Phaeochromocytoma—recent progress in its management

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Phaeochromocytoma is a rare tumour arising from chromaffin cells in the adrenal medulla or in other paraganglia of the sympathetic nervous system.[57] The name, meaning 'dusky-coloured tumour', was first used by Pick[74] in 1912 although the tumour had been recognized earlier by von Frankel.[25] Successful surgery for excision of phaeochromocytoma was first performed by Roux (1926) and Mayo (1927).[101] The tumour can exist sporadically or in conjunction with other endocrine tumours in the multiple endocrine neoplasm (MEN) series.[27 50 85 87] Patients present with a variety of symptoms which reflect excessive secretion of norepinephrine, epinephrine or dopamine into the circulation. Patients with predominantly norepinephrine-secreting tumours present with hypertension, often severe and refractory to conventional therapy. Patients with predominantly epinephrine- (and dopamine-) secreting tumours present with a variety of symptoms, usually episodic, such as tachycardia with palpitations, panic attacks and feelings of doom. Few medical conditions pose such a severe but unpredictable threat to the patient's life, and it is therefore essential, as soon as a diagnosis is made, to commence medical therapy to inhibit the end-organ actions of the relevant catecholamines, pending surgical excision.

There has been an increasing tendency for patients with a definitive diagnosis of phaeochromocytoma to be referred to specialist endocrine surgeons, who in turn work with anaesthetists with specialist experience, and this can only be beneficial for such patients. Few anaesthetists have substantial experience of treating patients with phaeochromocytoma, but the review by Hull in this journal was a landmark,[37] reflecting his considerable experience in dealing with the diagnosis, preoperative preparation and anaesthetic management of the condition. In the 13 yr since that review was published, a number of new developments have occurred in various aspects of the medical, surgical and anaesthetic treatment of patients with these rare tumours. With the exception of historical landmark papers, I have restricted references to those which have appeared since 1980 and, generally, I have not duplicated those quoted by Hull.[37]

Histological and genetic origins of phaeochromocytoma

Cells embryologically derived from the neuroblasts of the neural crest develop in a variety of endocrine and non-endocrine tissues, where they secrete polypeptide hormones or hormone precursors (Fig. 1). These cells have a common cytochemical function in that they take up chemical precursors which they decarboxylate to produce a variety of biologically active amines; it is for this reason they have been classified as APUD cells (amine and amine precursor uptake and decarboxylation).[6 71] Chromosomal mutational changes in the *RET* proto-oncogene cause neoplastic changes in these cells,[65 66] resulting in the formation of tumours which may occur sporadically or as part of a familial syndrome. Phaeochromocytomas arise predominantly from chromaffin cells in the adrenal medulla, although about 6% occur in other tissues of neuroectodermal origin such as the paraganglial cells of the sympathetic nervous system, including those of the organ of Zuckerkandl.[12 57] There have been sporadic reports of phaeochromocytoma arising in the heart or pericardium.[45 80 89]

The majority (90%) of phaeochromocytomas occur sporadically and are benign.[57] In about 10% of patients with phaeochromocytoma the adrenal tumour is part of a familial disorder such as the MEN syndromes, von Recklinghausen disease or von Hippel–Lindau syndrome.[61]

MEN syndromes

The term MEN describes a series of syndromes which were originally identified as familial by the study of specific kindreds,[65] and which are now known to be genetically linked.[61]

MEN 1

For completeness it is worth describing Wermer's syndrome (MEN 1),[102] a rare autosomal dominant disease which has been widely studied in nearly 2000 descendants of an English migrant to Tasmania.[84] It consists of tumours of the parathyroid glands, pancreatic islets (insulinomas) and

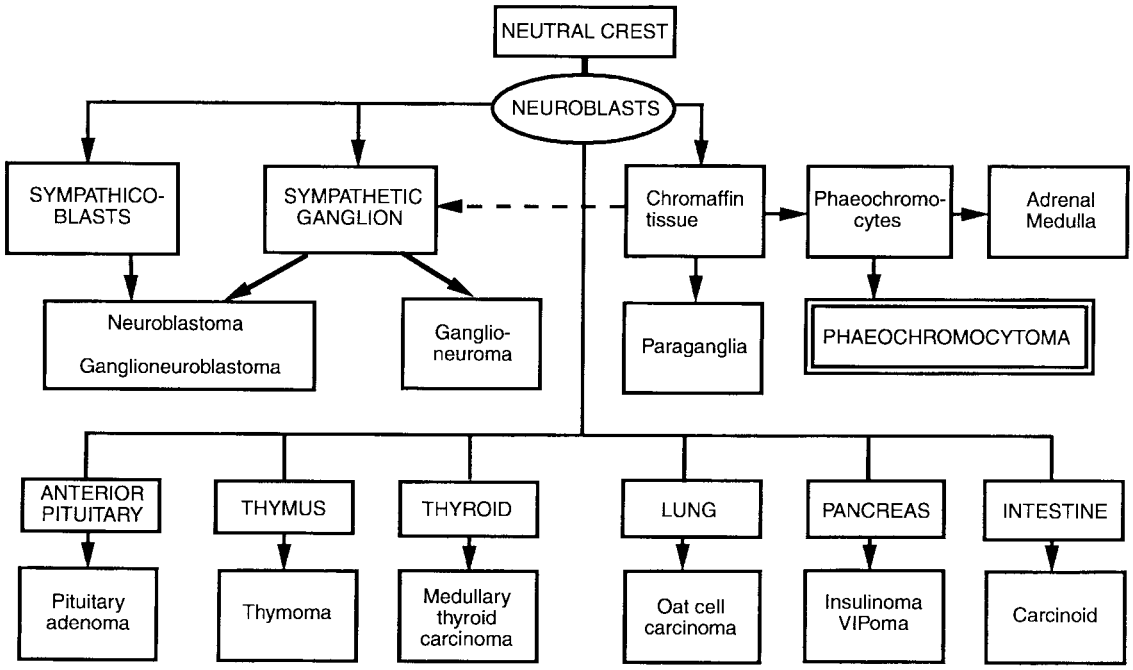

Fig 1 Classification of tissues and associated tumours derived from ectodermal cells of the neural crest.[6 71]

anterior pituitary, but phaeochromocytoma is not a feature in this syndrome.

