose drink.

The patients rested in bed before and during the test. Venous blood was drawn from an unexercised arm, usually without venous occlusion but occasionally the venous return was occluded by a sphygmomanometer cuff inflated to 60 mm.Hg for not more than 30 seconds. The pyruvate concentration was determined according to the method of Hockaday (1961), which depends on the isolation of pyruvate 2,4-dinitrophenylhydrazone by paper chromatography in an acetic acid system (Bush and Hockaday, 1960). As with other chromatographic methods for estimation of blood pyruvate (El Hawary and Thompson, 1953; McArdle, 1957), pyruvate added to a mixture of blood and the protein precipitant (metaphosphoric acid) is not completely recovered. The recovery of pyruvate (3-21 μg.) averages 76% ± S.E.M. 2% by the present method. The values of pyruvate as measured have therefore all been multiplied by 1.32 (100 ± 76).

The pyruvate concentrations obtained by this method from 12 healthy subjects of both sexes (aged 16 to 56 years) in pyruvate metabolism tests were: initial 0.34 ± S.D. 0.08 mg./100 ml. (range 0.19-0.56); at 60 min., 0.49 ± S.D. 0.12 mg./100 ml. (range 0.30-0.68); and at 90 min., 0.59 ± S.D. 0.14 mg./100 ml. (range 0.42-0.82).

Blood glucose concentrations were measured in the clinical biochemical laboratory by a glucose oxidase method on an autoanalyser (Discombe, 1963). A mixture of calcium oxalate and fluoride was used as anticoagulant. The values for case 1 were obtained by the Folin-Wu method.

CASE REPORTS

CASE 1 (Radcliffe Infirmary No. 218834) This was a case of steadily progressive motor and sensory neuropathy with death after 10 years.
Mrs. A.M., a 57-year-old housewife, was admitted under Dr. W. R. Russell for the first time in 1956. She had had slowly progressive weakness of the arms and legs since the onset of weakness in the left leg six years previously. Numbness of the feet had begun two years later, and spread slowly upwards to the hips. She had no paraesthesiae. Her arms were first affected two years before admission, with numbness spreading to the elbows and weakness of the hands. For the last year she had been unable to do any housework and for the last two months she was unable to walk or stand and had great difficulty in feeding herself even when food was cut up for her.

In general she had felt well. Menstruation had ceased at age 52. She had no history of previous illness except for anaemia in early adult life. Her mother had diabetes (and died aged 73 years) while a maternal aunt developed 'paralysis' in middle age.

On examination the tongue and mucosa were normal. The blood pressure was 180/120 mm.Hg but fell later to 165/100, and there was no cardiomegaly, heart failure, or retinal abnormality. In the central nervous system the cranial nerves were normal. There was peripheral wasting and weakness in the limbs, with hypotonia and absent tendon reflexes. The abdominal reflexes were absent and the plantar responses down-going. There was marked dorso-lumbar scoliosis. The patient was unable to stand without assistance and her legs were grossly ataxic in attempting to walk. All sensory modalities were affected distal to the elbows and knees. Position sense was absent at the fingers, toes and ankles, present only for gross movements at the wrist, and only sometimes correct at the knees and elbows. Vibration sense was present over the clavicles but absent up to the iliac crests and elbows. Light touch and temperature perception were absent below the elbows and knees, but pain was appreciated more distally, although with reduced sensitivity.

Investigations showed a normal haemoglobin (Hb 103%) and total white blood cell count, with 5% eosinophils. Serum electrolytes were normal. There was a histamine-fast achlorhydria but the serum vitamin B12 concentration was normal (200 μg/ml). Cerebrospinal fluid, obtained at normal pressure, contained protein 200 mg./100 ml. but only four white cells (all lymphocytes) per c.mm. The Wassermann reaction and Lange curve were negative. Urinary porphyrins showed no abnormality. Plasma proteins were normal. She thought that her weight was unchanged at 8 st. 10 lb.

A carcinomatous neuropathy was suspected despite the long history but there was no evidence of neoplastic disease. The patient was discharged home where she remained bed-ridden. Her weakness slowly but steadily increased, and she developed difficulty in chewing and swallowing and nasal regurgitation. Her right eyelid began to droop. She easily became breathless and was orthopnoeic.

On readmission in November 1959 her blood pressure was 180/110 mm.Hg but there was no other evidence of hypertensive disease. Her chest expansion was very limited (vital capacity 700 ml.). In the cranial nerves there was now limitation of upward movement of both eyes and of adduction of the right eye, and marked right ptosis which improved on treatment with prostigmine. The masseter and upper facial muscles were slightly weak on both sides. There was weakness of the left deltoid and in all movements distal to both shoulders, more severe peripherally. There was similar weakness below the hips, and marked weakness of the abdominal and back muscles. Muscle wasting was widespread, the tendon reflexes remained absent, and sensory loss was slightly more extensive.

