Death from phaeochromocytoma: lessons from a post-mortem survey

ABSTRACT—Despite advances in biochemical assessment and imaging, phaeochromocytoma remains a difficult diagnosis. Using the names of patients whose death certificate listed phaeochromocytoma as a cause of death, a retrospective survey of 62 deaths from phaeochromocytoma (48 benign, 14 malignant) was carried out. All deaths occurred between 1981 and 1989, so the pitfalls uncovered reflect recent practice. A substantial proportion presented with abdominal pain and vomiting, dyspnoea, left ventricular failure or hypotension rather than the classical symptoms. These presentations were more common in this autopsy series than in prospective series of consecutive patients. Diagnosis in the presence of classical symptoms was often delayed but, once it was made, elective excision was relatively safe. A personal or family history of symptoms suggesting inherited diseases associated with phaeochromocytoma was not always given due weight. Biochemical tests, particularly 24 hour urinary vanillyl mandelic acid, often gave contradictory results; the limits of their predictive power should be better appreciated. Anaesthesia and surgery in the presence of undiagnosed phaeochromocytoma was the cause of death in 16 of 62 cases. Recommendations to improve the accuracy of diagnosis are made.

Phaeochromocytoma is a catecholamine secreting tumour present in 0.1-1% of patients with arterial hypertension [1,2]. In 90% of cases the tumour is benign yet deaths still occur because of its rarity as a cause of hypertension, intermittent or absent symptoms, lack of specific signs, the limitations of diagnostic tests and the hazards of anaesthesia and surgery. We undertook this survey of patients who had died from phaeochromocytoma to investigate the influence of these factors.

Methods

The names of patients who had an adrenal diagnosis recorded on their death certificates were obtained from the Office of Population Censuses and Surveys of the United Kingdom. Of these, 127 listed phaeochromocytoma as a cause of death. We obtained the case notes of 67 of them but in six the documentation was insufficient to verify the diagnosis. All the remaining 61 died between 1982 and 1986; we added a 62nd case known to us from 1989. From the case notes we extracted data on the onset, duration and development of symptoms and signs, family history, investigations performed, operative data and post-mortem findings.

Results

Prevalence

There were 40 women and 22 men, a female preponderance of 1.8:1. The age at death ranged from 13 to 85 years with a median of 56 (Fig 1). Age at presentation was 13 to 85 years with a median of 52 years. The median time interval between presentation to a physician and death was 19 days (range 15 minutes to 34 years). The diagnosis was made prior to death in 17 patients (27%) and after death in 45 (73%); it was unsuspected at the time of death in 31 patients (50%). In a further 14 patients (23%) the diagnosis was suspected but not confirmed.

Four benign phaeochromocytomas were diagnosed ante-mortem; two died within hours of elective removal. The third collapsed with occipital headaches and weakness of arms and legs after seven years of typical symptoms; he had labile hypertension and epigastric pain due to pancreatitis and a serum CPK of 13,000 IU/1 suggesting rhabdomyolysis. He died in renal failure seven days later. The fourth, aged 68, died of chronic renal failure and left ventricular failure (LVF) which were present before and after removal of a phaeochromocytoma 21 months earlier.

Malignant phaeochromocytoma was present in 14 patients (23%); thirteen of these were diagnosed ante-mortem. The 14th patient was a teenager with neurofibromatosis who presented with a right hypochondrial mass and metastatic disease.

Symptoms and signs

Typical symptoms of phaeochromocytoma were present for over three months prior to death in 38 patients (61%), 25 benign and 13 malignant; the most common were palpitations in 20, episodic sweating in 19, dyspnoea in 15 and headaches in 14 (Fig 2). Symptoms were present for less than three months in 18 patients (29%), 17 benign and one malignant, and hypertension alone for over three months was present in six (10%). Most of the symptoms occurred with
both benign and malignant tumours but bone pain, anorexia and paraplegia occurred exclusively, and weight loss predominantly, with malignant tumours. Episodic symptoms were often nocturnal.