MEN 2

MEN 2 is an autosomal dominant syndrome with high penetrance and varying expression. Three sub-types are now recognized: MEN 2A, B and C. In MEN 2A (Sipple's syndrome),[85] medullary thyroid carcinoma is associated with phaeochromocytoma (in about half the patients) and hyperparathyroidism. Phaeochromocytomas in this syndrome are frequently bilateral, although sometimes the tumour is unilateral and the other adrenal is diffusely enlarged and nodular. The medullary thyroid carcinoma is diagnosed by immunocytochemical staining for calcitonin in needle biopsies, and the diagnosis is usually made earlier than that of phaeochromocytoma, whether linked or sporadic. Patients who have been treated for medullary thyroid carcinoma should be screened for phaeochromocytoma. Urinary screening reveals a higher incidence of epinephrine-secreting tumours in MEN 2A by comparison with sporadic phaeochromocytoma. Genetic screening for medullary thyroid carcinoma has been used to identify children at risk of developing the MEN syndrome, and I have anaesthetized two such children, aged 10 and 12 yr, for prophylactic thyroidectomy. These children will require regular screening to detect the probable future development of phaeochromocytoma. In MEN 2B there is medullary thyroid carcinoma, phaeochromocytoma and a specific phenotype consisting of a Marfan-like body habitus, mucosal neuromas and intestinal ganglioneuromas.[27 50] Parathyroid involvement is very uncommon in this syndrome. Phaeochromocytomas are generally a late manifestation in this syndrome, and are rarely bilateral or malignant. This subtype, which has previously been classified as MEN 3,[50] accounts for about 5% of all MEN 2. MEN 2C consists of patients having familial inherited medullary thyroid carcinoma without any other endocrine manifestation.[61]

It seems probable that *RET* gene mutations occur in thyroid parafollicular C cells, adrenal chromaffin cells and autonomic and intestinal paraganglia, causing the neoplastic changes in these syndromes.

Von Recklinghausen disease (neurofibromatosis)

Type 1 neurofibromatosis (NF1) is a rare (one in 3000) autosomal dominant disorder produced by somatic mutations in the *NF1* gene on chromosome 17, but only 1% of patients with this condition develop phaeochromocytoma.[61] The clinical association of *café-au-lait* spots and neurofibromata should raise a suspicion of a phaeochromocytoma.

Von Hippel–Lindau syndrome

This rare and complex syndrome includes retinal angiomatosis (von Hippel disease), cerebellar haemangioblastoma (Lindau disease), pancreatic cysts, renal cysts and carcinoma and epididymal cystadenoma. The adrenal glands may be involved, with an associated phaeochromocytoma.[11]

Clinical presentation

Hypertension is one of the commonest clinical conditions with which patients present to their general practitioner. Hypertension is the commonest presenting sign in patients

with phaeochromocytoma. However, only one in 400–800 hypertensive patients has a phaeochromocytoma. Most general practitioners and, indeed, most physicians do not think 'phaeochromocytoma' when they encounter a new hypertensive patient in their practice or clinic. A substantial proportion of phaeochromocytomas secrete predominantly norepinephrine, often in huge quantities, sometimes paroxysmally, but usually sustained; thus sustained hypertension is the commonest presentation for this tumour.[57] Headache, the commonest symptom secondary to hypertension, is unlikely to alert the attending physician to the possibility of such a rare tumour. However, when the headaches are intermittent but regular, severe and associated with nausea and vomiting, or with slow palpitations (baroreceptor-induced bradycardia), the inconceivable possibility should cross the physician's mind. In my (recently published) series,[77] 85% of patients first presented with hypertension, subsequently linked with markedly increased urinary norepinephrine secretion. Prolonged exposure of the circulation to high circulating norepinephrine concentrations results in constriction of both arteriolar and venous segments with a marked decrease in circulating blood volume. Such events used to be more common when phaeochromocytoma was less frequently diagnosed and treated. However, patients with unrecognized phaeochromocytoma may be anaesthetized for other types of surgery; under these circumstances, induction of anaesthesia may cause widespread venodilation and thus cause profound arterial hypotension. Some patients present with increased blood glucose concentrations as a result of glycogenolysis together with impaired insulin release by the islet cells of the pancreas.[34 37] The overall picture depends on the relative proportions of norepinephrine and epinephrine secreted by individual tumours. Persistent, untreated hypertension in patients with norepinephrine-secreting tumours may result in left ventricular failure with systemic arterial shutdown, leading to severe metabolic acidosis and death.[37 44]

Only a small proportion, about 10–17%, of patients with phaeochromocytoma present with paroxysmal symptoms which reflect excessive secretion of epinephrine and dopamine—paroxysmal tachycardia sensed by the patient as palpitations, trembling, sweating and blanching, associated with feelings of panic and doom. The role of circulating epinephrine in the genesis of these symptoms was established as long ago as 1936;[5 68] the role of circulating dopamine is not established, though it is likely that symptoms relating to vasodilation in the gastrointestinal tract, such as nausea and vomiting, can be explained by high dopamine concentrations. The relevance of dopamine secretion in malignant and aberrant phaeochromocytomas was hinted at more recently.[1 3] Increased dopamine secretion by a malignant phaeochromocytoma has been described as a cause of increased outlet resistance of the prostatic urethra.[1] When symptoms of palpitations, sweating and fainting, accompanied by hypertension, occur after voiding urine, a phaeochromocytoma of the urinary bladder should be considered.[94 95] They account for 0.06% of all bladder tumours. Although it has been possible to measure free dopamine concentration in both blood and urine for >20 yr, few clinical biochemical laboratories routinely report dopamine excretion in 24 h urine collections. Excessive epinephrine secretion also causes hypermetabolism with weight loss, and stimulation of insulin release through a β_2-adrenoceptor mechanism,[34] although the latter may be offset by the effects of circulating norepinephrine.

Prolonged exposure to increased concentrations of circulating catecholamine may result in a form of dilated cardiomyopathy linked with ventricular failure in about one-third of patients [37 39] though it is not clear whether this results from α- or β-adrenoceptor activation. The histological picture is of myofibrillar degeneration with interstitial infiltration by mononucleocytes, with secondary fibrosis and calcification. A similar catecholamine-induced cardiomyopathy has been described in patients with prolonged sympathetic overactivity in tetanus. By contrast, hypertrophic cardiomyopathy may result from norepinephrine-induced hypertension.[82]

Phaeochromocytoma is a great mimic and may present in a huge variety of ways. Darby and Prys-Roberts[17] described a patient who presented in high-output left ventricular failure resulting from arterio–venous shunting through a huge suprarenal mass which turned out to be a phaeochromocytoma. High output failure has also been described as a complication of excessive epinephrine production with cardiomyopathy,[77] and one can only wonder whether excessive dopamine excretion could have been a contributory cause. Acute pulmonary oedema may complicate phaeochromocytoma at any time; it has been described as arising during recovery from anaesthesia[23] and as a response to a small therapeutic dose of propranolol.[77]

Phaeochromocytoma can present during pregnancy and mimic the usual symptoms and signs of toxaemia, either as simple hypertension or fulminant eclampsia. Management of anaesthesia and surgery during pregnancy follows the same principles as for the general population.[31 36 46 93] Previously undiagnosed phaeochromocytoma has been reported as complicating Caesarean section.

Phaeochromocytoma is an extremely rare tumour in children[73 91] but should be searched for in those presenting with episodic hypertension, and in the children of families with known histories of medullary thyroid cancer or phaeochromocytoma or both. Pre- and intra-operative management should follow the same principles as for adults.

