

above. Disseminated malignancy was diagnosed, and palliative radiotherapy to the thoracic spine relieved pain. Blood pressure settled spontaneously at 120/80 mm Hg after four days in hospital. The patient went home two weeks after admission but was readmitted two weeks later with a recurrence of back pain and absolute constipation since her discharge. She was pale and clammy; blood pressure was 168/100 mm Hg and pulse 100/min. The abdomen was greatly distended, with easily palpable hard faecal masses. Abdominal discomfort necessitated a colostomy under general anaesthesia.

During the operation diastolic blood pressure varied between 100 and 110 mm Hg and immediately afterwards blood pressure was 170/100 mm Hg. The next day it was 260/160 mm Hg and the patient remained cold and sweated profusely. Two minutes after an intravenous bolus of phentolamine (5 mg) blood pressure fell to 130/70 mm Hg and remained controlled with alpha- and beta-blockade. The patient, however, continued to deteriorate and died suddenly two days later, one year after the onset of symptoms.

Phaeochromocytoma was biochemically confirmed with a 24-hour urine sample collected during the last day of life: total catecholamines 5.6  $\mu\text{mol}/24\text{ h}$  (1031 mg/24 h) (normal < 1.09  $\mu\text{mol}/24\text{ h}$  (< 200 mg/24 h)); normetadrenaline 27  $\mu\text{mol}/24\text{ h}$  (7.4 mg/24 h) (normal < 4.7  $\mu\text{mol}/24\text{ h}$  (< 1.0 mg/24 h)).

Necropsy showed a large (200 g) phaeochromocytoma completely replacing the right adrenal gland, with metastases in ribs, vertebral bodies, and abdominal lymph nodes. All sites showed histological features of phaeochromocytoma. There was extensive recent left ventricular infarction with minimal coronary atheroma and no thrombosis. The large bowel was loaded with hard faecal material. The primary tumour contained 75  $\mu\text{g}$  of catecholamine (predominantly noradrenaline) per gram of wet weight of tissue.

### Comment

There can be little doubt of the diagnosis of malignant phaeochromocytoma as metastases were found in areas not normally the site of chromaffin tissue. While skeletal metastases are common in malignant phaeochromocytoma (occurring in nearly 50% of cases<sup>2</sup>) it is not often recognised that phaeochromocytoma can present with obstinate constipation. In a series of 68 cases<sup>1</sup> constipation was recorded in only 8%, although other abdominal complaints featured more prominently: pain 35%; nausea and vomiting 56%. Paralytic ileus and megacolon have also been noted occasionally.<sup>3</sup> These events can be predicted from the pharmacological effects of catecholamines and have been produced experimentally in animals.<sup>4</sup> The focal myocardial lesions probably caused death, and these too may have resulted from the effects of catecholamines. Similar lesions have been described in animals infused with noradrenaline and patients dying of phaeochromocytoma.<sup>4</sup>

<sup>1</sup> Hume, D M, *American Journal of Surgery*, 1960, **99**, 458.

<sup>2</sup> Schönebeck, J, *Scandinavian Journal of Urology and Nephrology*, 1969, **3**, 64.

<sup>3</sup> Cruz, S R, and Colwell, J A, *Journal of the American Medical Association*, 1972, **219**, 1050.

<sup>4</sup> Blackett, R B, Pickering, G W, and Wilson, G M, *Clinical Science*, 1950, **9**, 247.

<sup>5</sup> Szakacs, J E, and Cannon, A, *American Journal of Clinical Pathology*, 1958, **30**, 425.

