

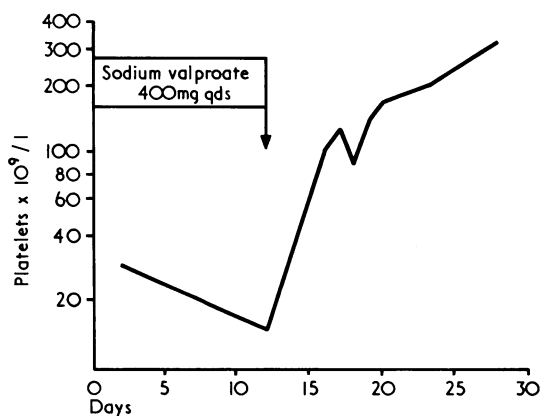
## Sodium valproate and thrombocytopenia

Published reports on the value of sodium valproate (Epilim) as an anticonvulsant drug have been encouraging.<sup>1</sup> Acquired platelet function defects of doubtful significance have been found and attributed to this drug,<sup>2</sup> and there have been two reports of haemorrhages, prolonged bleeding times, and thrombocytopenia in patients on sodium valproate with other anticonvulsant drugs.<sup>3,4</sup> The patient we report here developed thrombocytopenia when taking sodium valproate alone, and the investigations are recorded.

### Case report

A 6-year-old boy weighing 20 kg had been having major and minor seizures for two years and had failed to respond to other anticonvulsant drugs. On treatment with sodium valproate 400 mg four times a day, all other drugs having been stopped, he was rendered fit-free for eight months. His mother then reported that he had developed hair loss and multiple spontaneous bruises. The bleeding time was prolonged and the platelet count was  $15 \times 10^9/l$ , but other tests of coagulation were normal. Sodium valproate was immediately discontinued. The serum level at this time was very high (244  $\mu g/ml$ ).

At the time of the peripheral thrombocytopenia aspiration of bone marrow showed increased numbers of megakaryocytes, and his serum was therefore investigated to detect the presence of an antibody against a pooled platelets/sodium-valproate combination. On using both a complement fixation test at 37°C and a [<sup>14</sup>C] serotonin platelet release technique<sup>5</sup> negative results were obtained at drug concentrations of 0.0065 g/l, 0.065 g/l, and 0.65 g/l. The antibody investigations were repeated 10 months after the thrombocytopenic episode and at a time when the patient's platelet count was within the normal range; negative results were again obtained. To determine whether in-vivo drug-induced platelet aggregation accounted for the thrombocytopenia citrated platelet-rich plasma taken in the recovery phase was mixed in an aggregometer with sodium valproate at a final concentration of 0.15 g/l. No platelet aggregation was detected over 10 minutes. The platelet count rose rapidly during the 48 hours after stopping the sodium valproate and was normal within a week (see figure). Unfortunately his fits recurred after stopping the sodium valproate but were subsequently fully controlled with clonazepam.



Sodium valproate therapy and platelet count changes.

### Discussion

In a further 32 of our patients on sodium valproate, including several who were on large doses and had high serum levels of the drug, and five who also complained of hair loss, no other cases of haemorrhage or platelet counts below  $100 \times 10^9/l$  were detected.

Apart from the sodium valproate with the very high serum level in our patient we found no other cause for the thrombocytopenia, which we therefore considered was probably due to the drug. The finding of increased numbers of megakaryocytes in the bone marrow, together with the rate of platelet recovery on discontinuing the drug, is suggestive of an immunological mechanism, though circulating platelet antibodies could not be detected in vitro. The negative results obtained during the thrombocytopenic phase may be explained by consumption of the antibody in vivo, though this mechanism cannot account for the negative findings in the recovery phase. A further possibility for the negative in-vitro results is that the circulating antibody is developed to a

metabolic product of sodium valproate and not to the drug itself. It was considered unjustifiable to subject our patient to a further test dose of the drug, but it is of interest that in one of the previously reported cases of thrombocytopenia<sup>3</sup> the platelet count recovered on stopping the sodium valproate but immediately fell on recommencing the drug.

As a result of these findings we recommend that any excessive or unexplained bruising or bleeding in a patient on sodium valproate is an indication for immediate platelet assessment.

We are grateful to the Regional Blood Transfusion Centre, Sheffield, for the platelet antibody studies.

<sup>1</sup> Clinical and Pharmacological Aspects of Sodium Valproate (Epilim) in the Treatment of Epilepsy. *Proceedings of a Symposium held at Nottingham University 23-24 September 1975*, MCS Consultants, England, 1976.

<sup>2</sup> Richardson, S G N, *et al*, *British Medical Journal*, 1976, **1**, 221.

<sup>3</sup> Sutor, A H, and Jesdinsky-Buscher, C, *Medizinische Welt*, 1974, **25**, 447.

<sup>4</sup> Voss, H von, *et al*, *British Medical Journal*, 1976, **2**, 179.