Haemoglobin was 90% and there was a neutrophil leucocytosis, but no eosinophilia. The E.S.R. was 72 mm./hour (Westergren). A chest radiograph showed a small area of collapse at the right base, which later cleared. Urinary porphyrins again showed no abnormality. Cerebrospinal fluid protein was 115 mg./100 ml.

Pyruvate tolerance tests were abnormal, and are discussed in detail later (see below and Table I). Electrolymographic studies were not performed.

She became more dyspnoeic, with aspiration into the lungs and had a brief episode of cyanosis and unconsciousness, requiring tracheostomy and assisted respiration, but she responded to treatment and was discharged home with the neurological signs very similar to those on admission, except that the right ptosis had much improved.

She survived at home for almost a year but then died from a further chest infection 10 years after the onset of her illness. A post-mortem examination was not made.

Pyruvate tolerance values Pyruvate tolerance tests were performed in December 1959, and again in January 1960 after treatment with parenteral thiamine, and again in February 1960 after recovery from the episode of aspiration pneumonia (Table I).

The fasting blood pyruvate concentration was raised on two out of three occasions and the concentrations after glucose were always markedly abnormal. On two occasions the fasting blood sugar concentrations were a little high but in the second test the blood sugar values did not rise unduly, although they rose to 269 mg./100 ml. at 60 min. in the third test, a value above the normal values for glucose in this test (Matthews, Magath, and Berkson, 1939).

CASE 2 (Stoke Mandeville no. 26020) This case was primarily of motor neuropathy, with deterioration continuing for one year, followed by slow but full recovery, maintained for three and a half years.

Mrs. W.R., a 61-year-old housewife, was transferred from another hospital to the care of Dr. W. R. Russell in October 1961 for diagnosis.

She had pneumonia in 1932 but had otherwise been well until September 1960 when, half an hour after hearing bad news of her husband's health, she had a feeling of weakness, and a sensation of being gripped, in both arms. The weakness worsened while she nursed her husband until his death from carcinoma six weeks later. About one month after his death she collapsed when standing because her legs had given way. She next noticed difficulty in climbing stairs and in dressing. She observed no abnormality of sensation.

She was investigated in hospital in January 1961 and a diagnosis of hysteria was made. At home again, she fell frequently when walking because of weakness of the legs.
She was admitted to a second hospital where all the deep tendon reflexes were noted to be absent; at this time the E.S.R. was raised but the cerebrospinal fluid was normal. Hysteria was again diagnosed and she was discharged on treatment with imipramine. She felt progressively weaker and had little power left in her limbs. Two months after her discharge, she noticed slight improvement in her strength, but, for the first time, a painful tingling at the back of both thighs.

When admitted under Dr. Russell six months later (October 1961) she was unable to walk, stand, dress, or feed herself. Apart from her great weakness, her fingers felt stiff and numb with occasional tingling at their tips. Her forearms and calves often felt stiff and ached but were never tender.

Her general health had remained good throughout, and she had noticed no recent change in weight.

On examination, the only abnormalities were in the nervous system. There was weakness and wasting of all limb muscles, more marked distally. The deep tendon reflexes were absent, and the plantar responses flexor. Coarse fasciculation was seen occasionally in both forearms. There was no objective sensory deficit, and the sweating response to body warming was normal.

Investigations showed Hb 85%, W.B.C. 7,000/c.mm., E.S.R. 40 mm./hr. (later falling to 13 mm./hr. after treatment of urinary infection). Serum electrolytes were normal. Gastric secretion contained free HCl and serum vitamin B12 was 180 μg/ml. Plasma proteins (total and A/G ratio) were normal. L.E. cells could not be demonstrated. Cerebrospinal fluid obtained under normal pressure contained protein 70 mg./100 ml. and no cells; protein fractionation was normal, and the Lange curve negative. Thyroid function tests were normal. An intravenous prostigmine test was negative. A chest radiograph, barium meal and enema, intravenous pyelography, cytology of sputum, and pelvic examination under anaesthesia revealed no abnormality. Biopsy from the right deltoid, a muscle unaffected clinically, showed a wide variation of fibre size (from 30 μ to 90 μ in diameter) with no pattern to the variation; this was the only abnormality: the muscle fibres appeared healthy and there was no degeneration or inflammation. There was no evidence of denervation, and the motor end plates were normal. Electromyographic findings are reported below.

Repeated studies of pyruvate tolerance were made before and after courses of vitamin B12, penicillamine, methionine, and corticosteroids (Table I). On clinical assessment none of these was effective; the changes in pyruvate tolerance are described in detail below.