Western Infirmary and Gartnavel General Hospital, Glasgow G12

IAN A SHORT, FRCP, consultant physician

PAUL L PADFIELD, MRCP, medical registrar (present address: MRC Blood Pressure Unit, Western Infirmary, Glasgow G11 6NT)

## Plasma levels of propranolol in treated patients with coeliac disease and patients with Crohn's disease

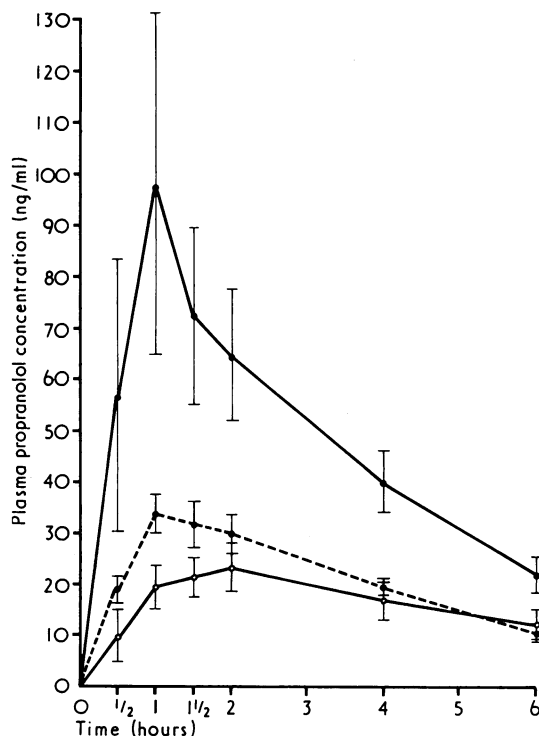
Parsons *et al*<sup>1</sup> claimed that after an oral dose of 40 mg of the beta-adrenoreceptor blocking agent, propranolol, the plasma propranolol levels were higher in patients with coeliac disease than in healthy subjects. This seemed intriguing in a disease notoriously associated with malabsorption and we decided to investigate this phenomenon further. One patient had exceedingly high plasma concentrations after an oral dose of only 20 mg of propranolol but was later shown to

be suffering from Crohn's disease, so the study was extended to include this disease. We later noticed that Parsons and Paddock<sup>2</sup> had found raised plasma levels of sulphamethoxazole in Crohn's disease.

### Patients, methods, and results

The plasma propranolol levels of eight patients with coeliac disease (two males and six females aged 15-68 years) in remission on a gluten-free diet and 10 patients (seven men and three women aged 26-58 years) with Crohn's disease were compared with those of 12 healthy volunteers (six men and six women aged 19-40 years). Neither controls nor coeliac patients were receiving any regular drug treatment. Eight of the 10 patients with Crohn's disease were on adrenocorticosteroids, one was on azathioprine, and one was on sulphasalazine. All subjects were given one 40-mg tablet of propranolol on an empty stomach and kept resting. Blood samples (10 ml) were taken before the test, then every half hour afterwards for two hours and at four and six hours. The plasma was stored at 4°C overnight and assayed the next day by the method of Shand *et al*.<sup>3</sup> Haematological and biochemical profiles were obtained.

The figure shows that the means of the plasma propranolol levels in the treated coeliac patients were higher than in the controls during the first four hours, but actually lower at six hours. The difference, however, was significant ( $P < 0.05$ ) only for the one-hour values. The area under the curve of the mean values of the patients with coeliac disease was not significantly greater than that of the controls. In those with Crohn's disease, however, the mean plasma propranolol levels were significantly higher than those of the controls at all times other than at half an hour. The significance of the differences of the means of this group from those of the controls ranged from  $P < 0.05$ - $P < 0.001$ .



Mean plasma propranolol concentrations ( $\pm$  SE of mean) in controls (O—O), treated patients with coeliac disease (● - - - ●), and patients with Crohn's disease (● — ●) after a 40-mg oral dose.

### Comment

Parsons *et al*<sup>1</sup> claimed that plasma propranolol levels in treated coeliac patients were significantly raised at three sampling times and that the area under the curve of their means was significantly greater than that of the controls. Parsons *et al* attributed this to "an increase in the rate of absorption combined with saturation of first pass extraction." We could not confirm this. Only at one hour was the difference significant ( $P < 0.05$ ). This was probably due to the peak levels being reached earlier in the patients (one hour) than in the controls (two hours). The two peak levels did not differ significantly from each other.