<sup>5</sup> Hirschman, R J, and Shulman, N R, *British Journal of Haematology*, 1973, **24**, 793.

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## Parkinsonism with a bovine cough: an unusual presentation

Limitation of coughing is a well-recognised feature of Parkinsonism usually seen late in the disease and predisposing the patient to chest infection and terminal bronchopneumonia. There appears to be no report of a patient with Parkinsonism having a bovine cough. This paper describes a patient in whom the first feature of Parkinsonism seems to have been a bovine cough, which preceded the other features of the disease by about two years.

### Case history

A 77-year-old man was first referred to the geriatric unit in July 1975 with poor mobility and increasing frailty. He had longstanding chronic bronchitis and bronchospasm, and was being treated with prednisilone, 10 mg thrice daily; salbutamol, 4 mg thrice daily; a combination tablet of amiloride, 5 mg, and hydrochlorothiazide, 50 mg, each morning; and promethazine, 50 mg, at night. In 1974 he had had two fractures of the right femur, which had resulted in 4-cm shortening of the leg. This physical disability and the severe dyspnoea from his chronic bronchitis were the causes of his poor mobility. Additionally, he had considerable asymptomatic prostatic enlargement, and a hoarse voice of low volume with a bovine cough. The only other neurological abnormality was a minor left upper motor neurone facial weakness. Both the patient and his wife confirmed that he had been unable to cough properly for about two years, and that this was slowly getting worse.

Both direct and indirect laryngoscopy failed to disclose any abnormality of the larynx, though an infraglottic tumour was suggested as possible cause of the bovine cough. Nevertheless, the results of barium swallow and tracheal tomography were normal. In view of his poor respiratory condition and general frailty further investigation was considered to be contraindicated. He regularly attended the geriatric day hospital, and at medical review in January 1976 was noticed to have developed a Parkinsonian tremor of the right hand; cogwheel rigidity in both arms; impassive facies, dyskinesia, and a positive glabellar tap. The bovine cough and feeble voice were still present. Treatment with a combination capsule of levodopa, 100 mg, and benserazide, 28.5 mg, was begun and the dose gradually increased to an optimum of one capsule thrice daily. As soon as he was first started on this treatment he began to produce normal explosive coughs; at first this occurred occasionally, but then, as the dose of the drug was increased, the bovine cough disappeared completely. At the same time the volume of his voice increased. His other Parkinsonian features also improved, resulting in better mobility, reduction in rigidity, and disappearance of dyskinesia.

In April 1976 he developed an acute exacerbation of his bronchitis accompanied by cor pulmonale. He failed to respond to treatment and died four days after admission to hospital. Necropsy examination was not performed.

### Discussion

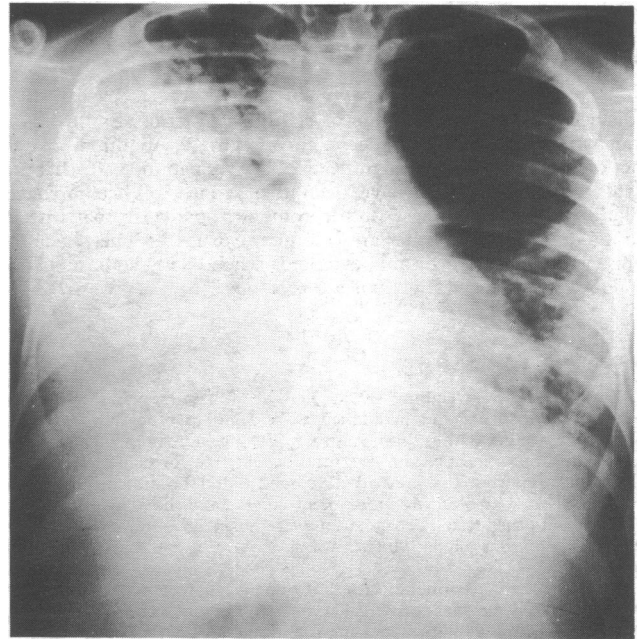
In view of the disappearance of this man's bovine cough at the same time as the improvement in his other Parkinsonian features during treatment with levodopa and benserazide, it is difficult to come to any other conclusion than that the bovine cough was the presenting feature of his Parkinsonism. So far as possible other causes of the abnormal cough were eliminated. In any case, it is extremely unlikely that a bovine cough due to another cause, and already present for two years, would respond so specifically to antiparkinsonian therapy.

The presence of the bovine cough with normal findings on laryngoscopy are difficult to explain other than on the basis that the laryngeal dyskinesia was insufficient to impair the production of normal cord movement during laryngoscopy, but that it was sufficient to impair the rapid movement and co-ordination of the vocal cords during coughing.

I would like to thank Dr M G Carter, Adverse Reactions Physician, Roche Products Ltd, for help in searching literature for possible previous reports of this phenomenon.

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Chest radiograph on seventh day of illness.

