Papers and Originals

Preoperative and Operative Management of Patients with Phaeochromocytoma

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Before the introduction of adrenergic blocking agents and pressor substances operative removal of a phaeochromocytoma was a hazardous procedure, with a mortality of up to 25% (Graham, 1951). A mortality of 50% has been reported in operations on patients with unsuspected tumours (Apgar and Papper, 1951; Riddell, Schull, Frist, and Baker, 1963). The dangers were hypertensive crises after induction of anaesthesia, extreme fluctuations of blood pressure during the surgeon's handling of the tumour, sudden hypotension which immediately followed removal of the tumour, arrhythmias from sudden release of large concentrations of sympathomimetic amines, coupled with sensitization of the myocardium to production of arrhythmias by the anaesthetic agent. Complications tended to be more prominent in patients with sustained hypertension.

The use of antagonists of adrenergic α -receptors (" α -blockers") such as phentolamine or phenoxybenzamine permits control over fluctuations of the blood pressure. The effects of catecholamines on the heart rate and rhythm are, however, unaltered because α -blockers have no influence on adrenergic β -receptors. These effects can be controlled by β -receptor antagonists (" β -blockers") such as pronethalol and propranolol.

This paper details our experience with the use of various adrenergic blocking agents in the operative management of 27 patients with phaeochromocytoma on 30 occasions and traces the evolution of a therapeutic programme designed to modify the effects of catecholamines on α - and β -receptors and so ensure safer anaesthetic and operative procedures.

Use of α -adrenergic Blocking Agents to Control Blood Pressure

1. Phentolamine

In the first 13 patients operated on in this hospital for removal of a phaeochromocytoma, no preoperative preparation was given with either α - or β -receptor antagonists. Papaveretum and hyoscine were usually used for premedication. Control of blood pressure after induction and during dissection and removal of the tumour was attempted by the use of repeated intravenous injections of phentolamine, 2.5 or 5 mg., into the rubber tubing of an intravenous infusion of normal saline.

The blocking effect of phentolamine is immediate but transitory; its hypotensive effect in these circumstances persists for only 5 to 10 minutes. Injections of phentolamine must therefore be repeated frequently, and control of blood pressure is erratic. Wide swings of blood pressure still occur, though hypertensive peaks caused by surgical manipulation of the tumour can be truncated. Phentolamine has the added disadvantage of causing tachycardia. Examples of its use are given below.

Case 1

A 37-year-old company director developed polyuria and intense sweating in 1955. Adrenaline was found in excess in the urine, and a large phaeochromocytoma was removed from his right adrenal gland. No special preparation with adrenergic blocking agents was given. During operation there were wide fluctuations in blood pressure, reaching 250/150 mm. Hg, while the pulse rate exceeded 150/min. (Fig. 1). The surgical procedure had to be stopped for

FIG. 1.—Case 1. Fluctuations of blood pressure and pulse rate during operation. No preoperative preparation with adrenergic blocking agents was given.

half an hour until control of the blood pressure could be obtained with intravenous phentolamine; in all, over 100 mg. of phentolamine was given. After resection of the tumour, which was incomplete, infusion with noradrenaline was necessary for four hours to maintain the systolic blood pressure at 100.

After operation his diabetes was controlled by diet alone, but in 1958 symptoms of sweating, thirst, and polyuria recurred and pressor amines reappeared in the urine. Laparotomy failed to reveal any tumour in the abdominal cavity.

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His hypertension was then treated with oral phenoxybenzamine, 60 mg./day, and his diabetes with 20 units of insulin zinc suspension. Hypertension, diabetes, and symptoms of anxiety and sweating were well controlled until 1963, when attacks of sweating recurred. He was reinvestigated at this time, but x-ray examination failed to locate the tumour and he was submitted to a further laparotomy. Details of this operation are given below (Case 4).

Case 2

An 18-year-old meat porter with a five-year history of headaches was transferred from King's College Hospital (Dr. J. L. Livingstone) for investigation of hypertension. At operation (by Mr. D. R. Davies) an extra-adrenal phaeochromocytoma was found at the hilum of the left kidney, which was ischaemic. Further details have been given by Rosenheim, Ross, Wrong, Hodson, Davies, and Smith (1963).

Premedication was with pethidine 50 mg., promethazine 50 mg., and hyoscine 0.4 mg. The pulse rate was 70/min. before induction of anaesthesia, rose to 150 during induction (with thiopentone, tubocurarine, nitrous oxide, and oxygen), then fell to 90–110 during handling of the tumour, when the blood pressure rose from 190/130 to 260+/170 mm. Hg. Phentolamine was then given and the pulse rate immediately rose to 160, falling to 110 as the effect of the phentolamine subsided. Bleeding was very slight, and only 1 pint (570 ml.) of blood was given.