In Crohn's disease the mean plasma propranolol levels were significantly raised at all sampling times apart from the first. The area under the curve was also significantly greater than that of the controls ( $P=0.01-0.001$ ). The values in Crohn's disease showed a much greater spread than those of the controls or the patients with coeliac disease. They fell into two groups: high values and those nearer control values. The high values seemed to relate to a rise in the erythrocyte sedimentation rate. Except in one patient who had a slightly lowered plasma albumin concentration, no abnormalities in liver function were found. The relevance of these findings to multiple dosing as used clinically is to be investigated.

We thank Professor O L Wade for his support and encouragement.

<sup>1</sup> Parsons, R L, *et al*, *Gut*, 1976, **17**, 139.

<sup>2</sup> Parsons, R L, and Paddock, G M, *Journal of Antimicrobial Chemotherapy*, 1975, **1**, 59.

<sup>3</sup> Shand, D G, Nuckolls, E M, and Oates, J A, *Clinical Pharmacology and Therapeutics*, 1970, **11**, 112.

#### University of Birmingham, Birmingham B15 2TH

R E SCHNEIDER, MD, FRCPED, senior research fellow, department of medicine

JANET BABB, BA, research technician, department of therapeutics and clinical pharmacology

HILARY BISHOP, research technician, department of medicine

M MITCHARD, PHD, MSc, senior lecturer, department of therapeutics and clinical pharmacology

#### Queen Elizabeth Hospital, Birmingham B15 2TH

A M HOARE, MB, MRCP, senior registrar

C F HAWKINS, MD, FRCP, consultant physician

#### Comment

Cardiac arrhythmias have been implicated as the major cause of death in patients with myocardial infarction; ventricular fibrillation has been present in 90% of these patients. So far intravenous lignocaine has been the most widely used antiarrhythmic agent for a variety of ventricular arrhythmias.

Our report illustrates a case of recurrent ventricular fibrillation after myocardial infarction that was resistant to intravenous lignocaine given at a rate of 2 mg/min over many days but which responded to oral disopyramide.

Disopyramide is one of the recent antiarrhythmic agents found to be effective in various arrhythmias, both atrial and ventricular.<sup>2-4</sup> It is said to possess both parasympatholytic and local anaesthetic properties, being as active as lignocaine in this latter respect.<sup>5</sup> The drug's apparent effectiveness is probably due to its ability to prolong the refractory period of the atria and the ventricles.<sup>2-4</sup> Supraventricular or ventricular tachycardias are thought to be due to re-entry mechanisms initiated by atrial or ventricular premature beats. Suppression of these premature beats by disopyramide in addition to prolongation of the atrial or ventricular effective refractory period should be a valuable effect for the termination of such tachycardias. Oral disopyramide may therefore be a useful alternative to intravenous lignocaine in preventing life-threatening ventricular tachyarrhythmias after myocardial infarction.

<sup>1</sup> Jennings, G, *et al*, *Lancet*, 1976, **1**, 51.

<sup>2</sup> Katz, M J, *et al*, *Clinical Therapeutic Research*, 1963, **5**, 343.

<sup>3</sup> Desruelles, J, *et al*, *Therapie*, 1967, **22**, 937.

<sup>4</sup> Vismara, L A, Mason, D T, and Amsterdam, E A, *Clinical Pharmacology and Therapeutics*, 1974, **16**, 330.

<sup>5</sup> Baines, M W, *et al*, *Journal of International Medical Research*, 1976, **4**, suppl No 1, 5.