The patient was discharged home with her condition unchanged, but on readmission in February 1962 she had noticed marked improvement. Muscle bulk appeared unaltered, but both triceps reflexes were now obtainable, her grip was considerably more powerful, and so were wrist and hip movements. Fasciculation was again noted. Improvement continued, so that by May 1962 she could feed, dress, and wash herself. She was walking better but still unable to stand on tiptoe. She still occasionally experienced a burning pain in the palms. Four months later, improvement had continued so that she could write, though fastening buttons was still difficult. All her tendon reflexes had returned. By July 1963 she could walk half a mile, and in 1964 she could mow her lawn. She felt that her strength had returned to normal. She has remained in excellent general health since; on re-examination in June 1965 some wasting was apparent in the small muscles of the left hand, and the limb musculature was generally rather thin and flabby. All reflexes were present and normal, and sensation was intact. Power was within normal limits.

Electromyographic findings Electromyography was performed in October and again in November 1961. Parenteral calcium was given for 48 hours before the second recording. Recordings were taken from two coaxial needle electrodes, which were inserted many times into all the muscles studied. In each muscle, spontaneous activity was recorded in the form of brief (1-5 msec.) potentials with amplitudes less than 300 μV. Some of these spontaneously occurring potentials were polyphasic. In the peronei, not only was this type of spontaneous activity present, but also short bursts of three or four identical potentials occurred, and these became more frequent on hyperventilation. As overbreathing continued, motor units became activated, greater around one recording electrode than the other, and this increased until a highly complex outburst of action potentials was recorded by both electrodes, and the muscle was clearly contracting tetanically.

On maximum voluntary effort, only single motor units of amplitude up to 300 μV were recorded from proximal muscles, and they were often polyphasic and unduly brief. In more distal muscles (such as in the first dorsal interosseus) a moderately complex pattern of activity could be evoked by voluntary effort, but the potentials were briefer than normal (under 9 msec.) and many were also polyphasic.

The conduction velocity of motor nerve fibres to the first dorsal interosseus averaged only 27 m./sec. in spite of normal limb temperature, and the peripheral delay was considerably increased (7-9 msec.). (The interval between stimulation of the ulnar nerve at the wrist and this muscle response should not exceed 5 msec.) The effects of maximum motor nerve tetani on the action potential of the first dorsal interosseus were normal, up to frequencies of 100/sec.

These findings were considered to indicate tetany and a peripheral motor neuritis. The spontaneous brief and polyphasic potentials and the low amplitude polyphasic brief potentials evoked on voluntary action were interpreted as due to muscle disease affecting, principally, the proximal muscles. It was suggested that the combined involvement of peripheral nerve and muscle might be associated with malignant disease, in spite of the normal muscle response to nerve tetanization in a peripheral muscle.

Pyruvate tolerance values Pyruvate tolerance tests were performed in October 1961, and repeatedly thereafter until May 1962 (Table I).

The patient only once had an abnormal fasting pyruvate concentration (December 1961) and this may well have been the result of the cortisone treatment she was receiving at the time (Lövgren, 1952). The values at
CASE 3 (Radcliffe Infirmary no. 321015) This patient had rapidly progressive weakness with muscle wasting, and died after six months.

Mrs. K.A., a 53-year-old housewife, was admitted to hospital in February 1962 because of progressive weakness of the right leg, first noted when climbing stairs eight weeks before admission. Subsequently the weakness made her limp.

On examination, the blood pressure was 180/90 mm. Hg, but general examination was otherwise normal. In the nervous system the right leg and the left arm were weak, with depressed tendon reflexes. The quadriceps and hamstring muscles were wasted on the right. The knee jerk on the left was abnormally brisk and the plantar response on this side was equivocal. Fasciculation was observed on only one occasion—in the right scapular muscles. There was no sensory loss, and no muscle tenderness.

Investigations showed Hb 89% and a normal total and differential white blood cell count. The E.S.R. was 13 mm./hr. Blood urea and plasma electrolytes (sodium, potassium, chloride) were normal but plasma albumin was only 3-0 g./100 ml., with an A/G ratio of 0-94; serum glutamic-oxaloacetic transaminase was 10 units. Plasma protein-bound iodine and 131I uptake studies were normal. There was a mild urinary infection (B. proteus). The cerebrospinal fluid was clear and under normal pressure but contained protein 100 mg./100 ml. No cells were seen, and the Lange curve and Wassermann reaction were negative. Myelography was normal. Biopsy from the left brachio-radialis showed probably normal muscle, but a few unusually small fibres (about 30 μ in diameter) were present.

The patient was readmitted late in March 1962 with further weakening of the right leg and the left arm, and development of weakness in the left leg so that she could no longer walk without help. She had lost 4 lb. in weight in the preceding three weeks, and this continued so that she lost 9 lb. during the next five weeks in hospital. General examination was again normal. There was now marked wasting throughout the left arm (especially in the small muscles of the hand) and of the proximal muscle of both legs. The tendon jerks remained present and were now all brisk, and sensation remained intact.

The plasma proteins and electrophoretic pattern had returned to normal. The E.S.R. had risen to 50 mm./hr. After two weeks in hospital, she developed patchy pneumonic changes in the posterior segment of the right lower lobe, which cleared considerably, although subsequently a pleuritic reaction developed in both costophrenic angles.

