Clinical details of patients

Case No	Sex	Age (years)	Symptoms	Urinary catecholamine concentrations (nmol/day)*			Findings on computed tomography	Findings of ^{131}I-metaiodobenzylguanidine scanning	Outcome
				Adrenaline	Noradrenaline	Dopamine			
1	F	81	Anorexia, nausea, labile hypertension, syncope, palpitations	405	62	1862	Left sided adrenal mass 10 cm in diameter	Left sided adrenal mass	Normotensive, well
2	F	74	Persistent hypertension, flushes and sweating, nausea, diarrhoea, palpitations	520	1175	332	Right sided adrenal mass 2·8 cm in diameter	Right sided adrenal mass	Normotensive, well
3	F	75	Persistent hypertension, nausea and vomiting, palpitations, sweating	433	350	11000	Left sided adrenal mass 5×7 cm	Multiple skeletal metastases†	Death
4	F	72	Neurofibromatosis, hypertension	110 (279)‡	100 (2185)‡	492 (2370)‡	Left sided adrenal mass 5·5 cm in diameter and pseudocyst of pancreas	Left sided adrenal mass. Repeat scan showed skeletal and hepatic metastases	Refused to have operation, death

*Catecholamine concentrations were measured by reverse phase liquid chromatography. Normal ranges: adrenaline 5-80 nmol/day, noradrenaline 40-780 nmol/day, dopamine 200-3500 nmol/day.
†Scan performed after patient underwent left sided adrenalectomy.
‡Repeat measurements.
Conversion: SI to traditional units—Adrenaline: 1 nmol/day≈0·18 μg/day. Noradrenaline: 1 nmol/day≈0·17 μg/day. Dopamine: 1 nmol/day≈0·15 μg/day.

cardiac arrhythmias and severe labile hypertension. Postoperative ^{131}I-metaiodobenzylguanidine scanning confirmed that the adrenal tumour was a phaeochromocytoma. Measurements taken a year later showed that urinary catecholamine concentrations were raised, and a ^{131}I-metaiodobenzylguanidine scan showed widespread bony and hepatic metastases. She became progressively more cachectic over the next month and died. At necropsy disseminated malignant phaeochromocytoma was confirmed histologically.

Case 3—An 81 year old woman with a two year history of poorly controlled hypertension and recurrent syncope presented with episodes of central abdominal pain associated with palpitations. A small thyroid nodule was noted, and thyrotoxicosis was confirmed biochemically. Urinary adrenaline excretion was raised, and both computed tomography and ^{131}I-metaiodobenzylguanidine scanning confirmed a left adrenal phaeochromocytoma. At operation a 9·5 cm brown bosselated tumour was removed. Postoperatively she remained normotensive and free of symptoms, but hyperthyroidism recurred when carbimazole treatment was stopped.

Case 4—A 74 year old woman with a history of four years of hypertension and a previous myocardial infarct presented with severe back pain. Computed tomography showed a right adrenal mass. During the three months before admission she had suffered two syncopal attacks and complained of flushing, sweating, and nausea. Urinary adrenaline and noradrenaline concentrations were raised, and a ^{131}I-metaiodobenzylguanidine scan showed a right adrenal tumour. A 3·5 cm encapsulated golden brown tumour was removed at operation. She was normotensive when discharged.

Comment

This is the first antemortem description of patients aged over 70 with malignant phaeochromocytoma. All four patients were women, all had hypersecretion of adrenaline, and one of the malignant tumours secreted excess dopamine.

The incidence of phaeochromocytoma in the elderly is reported to be much lower than that in younger patients.[1] A necropsy study that reviewed 54 tumours found, however, that 12 patients with benign tumours were over 68 years old, indicating a higher incidence in the elderly than has been suggested.[3] In nine of the 12 patients the clinical diagnosis was unsuspected. A contributory factor to the rarity of the antemortem diagnosis of phaeochromocytomas in the elderly may be a decrease in sensitivity to catecholamines with age.[4] Another possibility is pronounced variability in catecholamine secretion (see case 4 in table).

