of prednisolone was reduced to 5 mg daily without relapse. The direct antiglobulin test became negative three months after he started treatment. He has remained well and control of his myasthenia has been unaffected. Thymectomy has not been recommended because of his poor respiratory reserve.

Comment

The relation between myasthenia gravis and thymoma or microscopic hyperplasia of the thymus is well known.¹ The syndrome of PRCA and thymoma is also well established. Roland² reviewed 43 cases of the latter and reported the incidence of thymoma in PRCA in adults as 57%. Six of these patients had associated myasthenia gravis and about one-third also had depression of the myeloid or megakaryocyte series, or both. In three patients the thymomas were too small to be shown by radiography and were unsuspected findings at necropsy. Thirty-two of the 43 patients received specific therapy, including thymectomy, thymic irradiation, corticosteroids, androgens, and splenectomy in various combinations: but only one patient had a remission on corticosteroid treatment alone.

There is now much evidence pointing to an autoimmune basis to PRCA,³ and immunosuppressive drugs may be used in treatment, often with satisfactory results. A humoral inhibitor may be secreted by a thymoma, but a disruption of immunological homeostasis, possibly mediated by a loss of controlling function of T lymphocytes, seems more likely.⁴ IgG serum inhibitors have been demonstrated against erythroid marrow and also against circulating erythropoietin.⁵ These inhibitors have always disappeared with remission after thymectomy or immunosuppressive treatment. Our patient was unusual in that his peripheral red cells were coated with IgG. But the most remarkable feature of the case was the prompt and gratifying response to corticosteroids alone. This is rare among a series of reports of patients requiring multiple transfusions, major surgery, and immunosuppressive drugs to try to achieve remission.

¹ Castleman, B, and Norris, E A, *Medicine*, 1949, **28**, 27.

² Roland, A S, *American Journal of the Medical Sciences*, 1964, **247**, 719.

³ Krantz, S B, *British Journal of Haematology*, 1973, **25**, 1.

⁴ Allison, A C, Derman, A M, and Barnes, R D, *Lancet*, 1971, **2**, 135.

⁵ Marmont, A, *et al*, *Blood*, 1975, **45**, 247.

(Accepted 12 September 1978)

General Hospital, Nottingham NG1 6HA

J B HOUGHTON, MB, MRCP, senior registrar in haematology
P J TOGHILL, MD, FRCP, consultant physician

Subclinical lead exposure: a possible cause of gout

Joint pains have long been recognised as a symptom of lead poisoning. They occur in 25% of patients with chronic lead poisoning in the UK and are often associated with hyperuricaemia.¹ Serum urate values may be higher in lead nephropathy than in comparable degrees of renal failure from other causes,² and an increase in nuclear-protein turnover may contribute to this.³ While a history of frank lead poisoning is uncommon in patients presenting with gout in the UK, a study of the effects of chronic low-grade lead exposure from drinking water showed hyperuricaemia to be significantly associated with raised blood lead concentrations in a symptom-free population.⁴ We have studied the blood lead concentrations in patients with gout who gave no history of overt lead exposure.

Patients, methods, and results

We studied 32 patients suffering from gout. Their ages ranged from 18 to 70 years (mean 45.5 years), and all except a 68-year-old woman were men. All had clearly documented gouty arthritis, having been found to have hyperuricaemia and urate crystals in articular aspirate. Most of the patients had normal serum urea ($5.51 \pm (\text{SE of mean}) 0.2 \text{ mmol/l}$ ($33.2 \pm 1.2 \text{ mg/100 ml}$)) and creatinine ($89.7 \pm 2.3 \mu\text{mol/l}$ ($1.0 \pm 0.03 \text{ mg/100 ml}$)) concentrations, but serum urea was raised in five patients and serum creatinine in three. We also studied 32 age- and sex-matched controls. None had a history of joint

pain or hypertension or raised serum urea or urate concentrations. A history of known lead exposure was a ground for exclusion in both groups. Serum urate was estimated by a standard automated technique and the blood lead concentration by atomic absorption spectrophotometry using a Perkin Elmer 306 flameless atomic absorption spectrophotometer with HGA 72 graphite-cell power source.

As a group the patients with gout had higher blood lead values than the controls (see table). For example, none of the gouty subjects had a blood lead concentration of under $0.4 \mu\text{mol/l}$ ($8.3 \mu\text{g/100 ml}$), and, whereas only four controls had blood lead concentrations of over $1.5 \mu\text{mol/l}$ ($31 \mu\text{g/100 ml}$) 16 of the patients exceeded this concentration. In only three of the 32 pairs did the control have a blood lead concentration in a higher range than the patient. Reference to the binomial distribution yielded a highly significant result ($P < 0.001$).