Diagnosis

Once the combination of symptoms and signs has suggested a diagnosis of phaeochromocytoma, the best confirmatory test is to measure free catecholamines in a 24 h urine collection. High performance liquid chromatography with electrochemical detection allows accurate measurement of

Table 1 Normal values for catecholamines and their metabolites in plasma and 24 h urine collection

	Molecular weight	1 mg=x mol^{-6}	Plasma concentration (pg ml^{-1})	Urine concentration (nmol 24 h^{-1})
Epinephrine	183	5.46	40–100	<140
Norepinephrine	169	5.92	200–400	<800
Dopamine	152	6.58	<1400	
Metanephrine	197	5.08	<2000	
Normetanephrine	183	5.46	<5000	

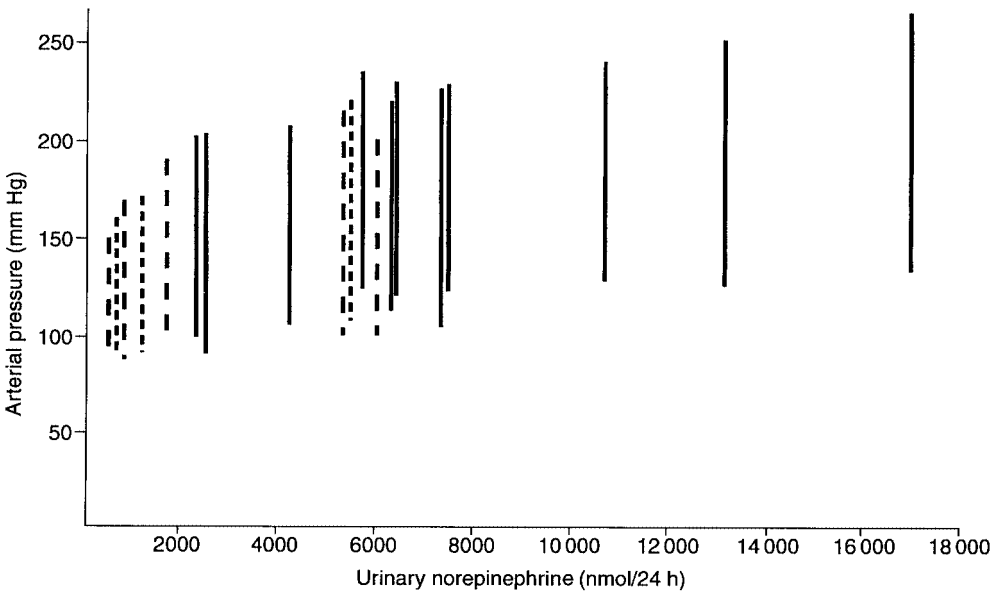

Fig 2 Relationship between systolic and diastolic arterial pressures at time of diagnosis of phaeochromocytoma and 24 h urinary norepinephrine excretion. Dashed lines indicate patients with predominantly epinephrine-secreting tumours; continuous lines indicate patients with predominantly norepinephrine-secreting tumours. Based on data from Prys-Roberts and Farndon.[77]

free epinephrine, norepinephrine and dopamine in body fluids, such as urine or blood.[47] This technique has fully superseded the older techniques for measuring urinary catecholamine metabolites, such as metanephrine or normetanephrine and their further co-metabolite vanillyl mandelic acid (VMA), sometimes referred to as hydroxy-methoxyphenyl glycol (HMPG). Dopamine is metabolized to homovanillic acid (HVA) sometimes confused with VMA. However, Eisenhofer and Lenders continue to extol the diagnostic virtues of plasma or urinary metanephrines as markers of phaeochromocytoma.[20 21] Table 1 shows the normal values for the three endogenous catecholamines, with indications of the equivalent values for metanephrines and VMA.

Manger and Gifford[57] state that no close correlation exists between arterial pressure and plasma catecholamine concentrations. That may well be the case if one considers all phaeochromocytomas, both epinephrine and norepinephrine secretors. However, in my series of 19 patients in whom measurements of free urinary catecholamines were made, 16 patients showed predominant norepinephrine secretion of whom 13 had normal epinephrine concentrations, and a further three had slightly increased epinephrine secretion.[77] Only three patients showed predominantly elevated epinephrine secretion which was consistent with their pre-diagnosis symptoms. Five patients also showed markedly elevated dopamine secretion, the highest levels being in the three patients who showed predominantly epinephrine secretion. In those patients who had a predominant norepinephrine secretion there was a correlation between systolic and diastolic arterial pressure and the 24 h urinary norepinephrine secretion (Fig. 2). The major unknown factor is the role of dopamine in the causation of symptoms in patients with phaeochromocytoma. In my series, excessive dopamine secretion was present in five patients.[77] Such a low proportion of patients secreting epinephrine may disallow the concept that if epinephrine is the predominant catecholamine then the location of the tumour is likely to be adrenal or the organ of Zuckerkandl.

Plasma concentrations of catecholamines may give good correlations with urinary catecholamine or metabolite concentrations in patients with sustained rather than

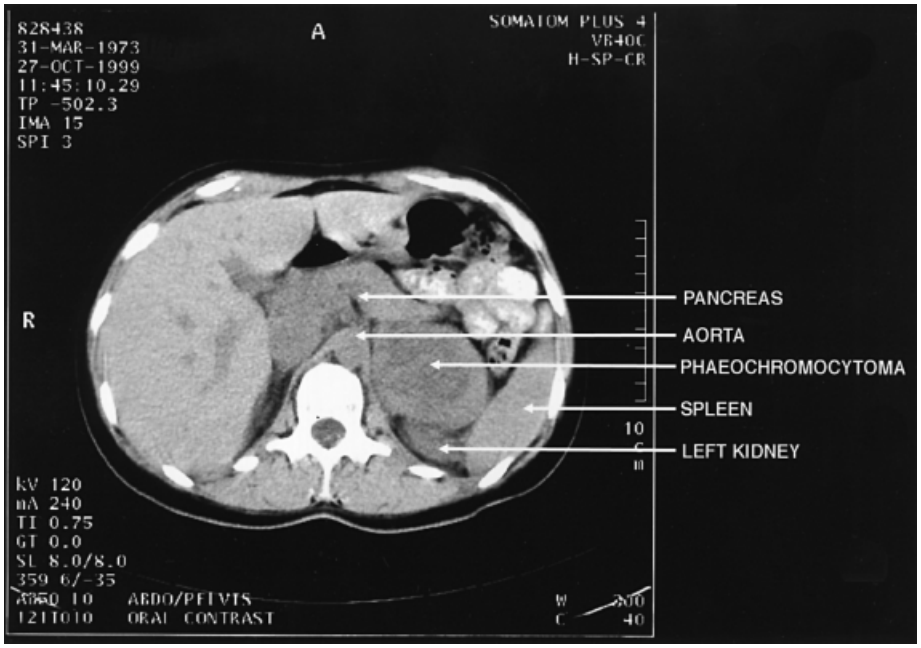

Fig 3 MRI scan of a patient with a moderately large left-sided phaeochromocytoma.

episodic symptoms. Measurements of plasma catecholamine concentrations made during an episode of cardiovascular instability may exaggerate the nature of the phaeochromocytoma.

Localization

Once the diagnosis of phaeochromocytoma has been confirmed by elevated urinary catecholamines, it is essential to start the process of localization. Shortly after Hull's review,[37] magnetic resonance imaging (MRI) was introduced and rapidly acquired a reputation for being preeminent as a method for identifying phaeochromocytoma.[24] Over the past 10 yr, it has become apparent that MRI (Fig. 3) and computerized tomography (CT) both provide accurate and consistent identification of the majority of phaeochromocytomas, particularly when the tumours occur in the suprarenal area.[41] Tumours as small as 1 cm can be recognized. Cystic phaeochromocytoma may be particularly easy to diagnose by MRI because such tumours have a high water content and so give a good signal.