The patient was discharged on 2 May 1962, but her condition continued to deteriorate, and she developed headache, restlessness, and dyspnoea. She died at home of respiratory failure on 2 July 1962.

At post-mortem examination the only wasting obvious externally was in the small muscles of the left hand. There were small areas of collapse in the lower lobes of both lungs, and microscopical examination showed the changes associated with inhalation of gastric contents.

There was considerable congestion of the cerebral cortex. The pyramidal tracts were normal but the large neurones of the hypoglossal nuclei were reduced in number and there was a glial reaction in these nuclei. The spinal cord throughout showed a similar depletion of large motor neurones of the anterior horns, with shrinkage of the remaining cells. There was reactive gliosis, mostly by microglia, but a few large astrocytes were present, and there was an excess of astrocytic fibres. One motor neurone was undergoing neuronophagia. There was no evidence of long tract degeneration although in the fourth thoracic segment there was a spongiform degenerative change of the white matter next to the anterior edge of the anterior horn, worse on the right than on the left side. In the lumbar cord there was a peripheral rim of pale-staining myelin. All the anterior roots showed depletion and degeneration of nerve fibres and disintegration of myelin sheaths. The posterior roots appeared normal. Intramuscular nerves were greatly reduced in number without evidence of regeneration. Some axon degeneration was evident. The muscles showed fibre degeneration in a pattern that suggested involvement of motor units, but the typical small fibrotic fascicules of 'motor neurone disease' were not seen.

Electromyographic findings Electromyography was performed in February, and again in March 1962, the last examination being 14 weeks before the patient's death.

On the first occasion, many spontaneous brief potentials (1-5 msec.) were recorded from all the muscles studied, but their amplitudes were often surprisingly large (1,000 μV). Maximum voluntary effort evoked a moderately complex pattern of activity up to about 2,000 μV, and individual action potentials were highly polyphasic and their durations were normal or slightly reduced. In the right gastrocnemius and right extensor digitorum brevis the response to volition was much reduced; action potential size did not exceed 500 μV, and the potentials were not unduly polyphasic. Their mean duration was within normal limits.

The conduction velocity of motor nerve fibres to the extensor digitorum brevis averaged 37 m./sec. and the peripheral delay was also normal.

A month later spontaneous activity was recorded as before, and also from proximal muscles of the arms. There was no response to voluntary activity in the right gastrocnemius, and only a single motor unit could be recorded from the right extensor digitorum brevis. It was polyphasic but of normal duration. Recordings from proximal arm and leg muscles showed a moderately complex pattern of activity in response to volition (in spite of
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considerable muscle weakness); action potential amplitudes were up to 2,000 μV, and many were unduly brief and polyphasic, with brief swings of potential change. Rapid fatigability occurred.

The conduction velocity of motor nerve fibres within the ulnar nerve was normal and so was the peripheral delay.

These findings were thought to be compatible with a combined picture of muscle disease (such as myositis) and rapidly increasing motor nerve involvement, either at root or motor neurone level. Again, the question of associated malignant disease was raised, and it was specifically stated that the electrical findings were unlike those of motor neurone disease.

**Pyruvate tolerance values** Pyruvate tolerance tests were performed on five occasions in February, March, and April 1962 (Table I). On each occasion the patient had normal fasting levels for blood pyruvate with abnormal values after glucose. These values were unchanged by treatment with courses of thiamine, vitamin B₁₂ (1,000 μg. weekly for four doses), dl-methionine (300 mg. t.d.s. for 12 days), and prednisolone (20 mg. q.d.s. for five days and 20 mg. t.d.s. for five days), nor did they show any deterioration during the two months of observation.

**Case 4 (Radcliffe Infirmary no. 327012).** This patient suffered from progressive weakness with muscle wasting and late sensory changes continuing for four and a half years.

Mrs. K.F., a 55-year-old woman, living separated from her husband, was admitted under the care of Dr. Russell in July 1962 because of progressive weakness for 18 months. This began in the left hand and soon after appeared in the left leg. Progressive weakness in all limbs followed, the left leg being most severely affected, and the left arm worse than the right. Paraesthesiae, continuous for hours at a time, were experienced in the right hand. Her weight was unchanged. She was examined at another hospital in November 1961 when the weakness was found to be maximal distally; the left ankle jerk was absent, and there was no objective sensory deficit. The plantar reflexes were downgoing. Fasciculation was suspected in the quadriceps and around the shoulders. The E.S.R. was normal. She reduced her rather excessive alcohol intake and was given injections of vitamin B₁₂ and of mixed B and C vitamins, without effect.