#### Mount Vernon Hospital, Northwood, Middlesex HA6 2RN

T D I M S DE LANEROLLE, MD, MRCP, registrar in general medicine

V EDMUNDS, MD, FRCP, consultant physician

A H WILCOX, MB, BCHIR, senior house officer in general medicine

## Disopyramide in a case of recurrent ventricular fibrillation

Disopyramide (4-di-isopropylamino-2-phenyl-2-(2-pyridyl) butyramide phosphate) given prophylactically after myocardial infarction has been known to cause a significant reduction in ventricular arrhythmias.<sup>1</sup>

We describe a patient with recurrent ventricular fibrillation after myocardial infarction that was resistant to intravenous lignocaine but responded to oral disopyramide.

### Case report

A 65-year-old welfare officer was admitted with a six-hour history of central chest pain. For a week before admission he had had twinges of pain in the same area on exercise. There was no other significant history. He was a non-smoker. His mother died of coronary heart disease at the age of 62.

On admission he looked fit and was in sinus rhythm with a pulse of 64/min and a blood pressure of 130/90 mm Hg. He had no evidence of heart failure. An electrocardiogram showed an anteroseptal and lateral infarction. The chest x-ray picture showed an enlarged cardiac shadow with clear lung fields. Cardiac enzymes—*aspartate transaminase* and *hydroxybutyrate dehydrogenase*—were 230 IU/l (normal 9-35) and 1660 IU/l (normal 50-325) respectively 24 hours after admission. After three days in bed he was gradually mobilised. On the 14th day, when he was fully mobilised, he suddenly collapsed. He was pulseless, with an unrecordable blood pressure; he was in ventricular fibrillation. He was restored to sinus rhythm with a DC shock of 200 joules, followed by a bolus of 100 mg lignocaine intravenously and an infusion of lignocaine at 3 mg/min, reduced to 2 mg/min four hours later. In spite of the intravenous lignocaine and boluses of intravenous phenytoin and procainamide, further cardiac arrests occurred at 12-24 hour intervals, with ventricular fibrillation shown on the monitor. By the 28th day his condition had deteriorated as the periods between arrests had decreased to one to two hours. His lungs remained clear on 80 mg of frusemide daily.

After 29 incidents requiring DC conversion, he was started on disopyramide, 200 mg four times a day, and lignocaine was tailed off. His last arrest (30th) was an hour after starting the drug.

He made an uneventful recovery and was discharged three months after admission. During his stay he was on prophylactic subcutaneous heparin. At one stage he developed acute urinary retention, a known complication of disopyramide. He remained on the drug, 100 mg four times a day, for 12 weeks after discharge.

## Cervical pregnancy managed by local excision

Cervical pregnancy is rare, the incidence recorded by Dees<sup>1</sup> being 1 in 18 000 pregnancies. It is often associated with considerable vaginal bleeding which usually necessitates emergency hysterectomy. In the case described below treatment was by local excision.

### Case report

A 26-year-old married primigravida with 12 weeks amenorrhoea was admitted as an emergency, complaining of painless vaginal bleeding for about 24 hours. Three weeks before admission she had had a similar, but smaller painless vaginal haemorrhage, which had lasted 18 hours but for which she had not sought medical advice. Symptoms suggestive of early pregnancy had been present but had diminished during the two weeks before admission.

Her general condition was good; abdominal examination showed no obvious abnormality apart from very slight suprapubic tenderness. Vaginal examination confirmed that she was bleeding briskly; findings on digital examination suggested that there were products of conception within the cervical canal, and it was also noted that the uterus was only slightly enlarged, with no masses in the appendages. Speculum examination confirmed the presence of a mass resembling products of conception in the cervical os, but attempted removal with sponge-holding forceps simply caused further bleeding. The patient was therefore transferred immediately to the operating theatre.

At operation, an intracervical mass, about 4 cm in diameter was found; it was visible through the partly dilated external os, and was adherent to the thinned-out cervix. There was heavy bleeding from a punctum on this mass.

After clamping each side of the cervix to occlude the lateral cervical blood vessels, the intact internal os was dilated using Hegar's dilators and the uterine cavity curetted. The mass was carefully dissected free from the