Recurrent tumours, metastases and tumours in unusual sites may have to be identified with the radiopharmaceutical agent [^{131}I]*meta*-iodobenzyl guanidine (MIBG).[92 103] MIBG has been effective in identifying uncommon sites such as the urinary bladder and the pericardium,[80] but has some disadvantages in that it may be taken up by neuroblastomas, medullary thyroid carcinomas, carcinoids and small-cell carcinomas of the lung. Drugs such as labetalol,[49] reserpine, adrenergic neurone blockers, calcium channel blockers and some tricyclic antidepressants are known to interfere with the uptake of MIBG.

Older techniques, such as the pentolinium[10] and clonidine suppression test,[7 48] glucagon provocative test[7] and selective adrenal vein blood sampling, are now rarely needed.

Preoperative pharmacological control

Once the diagnosis of phaeochromocytoma has been made, there is little doubt that surgery is the only curative procedure, but immediate pharmacological control of the adverse effects of circulating catecholamines is essential. Immediate surgery is rarely essential; the main objective is to control arterial pressure, heart rate and arrhythmias and, especially, to allow blood volume to be restored to normal.

α-Adrenoceptor antagonists

Phenoxybenzamine has been widely used since the early 1950s[40] as the mainstay of pre- and perioperative control of blood pressure in patients with phaeochromocytoma,[37 57 88] and was still being advocated recently.[9 26 55 78] Advantages claimed for phenoxybenzamine are that it has a long duration of action, allowing twice-daily oral ingestion, and that it produces non-competitive blockade as a result of covalent binding of the drug to the receptor.[35] The latter effect is claimed to prevent the effects of surges of catecholamine release during the preoperative preparatory period.[9 37]

Disadvantages of phenoxybenzamine are numerous. First, being a non-selective α-adrenoceptor antagonist, it blocks α_2-adrenoceptors, especially those on the presynaptic membrane of adrenergic neurone terminals which are part of a negative feedback loop regulating release of

norepinephrine.[51] Consequently, the release of norepinephrine at cardiac sympathetic nerve endings is uninhibited and what would otherwise be normal sympathetic nerve activity causes undesirable chronotropic and inotropic effects. Traditionally, these have been controlled by adjuvant β-adrenoceptor antagonists.[37 57] Second, the non-competitive covalent binding results in an irreversible block which has been attributed to alkylation of the α-receptor by a highly reactive carbonium ion formed by cleavage of the tertiary amine of phenoxybenzamine.[35] Although the pharmacological half-life of phenoxybenzamine is about 24 h, the prolongation of the receptor blockade depends on the rate of re-synthesis of the receptors.[32 33] One of the main findings of my recent study was the marked prolongation of α-adrenoceptor blockade in the postoperative period despite stopping the administration of phenoxybenzamine 24–48 h before the operation.[77] A number of postoperative problems can be attributed to such an effect. Patients who have been subjected to long-term phenoxybenzamine therapy are often very somnolent in the first 48 h after surgery,[37] and this may result from persistent central α_2-adrenoceptor blockade. As the systemic arterioles are insensitive to α-adrenoceptor agonists in such patients, it has been established practice to expand the intravascular volume in excess of predicted or measured fluid losses,[37] resulting in marked interstitial fluid retention and widespread peripheral oedema. Other disadvantages of phenoxybenzamine given before an operation are that it causes somnolence, headache and a stuffy nose—all central side-effects related to α_2-adrenoceptor blockade—and consistent and marked postural hypotension. The latter occurred in all eight of the phenoxybenzamine-treated patients in my series.[77]

Phenoxybenzamine should be started in small doses (10 mg, two or three times daily) and increased gradually until either all signs of pressor activity have been suppressed, or until the patient complains of the side-effects of postural hypotension or a stuffy nose, or both, usually when doses exceed 90 mg day^{-1}. Tachycardia should be controlled by the careful introduction of a β-adrenoceptor antagonist. In my series,[77] physicians chose a variety of β-adrenoceptor antagonists (propranolol 160 mg bd, atenolol 100 mg od, metoprolol 150 mg × 3, labetalol 100 mg bd).

Selective competitive α_1-adrenoceptor blockade with prazosin in patients with phaeochromocytoma was advocated by Wallace and Gill[100] and others in the Americas,[15 70] but failed to achieve widespread popularity. One reason for this may be that physicians were reticent to use greater doses of prazosin, then a new drug in the treatment of hypertension, to control patients' arterial pressure. Prazosin, a drug with high first-pass metabolism,[98] was therefore probably given in inadequate dosage, even though by sparing α_2-adrenoceptors, it would have minimized β-adrenergic activation in the heart.[28] Because of its high clearance (4–5 ml min^{-1} kg^{-1}) and its short elimination half-life (2–3 h), prazosin blood concentrations may decrease to ineffective levels at the time of surgery if the last dose was given on the previous night. Russell and colleagues[78] claim that phenoxybenzamine pretreatment provided superior intraoperative stability to prazosin, though this was a comparison of only one patient receiving prazosin (no dosage given) with 12 patients receiving phenoxybenzamine. The hypotensive effect of prazosin is concentration dependent and this drug may also have a profound hypotensive effect on the first dose. This latter effect may reflect the immediate effects of arteriolar dilation in a patient who has been in a state of venoconstriction and arteriolar constriction with low circulating blood volume,[38] a state characteristic of prolonged elevated norepinephrine secretion. Prazosin should be introduced in a dose of 1 mg every 8 h and gradually increased up to 12 mg daily.[37]

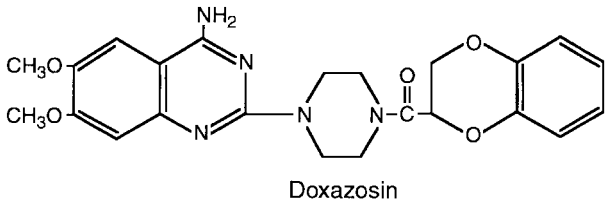

Fig 4 Structure of doxazosin, a selective α_1-adrenoceptor antagonist with a bioavailability of >70%, a low plasma clearance and a long elimination half-life. Doses of 2–16 mg day^{-1} can maintain effective α_1-adrenoceptor blockade over a 24 h period.