The pattern of symptoms was different in the 18 with a duration of less than three months (Fig 3). Sixteen suffered from abdominal pain and all 18 from vomiting. The pain was usually suggestive of an acute abdominal crisis and localised over the site of the tumour. In three cases it was caused by acute pancreatitis (serum amylase 1675, 2110 and 4310 Somogyi units). Dyspnoea, mostly from LVF, was present in 15, chest pain in 11, sweating in 9 and headaches in 4.

The physical signs during the final illness are shown in Fig 4. Hypertension was present in 45 (73%) but six (10%) were hypotensive. Ten patients under 50 had had hypertension for more than six months; of the four with benign tumours, three were undiagnosed. Signs of heart failure were present in 33 (53%) and a further 13 (21%) had tachycardia in the absence of heart failure. Retinopathy was recorded in 13 (21%) and pyrexia in 18 (29%). Abdominal tenderness was present in 10 (16%) and an abdominal mass was felt in 8 (13%). Pupils were dilated and reacted sluggishly to light in 11 (18%).

**Family history**

Three patients had a significant family history and another had neurofibromatosis without a family history. One patient had a strong family history of multiple endocrine adenomatosis type II, with mother and five maternal relatives having medullary carcinoma of the thyroid and/or bilateral phaeochromocytomas. There was a four year history of episodic palpitations, headaches, sweating and pallor, particularly at night, after exercise or alcohol. On two occasions 24 hour urinary vanillyl mandelic acid (VMA) excretion was normal. The patient woke one morning with palpitations, agitation, abdominal pain and haematemesis and had a cardiac arrest in the ambulance. Autopsy showed a haemorrhagic tumour with retroperitoneal haemorrhage.

Two patients had both family history and stigmata of neurofibromatosis. One teenager presented with a right hypochondrial mass with lung and liver metastases. He had been hypertensive for more than three months but one VMA measurement was normal so surgery was performed without alpha and beta blockade. He had a cardiac arrest as the tumour was mobilised during diagnostic laparotomy and died three days later. The second patient had a one year history of headaches, palpitations, hot flushes and hypertension treated with prazosin and metoprolol. Following an elective hysterectomy she developed hypertension and tachycardia and died 24 hours after surgery. The patient with neurofibromatosis and no family history is described under ‘Surgery and anaesthesia’.

**Investigations**

Urinalysis was reported in the case notes of 27 patients; it was normal in 12 (44%) and showed proteinuria in 15 with haematuria in 8. Renal function was recorded in 50 patients; serum urea was > 9.0 mmol/l and/or creatinine > 130 μmol/l in 31. Glycosuria was present in 9 of the cases in which it was recorded. Blood glucose was measured in 42 patients and was greater than 11 mmol/l, confirming diabetes, in 24 (57%). One diabetic patient had a normal glucose tolerance test after excision of a phaeochromocytoma.

![Fig 1. Age at death.](image-url)
but VMA excretion remained elevated; recurrence of diabetes led to the recognition of metastases from her malignant phaeochromocytoma.

VMA was measured in 24-hour urine collections from 22 patients (10 with malignant and 12 with benign tumours). Some had only one collection. The results were always high in 14 (64% of those tested; 7 malignant), occasionally high in 3 (14%; 2 malignant) and normal in 5 (23%; one malignant). Urinary metanephrines were elevated in all four patients tested, urinary catecholamines in 10 of the 11 and plasma catecholamines in 9 of 12. One patient had stimulation tests with glucagon and tyramine, both normal. One pentolinium test was positive; no clonidine suppression tests were performed.

A raised leucocyte count was present in 29 of the patients and a low haemoglobin in 6. One patient had a haemoglobin of 24 g/dl, possibly due in part to extracellular fluid depletion. The serum calcitonin was elevated in two patients, neither of whom had medullary carcinoma of the thyroid at autopsy.