Surgery has resulted in cure in over 90% of patients with phaeochromocytoma,[5] but this has been based on populations in which the mean age ranged from 45 to 50. The excellent outcome in cases 1 and 2, despite the patients' ages, suggests that phaeochromocytoma is a potentially remediable condition in the elderly.

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Pyrexia of unknown origin and colorectal carcinoma

Pyrexia of unknown origin is defined as a fever greater than 38·3°C of more than three weeks' duration that remains unexplained despite one week's observation of the patient in hospital.[1] Pyrexia is often associated with occult malignant disease,[2] most commonly of the reticuloendothelial system, lung, pancreas, kidney, and liver, though many other malignancies have been reported.

Patients with colorectal cancer rarely present with pyrexia of unknown origin without associated gastrointestinal symptoms. We report three such cases.

Case reports

Case 1—A 63 year old man presented with a six week history of intermittent fever and malaise. He had experienced sudden bouts of fever of up to 39°C with rigors that lasted for several hours. The fevers were occasionally associated with the passage of stool. Physical examination, including rectal examination, yielded normal results, as did all the tests routinely performed in patients with pyrexia of unknown origin, including a barium enema. Blood cultures grew *Escherichia coli*. As all the tests yielded negative results the patient was referred for laparotomy, at which a mobile Dukes's B carcinoma of the rectum was found and an anterior resection performed. The patient recovered and suffered no further episodes of fever.

Case 2—A 60 year old woman presented with a six month history of intermittent attacks of fever and rigors lasting for up to two hours. She underwent thorough medical investigation in two hospitals. All tests, including a barium enema, yielded normal results. Nine months after the onset of symptoms a transient swelling was noted in the right iliac fossa. Tests for faecal occult bloods yielded positive results, and a repeat barium enema showed a filling defect in the caecum. Laparotomy showed a mobile Dukes's B carcinoma of the caecum. A right hemicolectomy was performed, and the patient recovered and remained well for 12 years after surgery.

Case 3—A 68 year old man presented with a six month history of intermittent feverish episodes associated with malaise, rigors, and headaches. The attacks lasted about six hours, and his temperature rose to 39°C. General physical

examination, including rectal examination, was unhelpful. Investigations showed atypical coliforms in the urine but no protein or pus cells. Intravenous pyelogram was reported as normal. A barium enema was performed because of the similarity of the pattern of the fever with that in case 2 and showed a rectosigmoid carcinoma. At laparotomy the tumour was found to be adherent to the bladder, but the liver was clear. A sigmoid colectomy and partial cystectomy were performed. Histology showed a Dukes's B carcinoma of the colon. The patient remained well for 11 years after surgery.

Comment

Pyrexia of unknown origin remains unexplained in 10% of those who have it despite intensive investigation.[3] Colorectal cancer is not normally considered to be a possible cause because of the absence of gastrointestinal symptoms. The cases reported here show, however, that investigation of the large bowel in such circumstances can lead to relief of symptoms and may well be life saving.

The fevers seem to be transient (30 minutes to two hours) and are often associated with rigors. This suggests that they may be caused by recurrent, transient bacteraemias, a theory substantiated by the growth of *E coli* on blood cultures in case 1. Interestingly, *Streptococcus bovis* bacteraemias in patients with endocarditis have recently been reported to have a strong association with colonic neoplasia.[4] In those cases and the ones reported here the fever stopped after the neoplasm was removed.

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β Blocker treatment for angina with associated bradycardia

Views on the value of the intrinsic sympathomimetic activity of β blocking drugs have fluctuated over the past 12-15 years. In recent years, however, interest has tended to be revived, though clinical trials have failed to establish a role for the activity.