Blood lead concentrations in 32 patients with primary gout and 32 age- and sex-matched controls

Blood lead ($\mu\text{mol/l}$):	<0.4	0.8	1.2	1.6	2.0	2.4	2.8	3.2
No of patients	0	2	13	6	5	4	1	1
No of controls	5	12	6	5	2	2		

Conversion: SI to traditional units—Lead: $1 \mu\text{mol/l} \approx 20.7 \mu\text{g/100 ml}$.

Discussion

These findings leave no doubt that raised blood lead values and gout are associated, though they do not prove that lead helped to cause the gout in these patients. Gout nephropathy may have caused diminished renal lead excretion with a resulting increase in blood lead concentrations, but this group of patients mostly had normal renal function. Moreover, even severe renal failure may not depress renal lead excretion.⁵ Some unknown factor may reduce the excretion of both lead and urate. This, however, seems unlikely since urate is excreted by the renal tubules, whereas lead seems to be excreted mainly by glomerular filtration.

Thus our findings, taken with the association between lead and symptomless hyperuricaemia found previously,⁴ suggest that lead is sometimes a causal factor in gout. Gout may be another manifestation of subclinical lead poisoning.

¹ Campbell, B C, and Baird, A W, *British Journal of Industrial Medicine*, 1977, **34**, 298.

² Emmerson, B T, *Australasian Annals of Medicine*, 1963, **12**, 310.

³ Ludwig, G D, *Archives of Internal Medicine*, 1957, **100**, 802.

⁴ Campbell, B C, *et al*, *British Medical Journal*, 1977, **1**, 482.

⁵ Campbell, B C, and Elliott, H L, *British Medical Journal*, 1977, **2**, 581.

(Accepted 15 September 1978)

University Department of Materia Medica, Stobhill General Hospital, Glasgow G21 3UW

B C CAMPBELL, MD, MRCP, lecturer

M R MOORE, BSC, PHD, lecturer

A GOLDBERG, MD, FRCP, regius professor of materia medica (now regius professor of medicine, University Department of Medicine, Western Infirmary, Glasgow G12 8QQ)

Centre for Rheumatic Diseases, Glasgow

L A HERNANDEZ, MD, research assistant

W CARSON DICK, MD, consultant physician

Oral choline in cerebellar ataxia

There is no established drug treatment for cerebellar ataxia. Cerebellar physiology is well established but its synaptic chemistry is only partly understood. In particular, the nature of the excitatory synapses is uncertain and whether specific defects in synaptic transmission underlie cerebellar movement disorders is unknown. Anticholinesterases produce small improvements in cerebellar ataxia after a single dose but are of no long-term clinical use.¹ This preliminary report describes a patient whose ataxia was greatly improved by oral choline, another means of enhancing cholinergic neurotransmission.

Case report

A 56-year-old research engineer presented to the Hammersmith Hospital in 1972 with deteriorating balance, speech, and writing for nine months. Family history was negative. Examination showed titubation, slurred speech, horizontal nystagmus, cerebellar ataxia in the arms, and ataxia of gait. Tendon reflexes and sensation were normal. A cervical myelogram and vertebral arteriogram were normal. Air encephalography showed slight dilatation of the third ventricle and of cerebral cortical sulci. Malignancy, hypothyroidism, and other systemic diseases were excluded by full investigation, and late-onset idiopathic cerebellar degeneration was diagnosed. He deteriorated slowly over the next six years. By 1978 he could walk only with a stick.

He was given choline chloride 1 g four times daily by mouth. There was a dramatic improvement. He could walk without a stick even over irregular surfaces outdoors, which had been impossible for many years. More detailed observations were therefore made of his motor function both on and off choline. Without choline he walked on a wide base and needed a stick for support. He could not stand with his feet together, let alone perform Romberg's test or tandem standing. Within two days of starting choline he

Helices drawn with wrist unsupported. Left, untreated, right, on choline.

could do all these things and could hop on either foot alone. Ataxia also improved markedly in the arms: helices drawn with the wrist unsupported are shown in the figure, and the times taken for various tests of finger dexterity were reduced by 50% or more. Titubation improved, but there was no observable change in speech or nystagmus. He was stabilised on 5 g choline daily, which he felt was better than 4 g. When choline was stopped he deteriorated again within two days. Propantheline at 15 mg four times daily reduced the choline effect, and at 15 mg six times daily abolished it. Oral physostigmine 6 mg daily, instead of choline, did not benefit him.

Comment

Choline is a rate-limiting substrate for the synthesis of acetylcholine by cholinergic nerves. Oral choline increases choline concentrations in plasma and cerebrospinal fluid and also brain acetylcholine and acetylcholine receptor concentrations.² Its therapeutic effect in chronic tardive dyskinesia is thought to be due to enhanced cholinergic transmission,³ and the same conclusion may tentatively be drawn in the present case. The great improvement on oral choline was abolished by an anticholinergic drug, suggesting that the therapeutic effect was taking place at cholinergic synapses. No improvement was obtained with physostigmine, presumably because anticholinesterases produce only small rises in brain acetylcholine.