Doxazosin (Fig. 4) is a competitive and selective α_1-adrenoceptor agonist which, being non-lipophilic, has a high bioavailability (70%) and does not readily cross the blood–brain barrier, and has a long duration of action allowing once-a-day dosing.[4 13 22] Mean peak plasma concentrations of about 8 μg $litre^{-1}$ can be achieved within 4 h of a single oral dose of doxazosin 1 mg, and increase linearly with doses up to 16 mg daily.[14] Doxazosin increases renal perfusion, decreases renal vascular resistance and does not modify the renal response to exercise.[18 86 104] I selected doxazosin in 1991 as a drug with a near-ideal profile for the preoperative management of patients with phaeochromocytoma. Since then 20 patients, 18 with phaeochromocytoma and two with paraganglionoma, have been treated successfully with doxazosin in doses from 2 to 8 mg day^{-1}.[77] Doxazosin was used alone in 11 of these patients, all of whom had been diagnosed as predominantly norepinephrine secretors based on urinary free catecholamine measurements. Five patients also received small doses of β-adrenoceptor antagonists because the primary physicians could not be persuaded to omit the drug! Only one patient complained of moderate postural hypotension. Preoperative control of arterial pressure was at least as good as that achieved with phenoxybenzamine (Table 2). As doxazosin does not block the presynaptic α_2-adrenoceptors which regulate norepinephrine release at cardiac adrenergic nerve endings, it is unnecessary to administer β-adrenoceptor antagonists unless the patient has an epinephrine-secreting tumour. Three patients with predominantly epinephrine-(and dopamine-) secreting tumours were treated effectively

Table 2 Preoperative blood pressures in patients treated with phenoxybenzamine or doxazosin.[15] Data are expressed as mean (SD)

	Phenoxybenzamine (*n*=8)	**Doxazosin (*n*=18)**	***P***
Pre-operative arterial pressure (mm Hg)			
systolic	162 (17.7)	150 (23.9)	0.220
diastolic	92 (15.3)	77 (15.5)	0.029
Heart rate (beats min^{-1})	71 (12.6)	75 (11.1)	0.451

with a combination of doxazosin (2–4 mg day^{-1}) and labetalol (200–400 mg day^{-1}).

While doxazosin controls arterial pressure satisfactorily in the preoperative management of the patient, there will still be a need for supplementary α- and β-receptor block during surgical manipulation of the tumour. In my series there was no significant difference in intraoperative phentolamine or labetalol requirements between the phenoxybenzamine- and doxazosin-treated patients.[77]

Terazosin is an alternative selective α_1-adrenoceptor antagonist with pharmacokinetic characteristics similar to those of doxazosin, but with a shorter half-life.

β-Adrenoceptor antagonists

There are two reasons for using β-adrenoceptor antagonists in the preoperative treatment of patients with phaeochromocytoma. The first is to limit symptoms and signs referable to increased circulating epinephrine, mainly manifest as tachycardia with or without cardiac arrhythmias. These will be evident in patients with predominantly epinephrine- (and dopamine-) secreting tumours. As the prime objective is to limit excessive tachycardia with or without arrhythmias mediated through β_1-adrenoceptors, it is logical to use selective β_1-adrenoceptor antagonists such as atenolol (100 mg day^{-1}) or bisoprolol (10–20 mg day^{-1}) in order to minimize undesirable side-effects in the bronchi or peripheral vasculature. Labetalol (100–400 mg day^{-1}) has been chosen because it antagonizes both α- and β-adrenoceptors. The α-adrenoceptor block is competitive but weak, but will supplement additively any pre-existing α-block resulting from the use of phenoxybenzamine, prazosin or doxazosin. Carvedilol (12.5–50 mg day^{-1}) is another β-adrenoceptor antagonist having weak α-blocking effects.[8] Other non-selective (i.e. mixed β_1 and β_2) antagonists such as propranolol (40–240 mg day^{-1}) or metoprolol (50–200 mg day^{-1}) may be used, but care must be exercised in preselecting patients who do not have a history of obstructive airway disease or peripheral arterial disease. Celiprolol (200–400 mg day^{-1}), which has β_1 antagonist and β_2 agonist effects,[59] may be the drug of choice in such patients.

The second reason is to block excessive cardiac sympathetic drive secondary to suppression of the presynaptic α_2-regulating mechanism by drugs such as phenoxybenzamine. In my series [77] it has been found to be unnecessary to use β-adrenoceptor antagonists with doxazosin, except in patients known to be epinephrine secretors.

Suppression of β-adrenoceptor-mediated cardiac sympathetic activity in the absence of adequate arteriolar dilation may precipitate acute pulmonary oedema.[37] A 17 yr old female in my series[77] went into acute pulmonary oedema shortly after a small intravenous dose of propranolol to control tachycardia after admission to hospital. It is therefore considered to be very unwise to administer β-adrenoceptor antagonists to patients with phaeochromocytoma without first ensuring adequate arteriolar dilation,[37] and then only under continuous cardiovascular monitoring.

Other drugs

Although there are devotees of the use of other antihypertensive drugs in the preoperative management of patients with phaeochromocytoma, there is little evidence to support their use. One report described exclusive use of calcium channel blockers in the pre- and intra-operative control of 10 patients with phaeochromocytoma.[76] Another suggested that nifedipine blocked surges of sympathetic activity in one patient with phaeochromocytoma of the urinary bladder,[52] and another reported suppression of symptoms in a patient with norepinephrine-induced cardiomyopathy.[82] The advantages of ACE inhibitors (ramipril) or angiotensin II antagonists (such as losartan or irbesartan) in reversing left ventricular hypertrophy are of doubtful value in the preoperative management of most phaeochromocytomas as the hypertensive stimulus (norepinephrine) usually reverts to normal after surgery.

Alpha-methyl-*p*-tyrosine (AMPT) was used in the 1960s to inhibit the rate-limiting conversion of tyrosine to dopa by suppressing tyrosine hydroxylase,[37] thus decreasing the synthesis of catecholamines by 40–80%. Its use has not stood the test of time, probably because of the high incidence of undesirable side-effects. However, there is an interesting report of its use in a child with catecholamine-induced dilational cardiomyopathy.[39]

Management of anaesthesia and surgery

Surgery

The management of anaesthesia and monitoring for surgery of phaeochromocytoma and paraganglionomas will depend to some extent on the surgical approach. Adrenalectomy for phaeochromocytoma has traditionally been performed by open lateral retroperitoneal surgery, though a transabdominal approach may be necessary in a few patients. Recently, laparoscopic transperitoneal excision of phaeochromocytoma has become feasible. Open surgery is usually quicker, but the patient may require longer postoperative hospitalization. In the absence of complications resulting from persistent adrenergic blockade, patients may be ready to leave hospital 36–48 h after laparoscopic surgery.

Manipulation of the tumour during open surgery, with its haemodynamic responses, may be inevitable but can usually be of short duration. In my experience, laparoscopic excision of a phaeochromocytoma requires persistent tissue traction and diathermy or ultrasound coagulation which may cause sustained haemodynamic consequences of at least the same severity as may be expected during open surgery, but for a rather longer period of time. The *quid pro quo* is the shorter postoperative hospital stay. Laparoscopic surgery may prove too difficult, requiring open surgery on the same occasion or subsequently. The surgical approach will also influence the anaesthetist's plan for postoperative analgesia.