On examination in July 1962 the presence of fasciculation, now widespread, was confirmed. There was wasting of the small muscles of the hands, worse on the left, and slight wasting of the left quadriceps. There was weakness of the ankle plantar and dorsiflexors, the quadriceps, and the left hip flexors. The tendon reflexes were increased, except the ankle jerks which were both thought to be normal. Lumbar puncture yielded cerebrospinal fluid at normal pressure but with a protein content of 100 mg./100 ml.; the Wassermann reaction was negative. Biopsy from the left brachioradialis muscle showed muscle fibre atrophy, distributed by motor units, and probably progressive, as the atrophied fibres varied considerably in size. The appearance was considered compatible with a diagnosis of 'motor neurone disease'.

The patient was given weekly injections of vitamin B₁₂ after discharge, with a presumptive diagnosis of polyneuritis. During 1962 she had transient disturbance of the sphincters (possibly associated with urinary infection). Her weakness progressed so that by February 1963 she needed crutches for walking. She developed a large area on the outside of the right thigh where she experienced pins and needles, and towards the end of 1963 similar paraesthesiae occurred in the tips of some fingers.

On examination in January 1964 she could do little useful with her hands. Her legs, which were mildly oedematous with peripheral cyanosis, showed marked flaccid weakness, still more pronounced on the left. The tendon reflexes remained brisk, but the abdominal reflexes were preserved, and the plantar responses equi-vocal. A prostigmine test was negative. Gastric aspirate contained free HCl. The E.S.R. was 33 mm./hr. Plasma proteins (total and electrophoresis) were normal. Blood Wassermann and Kahn reactions were negative. On repeat lumbar puncture the cerebrospinal fluid contained only 50 mg./100 ml. protein, and no cells. Electro-myography was repeated in April 1964 (see below).

Pyruvate tolerance tests showed impairment (see below and Table I).

By May 1964 objective sensory deficit was present in both hands, with loss of sharp discrimination, and light touch was subjectively altered. The ankle jerks were now unobtainable, although other reflexes remained brisk. By June 1965 the patient's disability had increased, so that she was confined to a wheelchair. She complained of persistent paraesthesiae in the right thigh, and occasional tingling in all fingers. Weakness, wasting and hypotonia, greatest distally, had progressed in all limbs, and all tendon reflexes in the legs were now unobtainable; the arm reflexes remained brisk. Abdominal reflexes were absent, and plantar responses unobtainable. There were also signs of bulbar involvement, affecting facial and jaw movement, speech and swallowing; a brisk jaw jerk was obtained.

**Electromyographic findings** Electromyography was performed on two occasions about two years apart, in February 1962 and again in April 1964.

On the first occasion, spontaneous, brief, low-amplitude potentials were recorded from several muscles, and many motor unit potentials were seen when the muscles were, apparently, at rest. Maximum voluntary effort evoked a moderately complex pattern of action potentials up to about 1,000 μV, but they were polyphasic and their mean duration was less than normal. Fatigue occurred readily. The conduction velocity of motor nerve fibres to the right first dorsal interosseus muscle was normal (55 m./sec.), but the peripheral delay was just outside the normal limit (6 msec.).

These findings were thought to be compatible with combined muscle and nerve disease, possibly carcinomatous neuromyopathy.

Two years later, spontaneous, brief, low-amplitude potentials as well as a few motor units were again recorded from some muscles at rest. In the right first dorsal interosseus muscle no activity at all was recordable, whether spontaneous, in response to volition, or in response to maximum stimulation of the ulnar nerve.
The conduction velocity of motor nerve fibres to the right abductor digiti minimi was 26 m/sec., and the peripheral delay 11 msec.

In other muscles of the arm, maximum voluntary effort evoked a moderately complex pattern of action potentials up to 1,000 μV in amplitude. They were polyphasic and their mean duration was in excess of normal.

The findings on this occasion were considered to be those of a peripheral neuritis.

Pyruvate tolerance values Pyruvate tolerance tests were carried out in April, May, and July 1964 (Table I).

This patient had one abnormal and two normal values for the fasting blood pyruvate but consistently abnormal values after glucose despite administration of vitamins B1 and B12, dl-methionine (2 g., t.d.s.) and prednisolone (in doses decreasing from 40 to 15 mg. daily over four weeks).

**DISCUSSION**

**ELECTROMYOGRAPHIC CHANGES** The electromyographic examination of three of these patients (cases 2, 3, and 4) revealed a number of interesting abnormalities, which were not always easy to interpret.

Spontaneous potentials were recorded from some relaxed muscles in all three patients. Recordings were made distal to the end-plate zone; the spontaneous potentials were biphasic with an initial positive wave, and were very brief and generally of low amplitude. Their durations ranged from just less than 1 msec. up to 5 msec., and their amplitudes from 50 to over 1,000 μV.

