experience they would wish to repeat. This rating was lower than we expected.

Dr Skidmore and colleagues state that they used urine tests to detect intravenous drug use. Urine analysis will detect which drugs have been consumed but hitherto has not provided information on the route of drug use. It would be a very interesting development to have a urine test that could distinguish between oral and intravenous drug use.

In the past 18 months we have noticed a steady rise in the number of urine specimens containing polyethylene glycol, which was detected by thin layer chromatography. This macromolecule is a constituent of the temazepam soft capsule formulation. We initially thought that the presence of polyethylene glycol in the urine was particular to users of intravenous temazepam, but recently we have detected it in the urine of two patients taking very high doses of oral temazepam (400 mg daily). Thus the presence of polyethylene glycol in a urine specimen should remind the doctor to examine the patient for evidence of fresh injection marks.

In the era of HIV and AIDS investigations that could distinguish between oral and intravenous drug use would help to monitor progress in encouraging drug users to stop injecting. Further work is required to explore the feasibility of such developments.

MICHAEL FARRELL
JOHANNA HERROD
BRIAN SMITH
JOHN STRANG

Drug Dependence Clinical Research and Treatment Unit,
Maudsley Hospital,
London SE5

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## Demoralised doctors

SIR,—Small wonder that Dr Debbie Parker and her contemporaries are demoralised[1] when the BMA, the Hospital Junior Staff Committee, and their unnamed parliamentary ally have failed to persuade the Department of Health to reduce the hours of junior staff to an average of 72 a week. It may interest readers to know that junior hospital resident medical officers in Queensland, Australia, obtained from the Industrial Court in that state a working week of 56 hours as long ago as 1944. Last year the Industrial Commission made further reductions to 88 hours a fortnight from March, 84 from July, and 80 with effect from 1 January 1990. The present salary of a first year resident medical officer in the metropolitan area is $A1093.70 (about £500) a fortnight.

Perhaps the HJSC should request an entry in the *Guinness Book of Records* to the effect that at the start of the last decade of the twentieth century junior hospital staff in the NHS were the most exploited body of workers in the Western world.

DEREK MEYERS

Brisbane 4000,
Australia

1 Parker DF. Demoralised doctors. *Br Med J* 1990;**300**:56-7. (6 January.)

## Use of newsprint to wrap fish

SIR,—Minerva notes my publication of Ramazzini's *Diseases of Printers* and asks whether his reference to the use of printed paper to wrap fish is the first.[1] The answer is no. Education in the seventeenth century would have entailed a large dose of the classics, and Ramazzini almost certainly would have been familiar with Catullus (circa 50 BC), who wrote a poem about the bad poetry of some other poets,[2] ending with the lines: "But the Annals of Volusius will die by the river Padua where they were born, and will often furnish a loose wrapper for mackerels."

Ramazzini would also have known Horace's reference to bad poetry[3]: that the works of a bad poet would be taken to "where they sell frankincense and perfume and pepper and everything else that is wrapped in useless paper."

I am indebted to Mr Desmond Costa of the University of Birmingham for these references.

D M G WISHART

Hayloft Press,
99 Oakfield Road,
Birmingham B29 7HW

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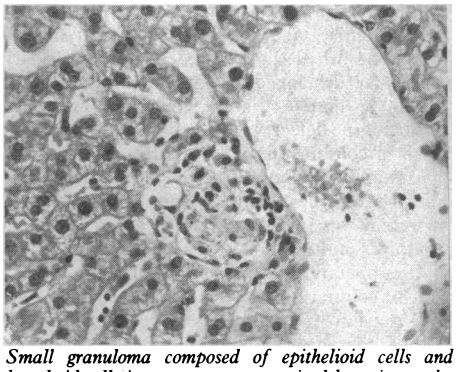
# *Drug Points*

### Quinine induced granulomatous hepatitis and vasculitis

Drs SANDIP MATHUR, JAMES DOOLEY, and PETER J SCHEUER (Royal Free Hospital, London NW3 2QG) write: Quinine produces a wide range of adverse effects.[1] Its D-isomer, quinidine, has been reported to cause granulomatous hepatitis, but this hepatic lesion has been reported only once with quinine sulphate,[2] and the histological diagnosis was later challenged.[3] We describe another patient who developed granulomatous hepatitis with histological features identical to those described in the first report.