Before the diagnosis of phaeochromocytoma was suspected a per-femoral aortogram was performed under general anaesthesia (thiopentone, suxamethonium, nitrous oxide, and oxygen). Since the blood pressure was high, 5 mg. of a ganglion-blocking agent, trimetaphan (Arfonad), was given. This produced gross cardiac arrhythmias. The aortogram showed the presence of a tumour compressing the left renal artery.

Case 2 is reported to show the tachycardia that can be produced by phentolamine in a patient with a predominantly noradrenaline-secreting extra-adrenal tumour, and also to illustrate the dangers of giving a ganglion-blocking drug, trimetaphan, in these circumstances.

2. Phenoxybenzamine

Greatly improved control has been achieved by the use of phenoxybenzamine (Dibenzylamine, Dibenzyline). This substance has a much longer duration of action than phentolamine. In the first patient to whom it was given (Case 3) the infusion of only 12 mg. of phenoxybenzamine over 40 minutes resulted in a gradual fall of blood pressure, eventually reaching a plateau

FIG. 2.—Case 3. Response of blood pressure to the intravenous infusion of 12 mg. of phenoxybenzamine.

at a pressure of about 110/80 mm. Hg (Fig. 2). This low pressure persisted for 12 hours and had risen to only 155/105 mm. Hg 24 hours later. A further 40 mg. was then given, and the pressure again fell to 110/70. The pulse rate was 152 before phenoxybenzamine was given, and remained at this rate when the α -receptor antagonist was given. At operation the maximum systolic blood pressure recorded was 150.

Other patients have required much greater quantities of phenoxybenzamine to block the pressor effects of catecholamines. As a general guide the initial dose given on the first day, four days before operation, was 1 mg./kg. body weight intravenously in 200 ml. of physiological saline over two hours. Further requirements were estimated on the response to this standard dose. The requisite dose is given intravenously on the third, the second, and the day before operation, and again on the morning of the day of operation, depending on the degree of block required. Larger doses were used subsequently. This is discussed below.

In some early operations phenoxybenzamine was given orally. Two examples of its use are given below. No β -receptor antagonist was used in the first four patients treated with phenoxybenzamine.

Case 3

An 18-year-old optician's receptionist had a history of intense sweating for six months and of failing vision for one month. She was admitted to St. Mary's Hospital, Eastbourne, under Dr. A. M. Lester, where she was found to have malignant hypertension. While being admitted to the ward of U.C.H. she was having convulsions, with a blood pressure of 210/140 mm. Hg and a pulse rate of 104/min. Perirenal oxygen insufflation showed a mass above the right kidney.

She was prepared for operation with phenoxybenzamine, given intravenously, 12 mg. five days before operation and 40 mg. four days before operation, and was then given 50 mg. twice daily by mouth on the remaining three days before operation. Promethazine 50 mg., papaveretum 20 mg., and hyoscine 0.4 mg. was given as premedication. Anaesthesia was induced with thiopentone and *D*-tubocurarine and maintained with nitrous oxide and oxygen. Her systolic pressure was 100 at induction and rose to a maximum of 150 during dissection of the tumour. It fell to unrecordable levels for five minutes when the main vein from the adrenal was clamped, but rose when blood was given without the use of noradrenaline. The pulse rate was 130 before induction, rose to 160 after induction, and fluctuated between 60 and 130 during dissection of the tumour, which was in the right adrenal gland and secreted principally adrenaline.

The abrupt fall of blood pressure when the tumour was removed resulted from sudden withdrawal of circulating amines responsible for maintenance of blood pressure in a patient presumably with hypovolaemia. In Case 3 the dose of phenoxybenzamine given was insufficient to effect adequate sympathetic block, so that the patient presumably had not re-expanded her circulating volume. The deficit was rapidly corrected by the administration of blood, and noradrenaline was not required.

3. Combined α - and β -receptor Blockade

In the operations reported so far phenoxybenzamine had given more satisfactory α -receptor blockade than phentolamine, reducing the rises in blood pressure encountered during operation. However, it had not prevented the effects of the sympathomimetic amines on the heart; tachycardia and arrhythmias remained a serious hazard. The advent of relatively specific β -receptor blocking drugs, initially pronethalol, which has now been superseded by propranolol, has remedied this deficiency. The following case reports illustrate the use of these agents.