The site at which cholinergic transmission was being enhanced is a matter for speculation. Acetylcholine concentrations are low in the cerebellum compared with the rest of the brain.⁴ The climbing fibre input from the inferior olives may be cholinergic,⁵ but the evidence is scanty. The site of action may not necessarily be within the cerebellum. The implications of this report are twofold: it suggests that a defect of cholinergic transmission underlies some cerebellar movement disorders; and it offers the possibility of effective treatment for a hitherto untreatable syndrome.

¹ Kark, R A P, Blass, J P, and Spence, M A, *Neurology*, 1977, **27**, 70.

² Morley, B J, *et al*, *Nature*, 1977, **266**, 848.

³ Growdon, J H, *et al*, *New England Journal of Medicine*, 1977, **297**, 524.

⁴ Shea, P A, and Aprison, M H, *Journal of Neurochemistry*, 1977, **28**, 51.

⁵ Marani, E, and Voogd, J, *Journal of Anatomy*, 1977, **124**, 335.

(Accepted 12 September 1978)

Department of Neurology, Hammersmith Hospital and Royal Postgraduate Medical School, Du Cane Road, London W12 0HS
N J LEGG, MB, MRCP, consultant and senior lecturer

Anaphylaxis after oral penicillin

Allergic reactions to penicillin are not uncommon, but anaphylaxis is rare. Anaphylaxis after oral ingestion is rarer still, and many doctors are unaware of its existence. We describe here two patients who suffered near-fatal anaphylaxis after taking oral penicillin who were admitted within ten days of each other to the Leicester Royal Infirmary.

Case 1

A 29-year-old woman was prescribed penicillin V for a sore throat. Within three minutes after taking the first tablet she developed generalised pruritis and flushing, followed by abdominal cramps, nausea, and one episode of vomiting. When first seen 30 minutes after ingestion, she was responding only to commands and had severe peripheral cyanosis, a tachycardia of 120 beats/min, and blood pressure of 70/50 mm Hg. She was initially treated with 0.5 ml 1/1000 adrenaline subcutaneously, 200 mg hydrocortisone intravenously, and 10 mg chlorpheniramine intravenously, and subsequently with an infusion of hydrocortisone for 12 hours. She regained full consciousness over the next 30 minutes and her blood pressure returned to normal after three hours. On subsequent questioning she admitted having taken penicillin on several previous occasions.

Case 2

A 47-year-old man was prescribed talampicillin for a cough of one week's duration. Thirty minutes after taking the first tablet he developed facial oedema, pruritis, and nausea and then lost consciousness. When first seen at home he was severely cyanosed and was responding only to painful stimuli. He was given 10 mg chlorpheniramine intravenously together with 200 mg hydrocortisone, and a 19-G needle was inserted into his trachea. After transfer to hospital and further treatment with antihistamines and steroids his conscious level and respiration improved but he remained hypotensive for several hours before recovering fully. Subsequently he said that he had taken penicillin preparations on several other occasions with no adverse effects, the last time being three months previously.

Comment

These two patients suffered severe anaphylactic shock after oral ingestion of penicillin and both had been treated with penicillin preparations previously with no symptoms suggestive of allergy. The incidence of anaphylactic shock in all patients treated with penicillin is between 0.015 and 0.04%, with death occurring in 0.002% of cases.¹

Anaphylaxis after oral ingestion is, however, even less common than after parenteral administration, and Batson² could find only 28 cases in a survey of published reports up to 1960. There have been four reports of fatal anaphylaxis due to oral penicillin preparations.³ Patients who develop anaphylactic reactions have usually been treated with penicillin before—for example, 25 of the 28 patients in Batson's series and three out of four patients quoted by Spark³ had received previous treatment.

The main antigenic stimulus in penicillin allergy is now thought to come from the breakdown products of the penicillin molecule: the penicilloyl group, with the "minor antigenic determinants," such as Na-benzylpenilloate and Na-benzylpenicilloate, being particularly relevant in the development of anaphylactic reactions. Since all semi-synthetic forms of penicillin are built around the same molecular nucleus, this accounts for cross-allergy to different preparations, and activation of allergy in already sensitised individuals often requires only minimal amounts of penicillin, particularly with regard to anaphylactic reactions. This was well illustrated by our patients. We want to draw attention to this point and also to the fact that oral penicillin preparations can cause as rapid and as severe an allergic reaction as parenteral preparations.

¹ Idse, O, *et al*, *Bulletin of the World Health Organisation*, 1968, **38**, 159.

² Batson, J M, *New England Journal of Medicine*, 1960, **262**, 590.

³ Spark, R P, *American Journal of Clinical Pathology*, 1971, **56**, 407.

(Accepted 15 September 1978)

Leicester Royal Infirmary, Leicester LE1 7RH

J SIMMONDS, MRCP, senior registrar
S HODGES, MB, CHB, house physician
F NICOL, BSC, MB, senior house officer
D BARNETT, MRCP, senior lecturer