Anaesthesia

To quote Hull,[37] 'Since the first successful operation by the Swiss surgeon Roux in 1926, almost every possible anaesthetic technique has been advocated.' I share Hull's view that a rational anaesthetic technique should be based on sound pharmacological principles rather than an 'idiosyncratic fondness for particular drugs or methods'! I differ from Hull only in preferring a combined regional and general anaesthetic technique, using a segmental mid- to low-thoracic epidural combined with adequate general anaesthesia, and selective adrenergic antagonists, phentolamine and labetalol to control haemodynamic surges in response to tumour manipulation. Schüttler has also advocated rational management during surgery based on measurement of catecholamine secretions.[81]

A practical rational technique

The following basic technique, with minor changes over a period of 32 yr, has been uniformly successful in >50 operations for phaeochromocytoma, in Oxford and Bristol. I changed from halothane to isoflurane when the latter became available in the early 1980s and substituted atracurium for alcuronium at about the same time. Apart from one patient who died of an inoperable malignant phaeochromocytoma within a week of attempted surgery, there have been no other deaths within 31 days of surgery, and no serious postoperative complications. In the earlier patients in my series, refractory hypotension in the early postoperative period can, with hindsight, be attributed to the undesirable lingering effects of phenoxybenzamine therapy (see below). Since the change to preoperative management with doxazosin in 1992, the subsequent 21 patients have been remarkably free of intra- or post-operative problems.

The last preoperative doses of adrenergic antagonists should be given at about 22.00 h on the evening before surgery, anticipating a start of anaesthesia at 08.30 h. Phenoxybenzamine, if it has been used preoperatively, should be withdrawn at least 48 h before surgery. Such a plan results in a patient whose relevant adrenoceptors are adequately blocked (see below), and whose haemodynamic state is stable up to the time of surgical manipulation of the tumour. Oral premedication with temazepam (10–30 mg) suffices in most patients.

Peripheral venous, arterial and central venous (antecubital or internal jugular vein entry) catheters are placed under local anaesthesia and haemodynamic monitoring is established together with ECG (CM5 lead) and pulse oximeter. I have only once felt the need for balloon-occluded pulmonary artery pressure measurement.[17]

After preoxygenation, I induce anaesthesia with fentanyl 5 μg kg^{-1} and propofol 1 mg kg^{-1} followed by atracurium 0.5 mg kg^{-1} when the patient no longer responds to command. Following tracheal intubation and insertion of a nasogastric tube, the patient's lungs are ventilated with a tidal volume of 10 ml kg^{-1} at a rate of 10–12 breaths min^{-1}, using a circle system, either without a soda–lime absorber, or with a soda–lime absorber with a partial bypass. This allows controlled partial rebreathing of carbon dioxide, allowing the patient's end-tidal P_{CO_2} to be controlled at 38 mm Hg (5.1 kPa). I maintain anaesthesia with isoflurane in an air–oxygen mixture to achieve an $F_{I_{O_2}}$ of about 0.5, and an end-tidal isoflurane concentration of about 0.9%. The patient can then be turned, carefully, on to their side for sterile placement of an epidural catheter at an appropriate site for the proposed surgical incision, usually a paraspinous mid- (T9–10) to low- (T12–L1) thoracic Tuohy needle placement, allowing a catheter length of 5 cm in the epidural space. I inject bupivacaine (4 ml of 0.5% solution) into the epidural space before placement of the catheter and I give further incremental doses of 4 ml of 0.5% bupivacaine at 1 h intervals throughout surgery. I have never seen a severe hypertensive or tachycardic response to turning the patient. The patient is then transferred to the operating theatre and positioned for the planned surgical approach. This technique is equally applicable for both open and laparoscopic surgical approaches. For laparoscopic surgery, the patient is placed in the full lateral position with the anticipated tumour site uppermost.

Once the epidural block is effective, further doses of fentanyl or neuromuscular blocking drug are rarely required for open surgery, although during laparoscopic surgery it may be necessary to use small doses of either drug to suppress the drive to breathe as carbon dioxide is absorbed from the peritoneal cavity.

Pharmacological control of catecholamine release during surgery

The combination of adequate regional anaesthesia with general anaesthesia sufficient to prevent the patient coughing on the tracheal tube provides satisfactory conditions for the initial surgical incision and exposure of the tumour. Manipulation of the tumour, however gently performed, usually causes a brisk haemodynamic response. In patients with norepinephrine-secreting tumours this response is predominantly a pressor response, the systolic arterial pressure rising from a basal 100–120 mm Hg about 20 s

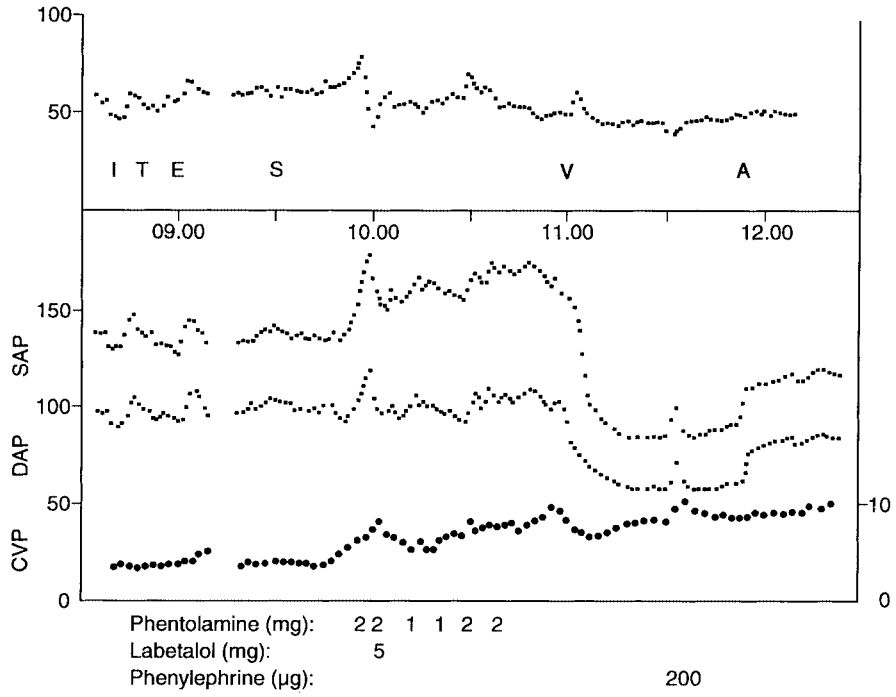

Fig 5 Computer reconstruction of patient record (Hewlett–Packard Merlin) for patient 20,[77] a predominantly norepinephrine secretor (7500 nmol 24 h^{-1}), showing changes of heart rate (HR), systolic (SAP) and diastolic (DAP) arterial pressures, and central venous pressure (CVP). Note the response to direct tumour handling at 09.50 h, in which systolic and diastolic arterial pressure increase swiftly together with an initial increase in heart rate. When the systolic arterial pressure reaches 160 mm Hg, there is a sudden reversal of the heart rate response, presumably as a result of a baroreflex response; this occurs before the phentolamine and labetalol have reached their relevant receptors. This biphasic response was observed in four other patients all of whom had predominantly norepinephrine-secreting tumours. Note also the sudden exponential decrease in arterial pressure immediately after the final vein draining the tumour had been ligated. This response was observed in all the patients having predominantly norepinephrine-secreting tumours. Note the diminished arterial pressure increase (approximately 16 mm Hg) in response to phenylephrine 200 μg, indicating a substantial degree of α-adrenoceptor blockade. Note also the step increase in arterial pressure when the patient recovers consciousness. Key: I=induction, T=tracheal intubation, E=turning the patient on to side to perform epidural, S=initial surgical incision, V=ligation of final connecting vein, A=patient awake and responding to command.