The electrocardiogram was normal in 8 of 43
patients and showed left ventricular hypertrophy by voltage criteria in 9, sinus tachycardia in 18, ischaemic changes in 5, myocardial infarction in 2, right bundle branch block in 2, left bundle branch block in 2, left axis deviation in 2 and atrial fibrillation in 2. Chest radiographs from 47 patients were normal in 15 and showed an increased cardiothoracic ratio in 8, pulmonary oedema in 5, pulmonary metastases in 5 and various abnormalities in 9. One patient with hypertension and LVF from an unrecognised phaeochromocytoma died following an intravenous urogram with niopam contrast medium. Another had a cardiac arrest during angiography. A third underwent arteriography without mishap but the procedure failed to locate the tumour. Renal vein sampling for catecholamines in three patients localised the tumour in two. Abdominal ultrasound was performed in 18 patients; the phaeochromocytoma was shown in 10 (55% sensitivity), 3 were reported normal and 5 showed other abnormalities: two 'masses' which were not present, two gallbladders containing stones and one enlarged liver. A CT scan was performed in 10 and showed the adrenal phaeochromocytoma in all. A diagnostic 131I-metaiodobenzylguanidine (MIBG) scan was performed in four patients and located the tumour in all.

Surgery and anaesthesia

Sixteen patients had an operation in the week prior to death; nine of these were for elective surgery in patients not known to have a phaeochromocytoma: hysterectomy 2, repair of vaginal prolapse 2, tubal ligation 1, cholecystectomy 2, abdomino-perineal resection 1, and nephroureterectomy for transitional cell carcinoma (opposite side to phaeochromocytoma) 1. Of these nine patients, five had symptoms typical of phaeochromocytoma before operation. Three had uncontrolled hypertension pre-operatively (diastolic pressure > 100 mm Hg), two had controlled hypertension and four were normotensive. Only one patient had no symptoms or hypertension pre-operatively. Two patients died during elective removal of a phaeochromocytoma. One, who had an ACTH secreting phaeochromocytoma, despite adequate glucocorticoid administration and adequate volume replacement became hypotensive and oliguric post-operatively. The second, a patient with neurofibromatosis, was impeccably investigated pre-operatively but was not sent to an ITU after operation. Hypoxia and hypotension developed during the night after surgery and the patient was found dead on the ward. A teenager with an unrecognised malignant phaeochromocytoma died during surgery as described under ‘Family history’.

The other four patients had emergency surgery. They were all critically ill pre-operatively. One had a ruptured spleen from a splenic metastasis. Another had a perforation at the recto-sigmoid junction secondary to the intractable constipation of malignant phaeochromocytoma [3]. A third presented three months post-partum with sudden onset of headache, upper abdominal pain, vomiting and diabetes; later that day she had a cardiac arrest and was resuscitated. Two days later she lost the pulses in her left leg, had an unsuccessful embolectomy followed by amputation and died of disseminated intravascular coagulation and acute renal failure. The fourth patient, aged 55, had sudden onset of epigastric pain and vomiting, a large left hypochondrial mass, a serum amylase of 4310 Somogyi units, a large left retroperitoneal haemorrhage at laparotomy and died of acute renal failure. Autopsy showed a haemorrhagic and necrotic phaeochromocytoma.

Two patients died more than a week after surgery for malignant phaeochromocytoma: one at nine days from acute renal and hepatic failure after radical surgery and the other seven months after a peri-operative stroke.
Malignant phaeochromocytoma

Fourteen patients in this series had malignant phaeochromocytoma, all but one with metastases at presentation. Three had a palpable abdominal mass. Two had features of spinal cord compression; one presented with paraplegia and metastases 20 years after removal of a paraganglionic tumour and survived a further 14 years; the other presented with cord compression from an extradural tumour and a year of hypertension, episodic headache and sweating. Seven had their phaeochromocytoma removed, two had chemotherapy, two metatyrosine, two radiotherapy, three therapeutic MIBG and two had no treatment. Median survival was 528 days (range 10 days to 34 years).