A 67 year old man presented with a 10 day history of fever and polyarthralgia. Joint pains had started insidiously and resolved five days before admission. The fever was intermittent with temperatures of up to 38·5°C but no rigors. One day before admission he developed a vasculitic rash over the front of his legs. There was no history of liver disease, jaundice, or alcohol abuse. He had never received blood transfusions and was heterosexual. He suffered from glaucoma, which was treated with carbachol hydrochloride. For two months he had taken quinine sulphate 300 mg at night for muscle cramps but stopped this medication one week before admission because of flatulence.

On examination he appeared well. He had a palpable vasculitic rash over his shins. His blood pressure was 140/90 mm Hg. There was pitting oedema of both feet extending to just above both ankles. Investigations showed haemoglobin concentration 125 g/l, white cell count $6·0\times10^9$/l, platelet count $438\times10^9$/l, erythrocyte sedimentation rate 75 mm in the first hour. Urea, electrolyte, and creatinine concentrations were normal. Liver function tests showed total bilirubin 11 μmol/l (normal 5-17), aspartate aminotransferase 100 U/l (normal 5-40 U/l), alkaline phosphatase 1668 U/l (normal 35-130), γ-glutamyl transferase 1140 U/l (normal 10-43), total protein 73 g/l (normal 60-80 g/l), albumin 30 g/l (normal 30-50). Histological examination of a liver biopsy specimen showed normal liver architecture with prominent Kupffer cells and a few small foci of liver cell necrosis and inflammation as well as small epithelioid cell granulomas which showed no necrosis (figure). There was no cholestasis or fatty change. The portal tracts contained a few lymphocytes and eosinophils. There was nuclear vacuolation in some hepatocytes, and increased numbers of mitoses were seen. Liver cell nuclei varied considerably in size. The skin biopsy showed a leucocytoclastic vasculitis.



*Small granuloma composed of epithelioid cells and lymphoid cells is seen next to a terminal hepatic venule. Haematoxylin-eosin*

All drugs were withdrawn and within a few days he was free of symptoms. The vasculitic rash disappeared over three days. By the fifth day of his illness platelet levels were normal and his erythrocyte sedimentation rate had fallen to 42 mm in the first hour. The aspartate aminotransferase returned to normal the day after admission, the alkaline phosphatase fell to 409 U/l by the fourth day, and the γ-glutamyl transferase to 447. When reviewed a month later his liver function values had returned to normal except γ-glutamyl transferase, which returned to normal six months later.

Our patient's symptoms, biochemical profile, and histological features closely resemble those described in the previous report of granulomatous hepatitis associated with quinine sulphate. In both cases the patients had been taking quinine sulphate in doses normally prescribed for treating nocturnal leg cramps—that is, 300 mg at night. Both presented with fever and polyarthralgia, and the symptoms were episodic with the arthralgia settling spontaneously. The erythrocyte sedimentation rate was raised in both cases, and liver function tests showed cholestatic features. The presence of small granulomas and an infiltrate including eosinophils is consistent with a drug reaction. These features also resemble the report of quinidine induced granulomatous hepatitis.[5] Drugs are responsible for about 2% of cases of granulomatous hepatitis,[5] and those implicated include sulphonamides, penicillin, erythromycin (personal observation), allopurinol, methyldopa, hydralazine, phenylbutazone, carbamazepine, isoniazid, nitrofurantoin, and diazepam. It is important therefore to look specifically for a drug as the causal factor in patients with cholestatic liver disease and hepatic granulomas, and quinine should be added to the list of drugs that may cause these features.

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### Convulsions induced by enoximone administered as a continuous intravenous infusion

Drs IAN APPADURAI, MAIR EDMUNDS, RICHARD WYATT, and THOMAS J SPYT (Department of Cardiothoracic Surgery, Groby Road Hospital, Leicester) write: Many neurological complications, including insomnia, agitation, anxiety, and headaches, have been documented after intra-

venous use of the type IV phosphodiesterase inhibitor enoximone.[1] We describe a case of tonic-clonic convulsions associated with intravenous administration of enoximone, a possible adverse effect that has hitherto not been reported.