## Leptospirosis presenting with profuse haemoptysis

About fifty cases of leptospirosis are diagnosed in the United Kingdom each year with a mortality of 5%.<sup>1</sup> Haemoptysis and pneumonitis are uncommon manifestations of the disease and both occurred in the patient described below.

### Case history

A farmer's son of 16 was admitted with an 18-hour history of frank haemoptysis. During the previous five days he had been unwell with fever, night sweats, general malaise, and muscle aches. These initial symptoms improved for twelve hours before the onset of cough and haemoptysis. Examination on admission showed signs of right lower lobe consolidation, cyanosis, blood-stained sputum, tachypnoea, and fever (39°C); he had eczematous areas on both hands. Investigations disclosed haemoglobin 9.5 g/dl; white blood count  $9.7 \times 10^9/l$ ; platelet count  $70 \times 10^9/l$ ; serum urea concentration 8.3 mmol/l (50 mg/100 ml); and bilirubin concentration 27 mmol/l (1.73 mg/100 ml).

On the assumption that he had an overwhelming bacterial infection treatment was started with intravenous benzyl-penicillin 2 mega-units four-hourly. Eighteen hours later cloxacillin, 0.5 g intravenously six-hourly, and dexamethasone, 4 mg intravenously six-hourly, were added because of increasing respiratory distress and toxæmia. The day after admission haemoptysis increased. Clinical signs of extensive right lung consolidation with spread to the left lower lobe were found. The chest radiograph (see figure) showed extensive opacities in the right lung field and opacities developing in the left lung field. The bleeding became so profuse that endotracheal intubation with repeated bronchial aspiration was needed to prevent asphyxiation by his own blood; a blood transfusion was given. Epsilon amino-caproic acid, 3 g intravenously four-hourly, with platelet transfusions were given to control haemorrhage; haematuria was now present. Clotting tests showed: fibrinogen 6.2 g/l, falling to 1.4 g/l on the third day; prothrombin time 16 seconds (control 12 seconds); partial thromboplastin time 32 seconds; platelets  $68 \times 10^9/l$ ; fibrin degradation products 10-40 µg/ml.

He was ventilated with a Cape ventilator using an inspired oxygen concentration of 100%, a tidal volume of 1000 ml, and a positive end expiratory pressure of 20 cm H<sub>2</sub>O. Despite this the pO<sub>2</sub> was only just maintained above 6.4 Kpa (50 mm Hg). To maintain the blood volume, 3.5 litres of whole blood and four packs of platelets containing about 20 ml each were transfused in the first four days. On the third day splenomegaly was noted. Mechanical ventilation was continued for five days and on the sixth day the patient was weaned from the ventilator. Recovery was then rapid and he remains in good

health eighteen months later. Complement fixation titres of leptospiral antibody rose from 1/10 on day of admission to 1/160 nine days later. Agglutination tests showed a rise from 1/10 to 1/100 for *Leptospira icterohaemorrhagiae*.

### Discussion

This case is presented to emphasise the severity of the haemoptysis, which nearly asphyxiated the patient. In the early stage of the illness there were many features of an infective pneumonitis, but the diagnosis was only made in retrospect by a rising titre of serum antibody to *L. icterohaemorrhagiae*. Leptospiral infections usually present with non-specific features of fever, muscle pains, and headache but should be considered in the differential diagnosis in cases with pneumonitis and haemoptysis.<sup>2</sup> Pneumonitis has been reported in 11% of cases, haemoptysis in 3%, thrombocytopenia in only 1%.<sup>3</sup> Splenomegaly is rare, occurring in less than 1%. The bleeding diathesis in this syndrome is said to be due to leakage through the vascular endothelium. Haemolysins are produced<sup>4</sup> and intravascular haemolysis occurs; our patient had some features of haemolysis and disseminated intravascular coagulation. The patient described was of the usual age, sex, and occupation<sup>3</sup> and probably acquired the infection through eczematous fissures on his hands from rat-contaminated cattle feed. He was treated with blood, platelets, corticosteroids in high dosage, and epsilon amino-caproic acid. Large doses of penicillin were also given initially and are recommended for this condition.<sup>5</sup> Which of these therapies contributed to his survival is uncertain, but without the skill of the intensive care staff he would have died.

We are indebted to Dr R J C Hart and Dr L H Turner of the Public Health Laboratory Service for making the diagnosis and to Dr J O P Edgcombe for his haematological advice.

<sup>1</sup> Turner, L, *Medicine*, 1975, 3, 125.

<sup>2</sup> Poh, S C, and Soh, C S, *Thorax*, 1970, 25, 75.

<sup>3</sup> Heath, C W, Jr, Alexander, A D, and Gatton, M M, *New England Journal of Medicine*, 1965, 273, 857.

<sup>4</sup> Beeson, P B, and McDermott, M D, *Textbook of Medicine*, p 438. Philadelphia, W B Saunders Company, 1975.

<sup>5</sup> Kocen, R S, *British Medical Journal*, 1962, 1, 1181.

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