Case 4

This patient has been referred to above (Case 1). His symptoms had recurred; no tumour could be located after extensive investigation. He was prepared for a further laparotomy with oral phenoxybenzamine 60 mg. daily and pronethalol 100 mg. t.d.s. for three days. Hydrocortisone 100 mg. was given intramuscularly on the morning of operation. Premedication consisted of morphine 15 mg. and hyoscine 0.4 mg. Anaesthesia was induced with thiopentone and suxamethonium, and was maintained with nitrous oxide and oxygen and tubocurarine to a total dose of 65 mg.

After induction the blood pressure fluctuated from 100/50 to 170/110 mm. Hg (Fig. 3). During manipulation of the kidneys and exploration of the adrenal site the blood pressure rose to 240–260/100–120, but the pulse rate did not rise above 100 except when there was loss of blood or when phentolamine was given for diagnostic purposes at the end of the operation. During removal of a small tumour behind the inferior vena cava the blood pressure rose above 260, but the pulse rate did not rise above 100.

FIG. 3.—Case 4. Fluctuations of blood pressure and pulse rate during operation. Preoperative preparation with both alpha- and beta-adrenergic blocking agents.

After removal of this tumour the blood pressure was still raised at 210/110. To check if catecholamine-secreting tissue was still present in the body 5 mg. of phentolamine was given; the pressure fell to 90/60. The presence of numerous very small tumours in the bed of the previously resected right adrenal gland was subsequently confirmed microscopically. At the time of writing this patient was still mildly hypertensive and mildly diabetic. He was being controlled by 10 mg. of phenoxybenzamine and 40 mg. of propranolol, both given by mouth five times daily.

Since the tumour had not been located before operation, an amount of phenoxybenzamine below that required for complete sympathetic blockade was deliberately given so that palpation of the tumour by the surgeon would still produce a rise of blood pressure. Though severe hypertension developed during the operation, comparison of Figs. 1 and 3 shows that the violent swings of blood pressure encountered when phentolamine was used as the adrenergic blocking agent were absent when phenoxybenzamine was given. Control of the pulse rate was also good, except when there was bleeding or when the test dose of phentolamine was given. Noradrenaline was not required after the small tumours had been removed; other seedling tumours remained in this patient.

Case 5

A 45-year-old civil servant had a history of palpitations, sweating, and tightness of the chest for nine months. On examination he had a blood pressure of 170–230/110–130 mm. Hg. A positive phentol-

amine test and measurement of urinary excretion of pressor amines confirmed the clinical diagnosis. The tumour was located above the left kidney by perirenal oxygen insufflation.

He was prepared for operation with phenoxybenzamine 80 mg. and propranolol 40 mg., both by mouth, daily for three days before operation. Premedication consisted of papaveretum 20 mg. and hyoscine 0.4 mg. Anaesthesia was induced with thiopentone and suxamethonium and maintained with nitrous oxide and oxygen, with intermittent injections of D-tubocurarine to a total of 70 mg.

The blood pressure rose slightly on induction but then fell to 90/60, rising again to 250/150 as the tumour was dissected (Fig. 4). There was a brisk haemorrhage during the dissection; the blood pressure fell to 110/70. The pulse rate was 100/min. at induction, fell to 60–70 during dissection of the tumour, but rose to 150 immediately after the haemorrhage. Extrasystoles and left bundle-branch block appeared at this time, but disappeared with the rapid transfusion of 3 pints (1.7 litres) of blood. After excision of the tumour the blood pressure fell to 90/70, but rose to 110/80 with transfusion of a further pint (570 ml.) of blood. Noradrenaline was not required. During the operation 6 pints (3.4 litres) of blood and 3 pints (1.7 litres) of plasma were transfused. The tumour was in the left adrenal gland.

FIG. 4.—Case 5. Fluctuations of blood pressure and pulse rate during operation. Preoperative preparation with both alpha- and beta-adrenergic blocking agents. Hypotensive effect of induction and of haemorrhage is shown.

The course of this operation shows that the heart rate was well controlled in this adrenaline-producing tumour even when there was a very considerable rise of blood pressure as the tumour was handled. But when extensive haemorrhage occurred there was an immediate rise of heart rate.

Case 6

A 12-year-old schoolgirl complained of nausea during exertion when she went to Scotland on holiday, and a medically qualified relative heard an apical systolic murmur. Exercise tolerance had been reduced over the previous two years. She sweated excessively. She was admitted to U.C.H. under Dr. K. E. Harris for investigation of a presumed congenital heart lesion, and was found to have malignant hypertension, with a blood pressure of 210/150 mm. Hg. Pressor amine excretion in the urine was excessive. A mass was visible above the left kidney on perirenal oxygen insufflation.