A 66 year old white man was admitted with a large anteroseptal myocardial infarction due to occlusion of the left anterior descending coronary artery. He developed a ventricular septal defect within 48 hours of admission. An emergency closure of the defect was carried out with a Dacron patch in combination with double aortocoronary bypass grafting. Before the operation the patient was in severe heart failure, and at operation the infarction was seen to have affected the anterior two thirds of the interventricular septum.

After operation the patient required intra-aortic balloon counterpulsation in addition to infusions of adrenaline (0·04-0·1 μg/kg/min), dopamine (10 μg/kg/min), and amiodarone (1·2 g over 24 hrs). When enoximone was added to this regimen as a continuous infusion (6 μg/kg/min) he developed an offensive, watery diarrhoea, a documented complication of treatment, and tonic-clonic convulsions. Both the diarrhoea and convulsions subsided when enoximone was discontinued. The patient also required a period of arteriovenous haemofiltration and haemodialysis in the early postoperative recovery period to combat acute tubular necrosis. Further recovery was satisfactory and he was discharged home 36 days after surgery. Neurological examination, including perimetry, during his hospital stay and after discharge did not show any abnormalities.

Enoximone is a new type IV phosphodiesterase inhibitor, which is an extremely useful inodilator in patients who are critically ill after cardiac surgery.[2] Other phosphodiesterase inhibitors have been shown to cause profound and potentially dangerous central nervous system stimulation, including focal and generalised convulsions, occasionally refractory to anticonvulsant treatment.[3] Could this be true of enoximone too?


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## Acute dystonia induced by midazolam and abolished by flumazenil


Drs Iwona H Stolarek and Michael J Ford (Eastern General Hospital, Edinburgh EH6 7LN)

write: Dystonic reactions are well recognised following the acute and chronic administration of phenothiazine and butyrophenone neuroleptic agents. Benzodiazepines have also been implicated in the development of tardive dyskinesias despite the fact that they are used to treat such disorders.[1] We describe a patient who developed an acute dystonic reaction after intravenous midazolam which rapidly reversed after administration of the benzodiazepine antagonist flumazenil.

A previously fit 14 year old schoolboy taking no drugs underwent upper intestinal endoscopy in the investigation of dyspepsia. Sedation was achieved with midazolam 5 mg intravenously (0·1 mg/kg). He became acutely distressed and appeared to be resisting the procedure, which was then stopped. On examination he was conscious but mute and crying abnormally with intense akathisia and lingual dyskinesia. The acute dystonia was rapidly abolished after the administration of flumazenil 250 μg intravenously.

Benzodiazepines facilitate the inhibitory effects of both γ-aminobutyric acid at the presynaptic junction and glycine at the postsynaptic junction. γ-Aminobutyric acid and glycine are the two major inhibitory neurotransmitters and act as neurotransmitters at 50-75% of all synapses within the central nervous system. Their effects at receptor sites are competitively antagonised by flumazenil, an imidazobenzodiazepine.[2]

There are no published reports of acute dystonic reactions after intravenous midazolam, though several cases have been reported to the Committee on Safety of Medicines (personal communication). Tardive dyskinesia has, however, been recorded after long term benzodiazepine treatment.[1 3]

The occurrence of an acute dystonia induced by midazolam and abolished by flumazenil is strong supportive evidence that benzodiazepines disrupt the interplay between dopamine and γ-aminobutyric acid receptors in the brain stem. Dystonic reactions, and especially akathisia, after intravenous sedation with benzodiazepines may occur more commonly than is recognised and be dismissed as resistance to the procedure. We suggest that practitioners should be more aware of this possibility and, when suspected, administer flumazenil.


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## Hypertensive crisis precipitated by a monoamine oxidase inhibitor in a patient with phaeochromocytoma


Drs R F Cook (St Bernard's Hospital, Southall UB1 3EU) and D Katritsis (Cardiac Department, St Thomas's Hospital, London SE1 7EH)

write: Pharmacological provocation of hypertension in patients with phaeochromocytoma has been described for such psychotropic agents as tricyclic antidepressants.[1] To our knowledge there has been no such report implicating monoamine oxidase inhibitors. We report a phaeochromocytoma that presented as discrete episodes of headache, anxiety, and hypertension after a single dose of the monoamine oxidase inhibitor tranylcypromine had been given.