Table 3 Supplemental doses of phentolamine and labetalol required in patients pretreated with phenoxybenzamine or doxazosin[77]

Dose (mg)	Phenoxybenzamine (*n*=8)	Doxazosin (*n*=18)	*P*
Phentolamine	9.6 (6.8)	11.1 (7.6)	0.652
Labetalol	33.1 (8.4)	15.8 (8.2)	0.080

after surgical manipulation. I attempt to give phentolamine 2 mg i.v. in anticipation of this event, partly to suppress it, and partly to assess the patient's response to such a dose. In the event that this pressor response is accompanied by tachycardia, I use 5 mg incremental doses of labetalol to suppress it (Fig. 5). Subsequently it is possible to control the surges of systolic arterial pressure and heart rate by judiciously timed combination of these two drugs, together with transient increased concentrations of isoflurane. The average phentolamine and labetalol requirements in my recent series[77] are shown in Table 3. In patients with a predicted predominant epinephrine (and dopamine) secretion I would anticipate an increase in heart rate by giving labetalol 20 mg i.v. over a period of 10 min before anticipated tumour handling, followed by phentolamine or labetalol, or both, to control anticipated or extant surges (Fig. 6). Esmolol, having an ultra-short elimination half-life, has been proposed as a suitable drug for the control of β-adrenoceptor-mediated haemodynamic changes.[69 79 105] There is little evidence that residual β-adrenoceptor blockade by longer-acting drugs is a drawback.

In most patients with a unilateral phaeochromocytoma it is possible to identify the moment the surgeon ligates the predominant or last major emptying vein from the tumour as an exponential decrease of arterial pressure over a 5 min period to a level below the pre-handling arterial pressure (Fig. 5).

In patients pretreated with phenoxybenzamine it has been my experience that mean (SD) systolic arterial pressure remains relatively low (100 (12) mm Hg) during the first 1–2 h after surgery despite vigorous attempts to fill the circulation with colloid solutions (previously dextran 70, now gelatin) to increase the central venous pressure to ⩾8 mm Hg. Such patients can be unresponsive to huge doses of α_1-adrenoceptor agonists such as phenylephrine, methox-

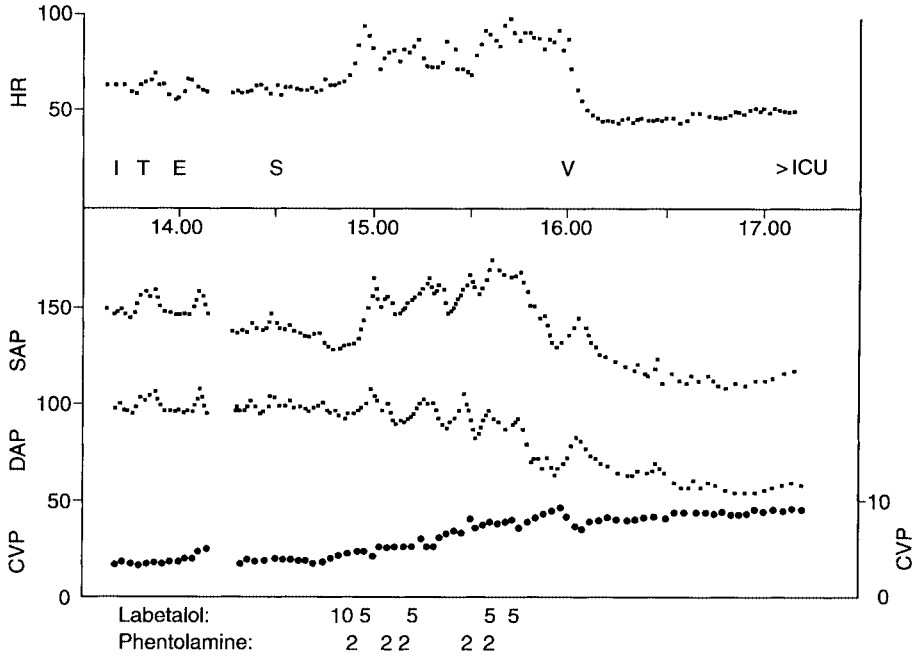

Fig 6 Computer reconstruction of patient record (Hewlett–Packard Merlin) for patient 17,[77] showing changes of heart rate (HR), systolic (SAP) and diastolic (DAP) arterial pressures and central venous pressure (CVP). This patient had a predominantly epinephrine- (1571 nmol 24 h^{-1}) and dopamine- (14 916 nmol 24 h^{-1}) secreting tumour. Note the tachycardia in response to initial tumour handling despite labetalol 10 mg given 5 min earlier, and the exponential decrease of heart rate to <50 beats min^{-1} after ligation of the final draining vein of the tumour. Key as in Fig. 5.

amine or norepinephrine (see below). Patients pretreated with doxazosin are much less refractory, indeed their systolic arterial pressure remains moderately low during the remainder of the surgical procedure but returns sharply to normal levels (118 (14) mm Hg) as soon as consciousness returns and cerebral arousal stimulates the sympathetic nervous system.[77] Such patients require much less fluid loading in the postoperative period and consequently have a significantly lower positive fluid balance in the first three postoperative days (2800 (1380) ml) compared with patients receiving phenoxybenzamine (4800 (2474) ml).[77] Most patients (93%) pretreated with phenoxybenzamine were clinically oedematous during this period, whereas only one of the 19 patients who received doxazosin was oedematous.

All patients have been returned, breathing spontaneously and with full analgesia, to a high-dependency bed in the intensive care unit (ICU) for monitoring and observation, and most have been discharged to the general ward the following day.

Assessment of adrenergic block

Since 1988, I have assessed the degree of α-adrenoceptor blockade in all patients with phaeochromocytoma.[77] This was done by constructing dose–response curves representing the increase in systolic arterial pressure to increasing intravenous doses of phenylephrine.[72] These curves were constructed before induction of anaesthesia in the awake patient in the anaesthetic room, during surgery before tumour handling, at the end of surgery before departing to the ICU and on the first and sometimes later postoperative days. These dose–response curves were an extension of a method which was validated for β-adrenoceptor antagonists.[16] Patients pretreated with β-adrenoceptor antagonists were tested in the same manner, deriving dose–response curves for isoprenaline.