Autopsy findings

The phaeochromocytoma was in the right adrenal in 26 (42%), left adrenal in 24 (39%), both adrenals in 2, extra-adrenal sites in 3 and disseminated and of uncertain origin in 1; the position was not recorded in 6. The full autopsy findings were recorded in 45 patients; 25 had left ventricular hypertrophy and 37 had pulmonary oedema. Cystic haemorrhagic change in the tumorous adrenal was seen in patients with and without pain.

Discussion

The mortality rate for phaeochromocytoma in the UK based on death certification 1982–6 was approximately 0.5 per million person years. A survey of incidence in Queensland [4] gave a figure of 1.55 and in Sweden 3.0 [5]. In Rochester, Minnesota (with a small population), eight phaeochromocytomas per million person years were seen [6]. A significant proportion of phaeochromocytomas are diagnosed only at autopsy, so a high autopsy rate is necessary to estimate reliably the number undiagnosed in life. In our series 50% were unsuspected in life, and in a further 23% the diagnosis was suspected but not finally confirmed. In other series in which full ascertainment was attempted, in Queensland (1970–83) 17 of 46 undiagnosed [4], in New York (1926–76) 30 of 100 [7], in Detroit (1951–82) 11 of 32 [8] and in Nashville (1950–83) 11 of 69 [9]. In the UK the autopsy rate is low, and often performed only if death was unexpected. Thus, our series is likely to have a bias, with undiagnosed cases over-represented. A more direct comparison may be made between our data and the Mayo Clinic autopsy series, where 41 of 54 (76%) cases (1928–77) were unsuspected clinically [10] and the Swedish Cancer Registry (1958–81) which showed that of 439 cases 40% were diagnosed at autopsy [5].

In the current series, 48 of the 62 patients had benign tumours (77%), but only 4 of these 48 were diagnosed ante-mortem. Failure to make the diagnosis of phaeochromocytoma in life was therefore the main cause of death in the benign cases, and the paucity of deaths in association with elective removal of benign tumours suggests that the mortality for benign phaeochromocytoma is very low once the condition has been diagnosed. Low operative mortality is now the rule. Deoreo et al (46 cases, 1952–73) and Desmonts et al (102 cases, 1964–76) both reported zero operative mortality [11,12]. Melicow had one death in 30 operations (1962–76) [7], and Scott and Halter 1 in 58 (1950–83) [9]. The value of fluid replacement at the time of surgery is emphasised in these series.

Twenty-five of the 48 benign cases had typical symptoms of phaeochromocytoma, present for longer than 3 months. Palpitation, sweating, dyspnoea, headache and dizziness were the most common. Other series show a similar distribution of symptoms [13]. Of the 25 cases with typical symptoms, 9 were on antihypertensive treatment, indicating that they had been under medical supervision for their blood pressure. Ten exhibited hypertension under the age of 50, of whom 3 had undiagnosed benign disease. Thus, failure adequately to investigate young hypertensives is a contributing factor in some cases. However, we found a significant difference in the pattern of symptoms exhibited by those patients with symptoms of short duration. A high proportion presented with abdominal pain and vomiting or dyspnoea, left ventricular failure and hypotension. In prospective series, the prevalence of abdominal pain is much lower [13,14] but was 20% in the Mayo Clinic autopsy series [10], in which 5 of 54 had an abdominal mass. Krane also reports that an abdominal mass was present in 6 of 11 cases where the diagnosis of phaeochromocytoma was unsuspected in life [8]. Thus, patients who present with abdominal pain or a mass seem less likely to have the diagnosis of phaeochromocytoma made in life, and are over-represented in autopsy series. Both benign and malignant phaeochromocytoma can present as acute abdominal crisis. The autopsy results lend support to the supposition that this is the result of tumour haemorrhage and infarction. Primhak et al [15] described a boy who was kicked in the abdomen in a football match, developed pain at the site of trauma accompanied by a catecholamine crisis and died soon after. At autopsy there was retroperitoneal bleeding from a large tumour. Phaeochromocytoma presenting with heart failure is also likely to be diagnosed only at autopsy [16]. Modlin et al found symptoms to be present for less than 1 year in 12 of their 14 undiagnosed cases [14]. Myocardial infarction and heart failure were the cause of death in half of these. Clearly, the early diagnosis of such patients with a short history of abdominal or cardiac symptoms is very difficult.