A 37 year old white man was admitted to hospital for treatment of neurotic depression. Examination revealed marked agitation, depressed mood, and prominent suicidal thoughts of a recurrent obsessional nature. Physical examination was unremarkable apart from a blood pressure of 190/100 mm Hg in both arms, lying and standing. There were no neck or abdominal bruits. Examination of the optic fundi showed grade 1 hypertensive retinopathy. Although his blood pressure had been found to be mildly elevated at several previous medical examinations, the remainder of the medical history was unremarkable. The family history showed hypertension in both parents.

Initial treatment with mianserin 90 mg daily and chlordiazepoxide 25 mg three times a day supplemented by a short course of electroconvulsive therapy (six treatments in all) did not produce a satisfactory response. A monoamine oxidase inhibitor was therefore added to the regimen, and after a single dose of Parstelin (10 mg tranylcypromine and 1 mg trifluoperazine) he had three discrete episodes of acute anxiety, flushing, headache, and hypertension. The highest blood pressure recorded was 220/110 mm Hg. The patient had not consumed any food containing tyramine during his stay in the hospital.

The 24 hour estimation of urinary vanillomandelic acid was 25-35 μmol (reference range up to 35 μmol). Abdominal ultrasound showed an echogenic area 4·5 cm in diameter in the left suprarenal region, and minor displacement of the upper pole of the left kidney was seen on intravenous pyelography. A computed tomography scan of the abdomen confirmed the presence of a smooth round suprarenal mass 4 cm in diameter, which was removed at operation. Although cystic in nature, the tumour was seen on histological examination to be typical of phaeochromocytoma of benign type. Postoperatively the patient's blood pressure returned to normal, although his mental state remained largely unchanged.

The actions of sympathomimetic amines are potentiated by monoamine oxidase inhibitors. The effect is greater with indirectly acting amines (tyramine, amphetamine) as catecholamines when given are largely inactivated by catechol-*O*-methyltransferase and by neuronal uptake.[2] As monoamine oxidase constantly deaminates intracellular norepinephrine in presynaptic adrenergic neurons, however, provocation of hypertension in patients hypersecreting norepinephrine should be expected. Spontaneous hypertensive episodes produced by monoamine oxidase inhibitors have been described,[3] and it seems possible that, unless hypertension is a rare idiosyncratic reaction to monoamine oxidase inhibitors, these patients had an undiagnosed phaeochromocytoma.


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## Clinical signs of amyotrophic lateral sclerosis developing after polyradiculoneuropathy associated with amitriptyline


Drs Didier Leys and Henri Petit (Department of Neurology, University of Lille, Hôpital B, 59037 Lille, France)

write: In 1987 we reported a case of acute polyradiculoneuropathy following an amitriptyline overdose.[1] We think we should report, three years later, further unexpected developments.

Six years after onset the previously reported clinical and electromyographical signs of polyradiculoneuropathy disappeared; clinical signs progressively mimicked those of amyotrophic lateral sclerosis: the patient developed severe and symmetrical weakness and amyotrophy in the proximal part of the legs, resulting in a severe rolling gait. Weakness and amyotrophy of both arms became severe and were associated with mild pseudobulbar palsy and very explosive stretch reflexes with bilateral Babinski's sign. The patient had no bladder dysfunction and no sensory disturbances. Signs of lesions of the anterior horns started to appear on electromyograms. Computed tomography and magnetic resonance imaging of the brain and cervical myelography showed no abnormality. The rate of progression was very slow.

These new developments greatly modify the signs of what we erroneously called "polyneuropathy." However, the association with the amitriptyline overdose still seems to be probable because of the time course of the events and the very slow rate of progression, which makes amyotrophic lateral sclerosis unlikely. The myelinic degeneration probably induced by amitriptyline might have affected simultaneously spinal roots and spinal cord, and signs of spinal cord disease might have been hidden by such severe initial peripheral signs. We should probably have paid more attention to the very early reappearance of stretch reflexes.


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