Thus patients treated with varying doses of adrenoceptor antagonists can be assessed before, during and after surgery, to enable the anaesthetist to control the patient's state of protection more precisely. The data obtained from patients receiving phenoxybenzamine established the extensive duration of non-competitive α-blockade,[77] up to 2 weeks after the drug has been discontinued; confirming previous evidence from studies in animals.[32 33] The data from patients receiving doxazosin confirm the competitive nature of the antagonism in patients with phaeochromocytoma and the very rapid return to normal within 24–36 h after discontinuing the doxazosin.[77]

Alternative anaesthetic and adrenoceptor antagonist strategies

Hull, in his 1986 review, preferred a balanced anaesthetic scheme of enflurane in nitrous oxide supplemented with an alfentanil infusion and sustained neuromuscular block.[37] This technique was supplemented by intravenous infusion of a potent vasodilator to control hypertension, and a β-adrenoceptor antagonist. In his review, Hull did not indicate

specifically his choice of arteriolar dilator, but indicated that sodium nitroprusside (SNP) 'is currently the most widely used'. While I would question the accuracy of this statement, even at that time, there is ample evidence that SNP has been successfully used.[9 67 96] While SNP may be effective in causing arteriolar dilation and suppressing the hypertensive response to circulating catecholamines, evidence from our own studies show that isoflurane is as effective as an arteriolar dilator and almost as rapid in onset, while avoiding the undesirable metabolic consequences of prolonged SNP infusions.[62 63] SNP was specifically advocated to supplement the 'anaesthetic' management (fentanyl 50 μg kg^{-1} alone) of an 11 yr old child with a single ventricle and phaeochromocytoma to avoid impairment of ventricular function.[96]

The most widely quoted alternative to SNP is phentolamine, a competitive α_1- and weak α_2-adrenoceptor antagonist, which can be given intravenously as an infusion or as incremental doses of 1–2 mg. Hull claims that 'phentolamine is less satisfactory because tachycardia is an invariable problem'.[37] I find this somewhat puzzling in that I have used phentolamine for all my phaeochromocytomas except two over the past 32 yr without observing a substantial tachycardia that could be attributed directly to phentolamine in any patient. Admittedly, most of my patients have also received a β-adrenoceptor antagonist during surgery and would therefore be unlikely to manifest such a tachycardia secondary to catecholamine release at cardiac nerve endings, but those are the very circumstances under which phentolamine should be used in the management of these patients.

Calcium channel blockers have been used by a number of authors, based on the concept that calcium ion transfer is essential for the release of catecholamines from the chromaffin cells of the adrenal medulla[19 54] and from adrenergic nerve endings.[99] A French group has advocated the use of calcium channel blockers exclusively in the preoperative preparation of patients[76] and there are a number of case reports in which nifedipine or nicardipine has been used.[2 52 58 64 82] By contrast, Munro and colleagues report poor pre- and intra-operative control of a patient with a malignant phaeochromocytoma.[67]

Takahashi and colleagues[93] report the use of prostaglandin E_1[29] combined with labetalol for the preoperative management of a pregnant patient who underwent Caesarean section at 35 weeks.

Much has been made of the dangers of using drugs which potentially release histamine because of the risk of provoking catecholamine release from chromaffin granules.[37] Three drugs which have been implicated are *d*-tubocurarine, morphine and atracurium. Morphine has been used safely[30] and, although Hull questions the safety of atracurium,[37] I have used 0.5 mg kg^{-1} as an intubating dose in 36 patients with phaeochromocytoma since 1984 without any adverse consequences.

Magnesium sulphate

James and colleagues have championed the infusion of magnesium sulphate as the main alternative therapeutic strategy to adrenergic block during anaesthesia and surgery for phaeochromocytoma.[42 43] James bases his technique on the principle that magnesium ions inhibit the release of catecholamines from the normal adrenal medulla,[19 54] and from adrenergic nerve terminals.[99] James[42] describes a series of 17 patients in whom preoperative control was achieved with either phenoxybenzamine (eight patients) or prazosin (eight patients), and in whom operative control was achieved with a loading dose of magnesium sulphate (40–60 mg kg^{-1}) followed by an infusion of 1–2 g h^{-1}, designed to achieve serum magnesium concentrations between 2 and 4 mmol $litre^{-1}$. Good stability, defined as an arterial pressure within 30 mm Hg of the preoperative value, was achieved in 12 of the 17 patients; sodium nitroprusside was required in five patients. Supplementary doses of magnesium sulphate were required in all patients at the time of tumour manipulation. In two of the five patients in whom plasma catecholamine measurements were made during surgery, magnesium sulphate was ineffective in blocking the release of catecholamines.

Two of the patients in James' series were pregnant at the time of surgery.[43] One had inadequate control because therapeutic concentrations of magnesium were not achieved, whereas the other, who also underwent Caesarean section, was well controlled.

Magnesium sulphate 2 g h^{-1} has also been used successfully in combination with epidural blockade in a patient with bilateral phaeochromocytoma complicating severe coronary artery disease.[75]

Whether the use of magnesium sulphate results in better outcomes than the use of phentolamine or sodium nitroprusside can be determined only by a properly designed randomized trial in which many variables, such as type of catecholamine-secreting tumour or preoperative drug therapy, have been controlled. In view of the rarity of the condition, such trials are unlikely to be undertaken, and in the final analysis anaesthetists will have to rely on their 'idiosyncratic fondness for particular drugs or methods'.[37] For completeness, the following anaesthetics/techniques have been reported during the past 12 yr, usually as single case reports: midazolam/sufentanil infusion,[83] midazolam/fentanyl infusion,[58] propofol/fentanyl infusion,[90] magnesium sulphate combined with glyceryl trinitrate,[31] desflurane,[53] sevoflurane with adenosine triphosphate[60] and esmolol infusion (despite the fact that the patient had a norepinephrine-secreting tumour).[79]

Postoperative management

The main postoperative complication of surgery for phaeochromocytoma is persistent arterial hypotension which may be refractory to intravascular volume replace-

ment and adrenoceptor agonists. This is an extension of the process referred to earlier and is the result of a number of factors. While the excised tumour was active, the catecholamine output of the contralateral adrenal gland was effectively suppressed and the patient's relevant adrenoceptors were down-regulated. Thus in the absence of catecholamines from the tumour, the only source will be norepinephrine liberated from adrenergic nerve endings. This depends on generalized sympathetic nervous activity which is considerably diminished during anaesthesia as a result of the lack of 'arousal' and its effects in stimulating the hypothalamus. In the 19 patients pretreated with doxazosin in my series,[77] mean (SD) systolic arterial pressure increased by 15 (8) mm Hg following recovery of consciousness to 118 (14) mm Hg; by comparison with an increase of 8 (6) to 100 (12) mm Hg in the eight patients who had been pretreated with phenoxybenzamine. However, the latter patients received an average of 1200 ml gelofusin, whereas those who had received doxazosin received an average of 350 ml gelofusin, both based on an attempt to maintain central venous pressure at about 8 mm Hg. It is tempting, therefore, to ascribe such problems to the use of phenoxybenzamine and the persistent α-adrenoceptor blockade. However, the shift of the phenylephrine dose–response curves was comparable in the two groups of patients during the first two postoperative hours, largely as a result of the additional effects of phentolamine used during surgery.

Conclusion

Phaeochromocytoma has a way of presenting unexpectedly, frequently during surgical operations for other conditions, creating a set of potentially dangerous circumstances. Even when the patient's condition is recognized and treated pharmacologically to control responses to catecholamine release, management of anaesthesia can be highly stressful for the inexperienced anaesthetist. Developments in surgical technique, such as laparoscopic excision, may not decrease the problems of intraoperative management, although the patient may well leave hospital much sooner than after open surgery. Patients with phaeochromocytoma or paraganglionoma should ideally be managed by an experienced team of endocrinologists, endocrine surgeons and anaesthetists.

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