Of the 25% in whom the diagnosis was suspected but not confirmed until after death, the reasons were multiple. The most common reason was that the
patient died within a short period of the diagnosis being suspected and the collections were not completed or the samples not yet assayed at the laboratory. In other patients, initial clinical suspicion was discounted by false negative biochemical or radiological results.

The current series includes patients whose symptoms were nocturnal, related to position or alcohol consumption. Constipation was also a feature of these cases and seems likely to be due to an adynamic intestine induced by catecholamine excess. Dilated pupils were reported in 18% of the cases reviewed here, a sign which has been reported before and is likely to be due to sympathomimetic stimulation of the pupillary dilator muscle [17]. Acute pancreatitis occurred in three cases and rhabdomyolysis and renal failure occurred in one of these. Elsewhere this phenomenon has been suggested to be due to catecholamine induced skeletal muscle ischaemia [18]. Van Heerden et al reported one case of pancreatitis in a patient with phaeochromocytoma [1].

The urinary VMA excretion was the most commonly used screening test, being clearly positive in 64% of patients and falsely negative in 36%. There was no apparent difference in its sensitivity in benign and malignant cases. Impaired renal function may have influenced the results in some of our cases. However, Bravo and Gifford found raised VMA excretion in only 18 of 43 patients (42% sensitivity) [19]; they collected samples from hospitalised patients and used patients with essential hypertension as controls. Urinary metanephrines were raised in 34 (79% sensitivity). These authors found plasma catecholamine measurement (94% sensitivity) to be the best discriminant between phaeochromocytoma and essential hypertension. Compiling data from nine earlier series, Manu and Runge concluded that metanephrine estimation correctly identified 96% of phaeochromocytoma patients whereas VMA only identified 84% [20]. In our series metanephrine and urinary and plasma catecholamine measurements all proved more sensitive than VMA but the numbers of patients who had these tests performed were relatively small. Radiological studies were also misleading—ultrasound showing phaeochromocytoma in 10 of 18, a 55% sensitivity. Present day ultrasonography may be more sensitive. In the few who had computed tomography scans, the tumour was localised in 100%. Prior to CT, arteriography and intravenous urography were sometimes used. This series gives examples of the poor sensitivity of these techniques, and the risks of contrast media in phaeochromocytoma patients.

The high proportion of malignant phaeochromocytomas (23%) reflects the manner of patient selection by post-mortem diagnosis. In series of consecutive patients, the prevalence of malignancy ranged from 6% to 13% [4,7,13,14,21]. It is generally accepted that histology alone is a poor guide to malignant potential and that malignant phaeochromocytoma is only proven by the presence of metastases. Extended follow-up may increase the proportion eventually considered malignant [9]. Survival with malignant phaeochromocytoma is very variable. Aggressive malignancies may be treated with combination chemotherapy [22].