In denervated muscle, brief biphasic potentials can be recorded which accompany the spontaneous fibre twitching (fibrillation). The potentials have an initial positive swing and they are thought to originate either from single, or from small groups, of denervated muscle fibres. Measurements on these potentials have generally shown them to have durations within the range 0.5–3 msec., with amplitudes 50–200 μV (Buchthal, 1957), a range of values lower than were found in these cases. During the last five years, more detailed studies of denervated muscle, by means of the multi-electrode as well as by the conventional coaxial needle electrode, have indicated that the limits of the parameters given above are much too rigid (Rosenfalck and Buchthal, 1960, 1962). These workers have found that the amplitude may be as high as 8,500 μV and the duration as long as 5 msec. It appears that these 'giant fibrillation potentials' originate from the spontaneous activity of about 20 denervated muscle fibres, as many as make up a normal subunit.

This type of spontaneous activity of groups of muscle fibres is not, however, confined to the state of denervation. It is common in both muscle dystrophy and in polymyositis (Lambert, Beckett, Chen, and Eaton, 1950; Lambert, Sayre, and Eaton, 1954; Norris and Chatfield, 1955), and one must look, therefore, for other electrical abnormalities to differentiate between weakness due to partial denervation and that due to muscle disease.

In muscle disease, the pathological process is scattered among individual muscle fibres, and only in terminal cases is it severe enough to destroy the whole of the motor unit. In less severe cases then, maximum voluntary effort will evoke a moderately

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**TABLE I**

RESULTS OF PYRUVATE TOLERANCE TESTS

<table>
<thead>
<tr>
<th>Date</th>
<th>Pyruvate (mg./100 ml.)</th>
<th>Glucose (mg./100 ml.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>60</td>
</tr>
<tr>
<td><strong>Case 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated Dec. '59</td>
<td>0.94</td>
<td>1.28</td>
</tr>
<tr>
<td>After vitamin B1 Jan. '60</td>
<td>0.40</td>
<td>1.12</td>
</tr>
<tr>
<td>Off respirator Feb. '60</td>
<td>0.79</td>
<td>1.51</td>
</tr>
</tbody>
</table>

| **Case 2** |     |     |     |     |     |
| Untreated Oct. '61 | 0.48 | 1.19 | 1.36 | 65 | 123 | 128 |
| After B1 Oct. '61 | 0.36 | 1.27 | 1.20 | 85 | 162 | 132 |
| After penicillin Nov. '61 | 0.40 | 1.12 | 1.32 | 75 | 170 | 135 |
| After methionine Nov. '61 | 0.53 | 1.12 | 1.02 | 105 | 175 | 145 |
| After cortisone Dec. '61 | 0.59 | 0.92 | 0.98 | 100 | 170 | 130 |
| Improvement begun Feb. '62 | 0.30 | 0.79 | 0.03 | 65 | 123 | 138 |
| Later, improvement marked May '62 | 0.28 | 0.56 | 0.76 | 30 | 145 | 50 |

| **Case 3** |     |     |     |     |     |
| Untreated Feb. '62 | 0.38 | 1.12 | 1.04 | 67 | 180 | 107 |
| After B1 Feb. '62 | 0.35 | 1.17 | 1.10 | 106 | 63 | 59 |
| After B12 Mar. '62 | 0.41 | 1.21 | 1.29 | 87 | 139 | 216 |
| After methionine Apr. '62 | 0.20 | 0.89 | 0.99 | 71 | 126 | 183 |
| After prednisone Apr. '62 | 0.40 | 0.99 | 1.13 | 103 | 199 | 238 |

| **Case 4** |     |     |     |     |     |
| After B1 and B12 Apr. '64 | 0.72 | 0.79 | 0.88 | 65 | 90 | 95 |
| After methionine May '64 | 0.51 | 0.86 | 1.00 | 93 | 125 | 83 |
| After cortisone July '64 | 0.52 | 0.77 | 1.02 | 85 | 146 | 130 |
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or highly complex pattern of electrical activity, but the individual action potentials will be much briefer than normal, polyphasic, and of relatively low amplitude, because of the great reduction both of the territory and of the fibre content of the motor unit (Kugelberg, 1949; Guy, Lefebvre, and Scherrer, 1950; Buchthal and Pinelli, 1953; Pinelli and Buchthal, 1953; Buchthal, Rosenfalck, and Erminio, 1960). These electrical features were apparent in some of the proximal muscles of our patients.

In muscle disease alone the conduction velocity of motor nerve fibres is normal (Lambert et al., 1954), whereas in two of our cases (cases 2 and 4) it was reduced to almost half normal (27 and 26 m./sec.) and the peripheral delay (interval between stimulation of ulnar nerve at wrist and response in abductor digit minimi) was in both cases increased above the maximum normal limit of 4 msec. This type of uniform reduction of motor nerve conduction velocity is typical of a peripheral neuropathy, affecting motor nerve fibres distal to motor roots.

Cases 3 and 4, especially, showed rapidly progressive denervation of some distal muscles. Two of our cases (cases 3 and 4) showed, in addition, excessive fatigability. In one of our cases (case 2), the responses to maximum motor nerve tetani at frequencies from 1/sec. to 100/sec. were quite normal, unlike those in myasthenia (Desmedt, 1958) or carcinomatous pseudo-myasthenia (Eaton and Lambert, 1957).