Resting bradycardia is usually considered to contraindicate treatment with β blockers. We describe a patient with angina and bradycardia who benefited specifically from a β blocker having intrinsic sympathomimetic activity rather than from one not having this property.

Case report

A 60 year old man presented with uncontrolled angina for nine months. He had also suffered a dizzy spell, but this may have been related to standing quickly after a hot bath. His family practitioner had been reluctant to try β blocker treatment in view of a pronounced resting bradycardia (48 beats/min), which was confirmed in our own clinic (46/min). Exercise testing confirmed that he had moderately severe ischaemic heart disease with an exercise tolerance of 5·5 minutes associated with ST segment depression reaching a maximum of 3·0 mm in lead aVF. Exercise was limited by breathlessness rather than angina. He agreed to participate in a brief trial of β blocker treatment in which we compared atenolol (no intrinsic sympathomimetic activity) 100 mg and pindolol (pronounced intrinsic sympathomimetic activity) 15 mg twice daily. Treatment was assessed by 24 hour electrocardiographic tape recording and repeat exercise testing.

Exercise testing showed that pindolol was superior to atenolol. Though atenolol greatly reduced ischaemic ST segment depression, exercise tolerance also was reduced slightly because of increased breathlessness; pindolol, however, achieved an equivalent degree of improvement in ST segment depression with an increase in exercise tolerance (all exercise tests were limited by breathlessness rather than angina). Resting heart rate was increased during pindolol treatment (51 beats/min *v* 43/min with atenolol) but control of the maximum heart rate was similar with the two drugs (pindolol 75 beats/min; atenolol 72/min). The table summarises performance in the exercise tests.

Summary of performance in exercise tests

	Total exercise time (min)	Maximum ST depression (mm)	Resting heart rate (beats/min)	Maximum heart rate (beats/min)
Original test	5·5	3·0	54	110
Atenolol 100 mg*	4·9	1·6	43	72
Pindolol 15 mg twice daily†	6·1	1·5	51	75

* No intrinsic sympathomimetic activity.
†Pronounced intrinsic sympathomimetic activity.

The 24 hour tape recordings also showed a considerable advantage from pindolol, with significantly less bradycardia (mean minimum hourly heart rate 42 *v* 39 beats/min; $p<0·01$ (Wilcoxon paired rank sum test)) and significantly higher maximum hourly heart rates (mean 54 *v* 49 beats/min; $p<0·01$), despite the similar control of heart rate during maximal sympathetic stimulation (exercise testing). There was also a significant reduction in the frequency of pauses (>1·5 s) during pindolol treatment ($p<0·01$); daytime pauses were almost completely abolished (eight hours completely pause free as compared with two with atenolol), and night time pauses were reduced in frequency. After the trial the patient elected to continue with pindolol.

Comment

Angina with a coincidental resting bradycardia is not a common finding, but when it occurs it always poses a clinical problem. It is still desirable to inhibit the exercise induced tachycardia, as it is then that the patient experiences his angina, but β blocker treatment enhances the resting bradycardia and may aggravate a potential conduction or sinus node disorder.[1] There have been reports of successful treatment of this condition by implantation of a permanent pacemaker and subsequently use of β blockade.[2 3] Though this treatment is clearly effective, it is expensive, invasive, and not without hazard. β Blockers having intrinsic sympathomimetic activity should not cause bradycardia at optimal dosage and are considerably less likely to cause conduction disturbances.[1 4]

In our patient pindolol prevented a detrimental exercise tachycardia and improved the resting bradycardia with no aggravation of 24 hour tape recorded evidence of pauses. By contrast, atenolol aggravated the resting bradycardia and increased the frequency of pauses. Atenolol also proved less effective in terms of exercise performance; since the limiting factor in the exercise tests was breathlessness, possibly the improvement with pindolol was also due to an increased heart rate responsiveness when there was submaximal β blockade.

This case may illustrate a specific indication for using intrinsic sympathomimetic activity in the treatment of angina; further prospective evaluation is warranted.

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