It is not a practical proposition to screen all hypertensive patients; selection is essential [23]. Symptoms are an important guide, and are well described in detail elsewhere [13,24]. A scoring system has been devised to aid prediction [25]. The majority of patients have intermittent paroxysms lasting less than one hour, tending to become more frequent with time. Sustained hypertension occurs in 50–60% often with superadded paroxysmal elevations. Postural hypotension may be a feature. Recently, 24 hour ambulatory blood pressure monitoring has been used to identify intermittent elevation of blood pressure, which may be nocturnal [26]. Screening should be undertaken in those with accelerated or progressive hypertension, hypertension occurring at a young age or not responding to conventional treatment, a paradoxical rise in blood pressure on administration of a beta-adrenoceptor blocking drug, and those with pressor responses to induction of anaesthesia, intravenous contrast media or labour. A family history of multiple endocrine adenomatosis type II or neuroectodermal syndromes substantially increases the chance of a phaeochromocytoma being present. Rigorous screening should be performed in all first and second degree relatives but particularly in those with hypertension and prior to any anaesthesia. Phaeochromocytoma should be considered in all patients presenting with a hypochondrial mass, and appropriate investigation undertaken if the initial imaging is consistent with this diagnosis.

Initial investigation remains biochemical. Twenty four hour urine collection into concentrated hydrochloric acid for metanephrines or free catecholamines is the optimum, and both are superior to the measurement of VMA. Urinary values > 1 µmol (170 µg) of noradrenaline/24 h or > 190 nmol (35 µg) of adrenaline/24 h provide a specificity > 95% [27]. Spot urine collections immediately after a paroxysm, with the result expressed relative to creatinine, can be used to support the diagnosis and appear to provide good discrimination using > 0.57 µmol total metanephrine/mmol creatinine (1 µg/mg) as diagnostic of phaeochromocytoma [28]. Plasma catecholamines are not routinely measured but do have a role in difficult cases. Samples taken during a paroxysm can be diagnostic [29], and selective sampling is sometimes necessary for localisation. Clonidine [30] or pentolinium [31] tests may be used to distinguish patients with borderline elevation of plasma catecholamines. Patients with autonomous catecholamine synthesis from a phaeochromocytoma show no suppression. In all situations where plasma catecholamines are measured, the conditions of sampling and specimen handling are critical. There is
preliminary evidence that plasma metadrenalines are much more reliable indicators of the presence of pheochromocytoma than the parent catecholamines [35].

CT or magnetic resonance scanning are the most reliable imaging techniques for pre-operative localisation and visualise virtually all adrenal pheochromocytomas. Phaeochromocytomas are intensely bright on T2 weighted MR images [29], although this is not a totally specific characteristic. Recent figures for the proportion of phaeochromocytomas that are extra-adrenal range between 15% and 22% [5,13,32]. The majority of extra-adrenal pheochromocytomas (> 85%) are found in the abdomen or pelvis [32]. Thus, if clinical suspicion remains despite the demonstration of normal 24-hour urinary metanephrine or catecholamine excretion, a CT or MR scan of adrenals and sympathetic chain (including the organ of Zuckerkandl) has considerable exclusion value. Metiodobenzylguanidine (MIBG) labelled with 131I or 123I is used primarily in the localisation of extra-adrenal tumours or metastases and in therapy [33,34].

Conclusion

In this autopsy survey of recent UK experience, the diagnosis of phaeochromocytoma was made before death in only 17 patients (27%), a figure similar to the 24% reported in a similar survey from the Mayo Clinic looking back over the years 1928–77 [10]. It is to be hoped that a wider appreciation of the possible clinical presentations, some illustrated above, and the appropriate use of modern investigative techniques will reduce the proportion of undiagnosed cases that predominate in these autopsy series.

Acknowledgements

We are grateful to Sue John who obtained the case notes of the patients in this study, and to Tracey Colman for invaluable secretarial assistance.