Neither the muscle biopsy nor the electromyogram was typical of motor neurone involvement in case 3, but the muscle taken at necropsy, approximately three months later, showed fibre degeneration in a pattern suggesting involvement of motor units, although without the small fibrotic fascicles of 'motor neurone disease'. It is clear that this patient did not have typical motor neurone disease, and it is possible that the motor neurone destruction found at necropsy was part of a biochemical lesion, of which an increased blood pyruvate level was one manifestation. If this were so, it would be reasonable to postulate that muscle-fibre function could be impaired, producing functional reduction of the motor-unit territory and thus brevity and polyphasicity of recorded action potentials with excessive fatigability with minimal histological changes. A disturbance of serum potassium levels has been shown to produce this type of functional reduction of motor-unit territory and subsequent changes of action-potential parameters (Hausmanowa-Petrusewicz, Emeryk, and Lao, 1962).

**PYRUVATE TOLERANCE ABNORMALITIES** Although thiamine deficiency, the classical cause of impaired pyruvate metabolism, was thought to be excluded in these patients (from the history, and by the lack of effect of its parenteral administration), the raised pyruvate concentrations that were found could still be due to an impaired breakdown of pyruvate by decarboxylation. The two other major reactions undergone by pyruvate are reduction to lactate and carboxylation to a 4-carbon compound, an important initial step if pyruvate is to be used in carbohydrate synthesis. Increased blood pyruvate levels could also result from its overproduction from carbohydrate or from alanine by transamination.

The oxidative decarboxylation of pyruvate is a complex reaction (Breslow, 1961; Fruton and Simmonds, 1958), involving many stages and several co-factors (magnesium, thiamine pyrophosphate, coenzyme A, and lipoic acid). It was with the hope of influencing one of these that vitamin B₁₂, penicillamine, and methionine were administered to these patients. Abnormal pyruvate metabolism has been corrected by vitamin B₁₂ in a few instances (Earl et al., 1953; Hornbrook and Marks, 1960), by methionine in African children with kwashiorkor (Edozien, 1959) and, occasionally, by thiol compounds (Joiner et al., 1950). Arsenicals, another cause of abnormal pyruvate metabolism (Peters, Sinclair, and Thompson, 1946), and of peripheral neuropathy (Ross and Reynolds, 1901), are thought to react with sulphhydryl groups of pantothenic acid, or of lipoic acid, or of both of these compounds.

An abnormality of pyruvate metabolism was possibly demonstrated in one patient with acute intermittent porphyria (Hierons, 1957) but no abnormality of urinary excretion of porphyrins or of porphobilinogen was found in the four patients. However, Richards and Brinton (1962) have shown how porphyria, clinically typical and with associated neuropathy, may be diagnosable chemically only after loading with glycine. Excess of insulin may cause ventral horn cell damage (Tom and Richardson, 1951; Rosner and Elstad, 1964), but again there was neither clinical nor chemical evidence of this.

The failure of the three agents tested to reverse the abnormal pyruvate metabolism does not, of course, exclude a defect in the pyruvate decarboxylase reaction. However, the duration of the treatments should have been adequate, by analogy with the rapid effect (within 24 hours) of thiamine on the abnormal pyruvate concentrations in thiamine deficiency (as opposed to its slow or even negligible effect upon the neurological state).

There was no reason to suspect impaired reduction to lactate in these patients, and on the two occasions (in one patient) when lactate concentrations were measured they were found to be elevated, and the lactate/pyruvate ratios were normal (case 4, after methionine and after cortisone).
The mechanism of all experimentally produced elevations of pyruvate concentration is not understood. Thus, in alkalosis, metabolic (Huckabee, 1958) or respiratory (Eldridge and Salzer, 1965), venous pyruvate concentration may increase. There was no evidence of alkalosis in any of these patients. The second determination on case 1 was made while she was receiving artificial respiration but there was no reason to think that she was being overventilated; moreover, the result was virtually the same when she was breathing naturally.

Abnormal pyruvate concentrations have been reported in patients with multiple sclerosis (Jones, Jones, and Bunch, 1950; McArdle, MacKenzie, and Webster, 1960), a disease in which no biochemical defect likely to produce such a change is known. The measurements were mostly made by the less specific Friedemann-Haugen method (with only partial purification of pyruvate 2:4-dinitrophenylhydrazone from other \( \alpha \)-keto acids before its colorimetric determination) (Friedemann and Haugen, 1943), but they were sometimes confirmed chromatographically. As pyruvate is the principal \( \alpha \)-keto acid in blood, it is likely to contribute most to changes in the Friedemann-Haugen values.