References

1 Van Heerden JA, Sheps SG, Hamberger B, Sheedy PF, et al. Phaeochromocytoma: current status and changing trends. Surgery 1989;91:967–73.
2 Manger WM, Gifford RW. Phaeochromocytoma. New York: Springer-Verlag, 1977.
3 Thurtle OA, Allen AP, Walters MT, Kitchen J, et al. Intractable constipation in malignant phaeochromocytoma: combined treatment with adrenergic blockade and cholinerigic drugs. J R Soc Med 1984;77:327–8.
4 Hartley L, Perry-Keene D. Phaeochromocytoma in Queensland—1970–83. Aust NZ J Surg 1985;55:471–5.
5 Stenstrom G, Svardsudd K. Pheochromocytoma in Sweden 1958–81. Acta Med Scand 1986;220:225–32.
6 Beard CM, Sheps SG, Kurland LT, Carney JA, Lie JT. Occurrence of phaeochromocytoma in Rochester, Minnesota, 1950 through 1979. Mayo Clin Proc 1983;58:802–4.
7 Melicow MM. One hundred cases of phaeochromocytoma (107 tumors) at the Columbia-Presbyterian Medical Center, 1926–76. Cancer 1977;40:1987–2004.
8 Krane NK. Clinically unsuspected phaeochromocytomas. Arch Intern Med 1986;146:54–7.
9 Scott HW, Halter SA. Oncologic aspects of phaeochromocytoma: the importance of follow-up. Surgery 1984;96:1061–6.
10 John Sutton M, Sheps SG, Lie JT. Prevalence of clinically unsuspected phaeochromocytoma. Review of a 50-year autopsy series. Mayo Clin Proc 1981;56:354–60.
11 Deoreo GA, Stewart BH, Tarazi RC, Gifford RW. Preoperative blood transfusion in the safe surgical management of pheochromocytoma: a review of 46 cases. J Urol 1974;111:715–21.
12 Desmonts JM, Le-Houelleur J, Remond P, Duvaldestin P. Anaesthetic management of patients with phaeochromocytoma. Br J Anaesth 1977;49:991–7.
13 Ross Ej, Griffith DNW. The clinical presentation of phaeochromocytoma. Q J Med 1989;71:485–96.
14 Modlin IM, Farrdon JR, Shepherd A, Johnston IDA, et al. Pheochromocytoma in 72 patients: clinical and diagnostic features, treatment and long-term results. Br J Surg 1979;66:456–65.
15 Primbak RA, Spicer RD, Varies J. Sudden death after minor abdominal trauma: an unusual presentation of phaeochromocytoma. Br Med J 1986;292:95–6.
16 Sardesai SH, Mournant AJ, Sivathanond Y, Farrow R, et al. Pheochromocytoma and catecholamine induced cardiomypathy presenting as heart failure. Br Heart J 1990;65:234–7.
17 Howard JE, Barkley WH. Paroxysmal hypertension and other clinical manifestations associated with benign chromaffin cell tumours (pheochromocytoma). Bull Johns Hopkins Hosp 1937;61:371–410.
18 Shemin D, Cohn PS, Zipin SB. Phaeochromocytoma presenting as rhabdomyolysis and acute myoglobinuric renal failure. Arch Intern Med 1990;150:2384–5.
19 Bravo EL, Gifford RW. Pheochromocytoma: diagnosis, localization and management. N Engl J Med 1984;311:1298–303.
20 mane P, Rung LA. Biochemical screening for pheochromocytoma: superiority of urinary metanephrine measurements. Am J Epidemiol 1984;120:788–90.
21 Remine WH, Chong GC, van Heerden JA. Sheps SG, et al. Current management of phaeochromocytoma. Ann Surg 1974;179:740–8.
22 Averbuch SD, Steakley CS, Young RC, Gehmann EP, et al. Malig- nant pheochromocytoma: effective treatment with a combination of cyclophosphamide, vincristine, and dacarbazine. Ann Intern Med 1988;109:267–73.
23 Naccoll CD, Gerard SK. Diagnosis of pheochromocytoma. N Engl J Med 1985;312:721.
24 Thomas JE, Roke ED, Krale WF. The neurologists’ experience with pheochromocytoma: a review of 100 cases. JAMA 1966;197:100–4.
25 Black HR, Bursten SL. A clinical scoring system for detection of patients with pheochromocytoma. Yale J Biol Med 1984; 57:259–72.
26 Sheps SG, Jiang NS, Klee GG, van Heerden JA. Recent develop- ments in the diagnosis and treatment of pheochromocytoma. Mayo Clin Proc 1990;65:68–95.
27 Sheps SG, Jian NS, Klee GG. Diagnostic evaluation of pheochromocytoma. Endocrinology and Metabolism Clinics of North America 1988;17:397–414.
28 Kaplan NM, Kramer NJ, Holland OB, Sheps SG, Gomez-Sanchez C. Single voided urine metanephrine assays in screening for pheochromocytoma. Arch Int Med 1977;137:190–3.
29 Fonseca V, Bouloxium PM. Phaeochromocytoma and paraganglioma. Bailleures Clin Endocrinol Metab 1993;7:599–44.
30 Bravo EL, Gifford RW, Fouad FM, et al. Clonidine-suppression test: a useful aid in the diagnosis of phaeochromocytoma. N Engl J Med 1981;305:623–6.
31 Brown MJ, Allison DJ, Jenner DA, Lewis Pj, Dollery CT. Increased sensitivity and accuracy of phaeochromocytoma diagnosis achieved by use of plasma-adrenalineline estimations and a pentolintension-suppression test. Lancet 1981;i:174–7.
International developments in health care
A review of health systems in the 1990s
Edited by Roger Williams

In the last ten years or so it has become evident to all nations in the developed world that simply spending ever more of their gross domestic product on health care is not enough to meet the level of health care expected by their peoples. Moreover, the ageing of nations will place an increasingly heavy burden on the income-generating sections of their populations. Individual countries have attempted to improve the effectiveness and efficiency of their health care systems. Such attempts, not surprisingly, have been heavily influenced by political considerations. To give those more closely concerned with delivering medical care the opportunity to learn how different systems operate, and to debate and discuss among themselves their pros and cons, the Royal College of Physicians arranged a meeting on which the edited chapters and discussion sections of this book are based. Contributors were drawn from North America, the Commonwealth countries of Canada, Australia and New Zealand, from mainland Europe including France, the Netherlands, Germany and Sweden, and from the UK. They included health care planners, members of government, clinicians from hospitals and general practice and officers of the medical Royal Colleges.

CONTENTS
Preface by Anthony J Culyer

PART 1 New Schemes in the Commonwealth
   An introduction to the Commonwealth scene by Robert Maxwell
   → Changed organisation in New Zealand by Peter Martin
   → Australia’s health reform by Dallas Ariotti
   → Canada’s health system: charting a new vision for the 21st century by Ray D Pagtakhan

PART 2 Developments in health care in the United States of America
   An introduction to the American scene by Richard T Kitney
   → Health care reform in the United States by Roz D Lasker
   → Attitudes of American physicians to health systems reform by Clifton R Cleaveeland

PART 3 Changes within Europe
   Introduction to European health care systems by John F Martin
   → Reforming the German health care system by Michael Moran
   → Government plans in France by Laurent Zylberberg
   → Restructuring health care in the Netherlands by Kieke GH Okma
   → The effects of market mechanisms in a public health care system; the case of Sweden by Johan Callorp

PART 4 Health reforms in the United Kingdom
   An introduction to the UK scene by Roger Williams
   → Managed competition in health care by Chris Ham
   → The way ahead by Alan Langlands
   → Impact of the general practitioner as a fundholder by David Colin-Thomé
   → Changes in hospital provision by John R Bennett

Price £15.00 (overseas £18.00). ISBN 1 86016 013 1
Soft cover, 165 pages.
Obtainable from the Royal College of Physicians and from bookshops

ROYAL COLLEGE OF PHYSICIANS OF LONDON