McArdle et al. (1960) found a correlation between abnormal pyruvate metabolism and spasticity, with perhaps a contribution from 'malnourishment' in the more severely ill patients. Spasticity was not a feature of the patients reported here. One patient (case 3) possibly had motor neurone disease but pyruvate metabolism tests in four patients with typical motor neurone disease have all been normal. Neither immobility nor muscle wasting would seem possible causes of the abnormal pyruvate results, both because of the normal results found in the main bulk of patients with peripheral neuropathy, and because of the normal result obtained in a patient severely incapacitated and wasted from poliomyelitis nine months previously.

Spasticity results in increased muscular activity due to hyperactivity of stretch reflex mechanisms, and any more or less continual postural muscular work might produce a rise in pyruvate level. Such a rise might be expected to be as apparent in the fasting values as in those after glucose ingestion, but it is probable that after fasting the main fuel of posturally active skeletal muscle is unesterified fatty acid (Rabinowitz and Zierler, 1962) and that, only as the blood glucose concentration increases, does carbohydrate become the main energy source, with a consequent increase in pyruvate formation. Indeed, the fasting values in the spastic patients with disseminated sclerosis were normal and became abnormal only after glucose. However, it should be noted that, although electromyographic recordings (in the three patients tested) showed spontaneous motor unit activity at rest, this was very slight in comparison with that coincident with the smallest voluntary movement.

That these four patients showed a similar abnormality of pyruvate metabolism does not mean that they all had the same disease, but, although the cause of the abnormal pyruvate metabolism is unknown, it may hold a possible clue to better understanding of the group; however diverse the aetiology of the patients' diseases, there may be common features in the pathogenesis of the observed abnormalities of peripheral nerve and muscle.

**CLINICAL ASPECTS** The clinical picture in these four middle-aged women was that of a flaccid weakness with wasting, more marked distally, with increased protein concentration in the cerebrospinal fluid, and with electromyographic changes indicating lesions of both muscle and peripheral nerve and, in one case, of anterior horn cells also. Fasciculation and a normal E.S.R. in the absence of intercurrent infection (pulmonary or urinary) also seem features. The clinical aspects of the cases are summarized in Table II. It can be seen that none of them are similar in all facets recorded, and that individual cases may show features not shared by any of the others, *e.g.*, severe sensory involvement in case 1, recovery (sustained for three and a half years) in case 2.

The diagnoses given these patients at various times in their clinical course are interesting. At one time or another, all four were suspected of exhibiting a carcinomatous neuropathy or neuromyopathy. No evidence of a carcinoma, however, was found in one post-mortem examination and during the long clinical course of the other three patients. The longest period recorded between onset of a neuropathy and the finding of a carcinoma, presumed to be in causative relation to the neuropathy, is three years (Henson et al., 1954).

Case 1 would seem an example of the chronic progressive polyneuritis of Hyland and Russell (1930), a rare disease. In the other three cases 'motor neurone disease' was a considered diagnosis, in the sense that this indicates a specific entity among diseases in which the motor neurones are affected. The abnormally high concentration of protein in the cerebrospinal fluid was against this diagnosis (Elkington, 1956), as were the electromyographic findings, with their evidence of decreased conduction velocity in the motor nerves and the relatively brief and low amplitude motor unit potentials. The polysphasic potentials of short duration with very rapid swings of potential are also unlike the findings in motor neurone disease or even in motor neuritis, and are much more suggestive of a myopathic
process with muscle fibre dropout. The recovery to normal strength in case 2 also rules out 'motor neurone disease' here. Thus, although many of the clinical features, and especially the post-mortem findings in case 3, indicate a disease of motor neurones, they do not suggest a diagnosis of 'motor neurone disease'.

Despite the similarities, it is unlikely that these patients all had the same disease. However, there are no features in the clinical findings that point to undoubtedly different processes. If it were to be accepted that the others had the same disease as case 2, this patient's apparently sustained recovery would be of great importance, indicating the potential reversibility of a most serious illness.

SUMMARY

Pyruvate metabolism tests were performed on 101 patients with generalized peripheral neuropathy. Abnormal results attributable to vitamin B₁ deficiency, vitamin B₁₂ deficiency with achlorhydria, and diabetes were encountered, but in four patients no underlying deficiency state or disease could be found.

The abnormal pyruvate values in all four patients were unaltered by vitamin B₁₂ injections, or by a variety of other treatments, including the administration of methionine, penicillamine, vitamin B₁₂, and corticosteroids. In the one patient who improved spontaneously the pyruvate metabolism returned to normal with clinical recovery.

The clinical features of the four patients are described. Although not identical, they contain no essential contrast. All the patients suffered a flaccid weakness with wasting, which evolved slowly (but regressed in one), and the cerebrospinal fluid in all contained elevated protein levels.

Electromyography and motor nerve conduction velocity studies (carried out in three of the four patients) showed evidence of neuropathy affecting motor nerve fibres at or distal to motor roots, and of primary muscle disease.

The possible diagnosis of motor neurone disease met unreconcilable features, while no carcinoma or reticulosis has appeared despite prolonged observation.

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Motor neuropathy associated with abnormal pyruvate metabolism unaffected by thiamine

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