She was prepared for operation with phenoxybenzamine, given orally at first, 20 mg. daily, and then intravenously in a dose of 50 mg. on the three days before operation. Propranolol was given in a single dose of 80 mg. daily initially, followed by 40 mg. three times daily on the three days before operation. On the morning of operation she was given 80 mg. of propranolol. Papaveretum 10 mg. and hyoscine 0.2 mg. were used as premedication. Anaesthesia was induced with thiopentone and suxamethonium and maintained with nitrous oxide and oxygen and intermittent D-tubocurarine.

The blood pressure was 146/106 before induction and rose to 240/170 after induction, while the pulse rate rose from 88 to 108. During dissection of the tumour the blood pressure remained high, the maximum reading being 258/190. The administration of propranolol reduced the pulse rate (Fig. 5); a total of 45 mg. was given intravenously during the course of the operation. Measured blood loss during operation was 1,200 ml.; a total of 2,000 ml. of blood was transfused.

The patient was inadequately prepared with phenoxybenzamine. Her weight was only 35.9 kg., and it was thought that 50 mg. daily of phenoxybenzamine, given intravenously, would be adequate. In retrospect, a further 50 mg. should have been given on the morning of operation. The pulse rate was adequately controlled by propranolol.

FIG. 5.—Case 6. Fluctuations of blood pressure and pulse rate during operation. Accidentally undertreated with alpha-adrenergic blocking agent.

Case 7

The patient was a 56-year-old company director. At a routine medical examination in March 1965 his blood pressure was 145/90 mm. Hg, but the electrocardiogram showed evidence of left ventricular strain, and urinary excretion of vanillylmandelic acid was found to be very high. He was symptom-free. Urinary vanillylmandelic-acid estimations were repeated, and the excessive excretion was confirmed. He was admitted for further investigation in June. His complaints were then of tiredness and occasional night sweats; he never experienced palpitations or headaches.

His blood pressure while in hospital ranged from 160/100 to 200/110. Histamine and phentolamine tests were diagnostic of a phaeochromocytoma. Biological and chemical tests for urinary pressor amines were also positive. The tumour was located by perirenal air insufflation medial to the upper pole of the left kidney. The plasma volume was reduced (35 ml./kg. body weight). The sedimentation rate was raised to 79 mm. in one hour for no apparent cause.

He was prepared for operation with phenoxybenzamine and propranolol. Three days before laparotomy he was given 80 mg. of phenoxybenzamine intravenously at 4 p.m. The blood pressure fell from 200/114 to 88/52 and extrasystoles appeared. Next morning the blood pressure was 110/60 and extrasystoles were still present. Propranolol 40 mg. was given by mouth, and the extrasystoles disappeared within 45 minutes. Phenoxybenzamine was again infused intravenously, 100 mg. over 50 minutes. The initial supine blood pressure was 140/90, falling to 120/75; the pulse rate was 76 initially and 80 at the end of the infusion. No further propranolol was given. Phenoxybenzamine 100 mg. was again infused intravenously next morning. The blood pressure initially was 150/84, and 158/78 at the end of the infusion. The pulse rate rose from 92 to 120. After three days of phenoxybenzamine administration the plasma volume was 44.1 ml./kg. Propranolol 80 mg. was then given by mouth. The pulse rate fell to 72 and the blood pressure to 120/78. An electrocardiogram taken on this day showed left ventricular preponderance with inverted T waves in all limb leads.

On the morning of the operation the patient's blood pressure was 150/90 and pulse 80. Phenoxybenzamine was not given. Pre-medication given was papaveretum 20 mg. and hyoscine 0.4 mg. Propranolol 120 mg. was also given with the premedication. Anaesthesia was induced with thiopentone 500 mg. and suxamethonium 75 mg. for intubation. Anaesthesia was maintained with nitrous oxide, oxygen, and intermittent D-tubocurarine to a total dose of 35 mg. The blood pressure fell from 110/76 to 60/? after induction, rising again to 80/65 (Fig. 6) when blood transfusion was started.

FIG. 6.—Case 7. Fluctuations of blood pressure and pulse rate during operation. Prepared preoperatively with alpha- and beta-blocking agent.

The tumour was found lying anterior to the upper pole of the right kidney and adherent to it and to the renal vessels. Dissection of the tumour from the kidney and renal vein was difficult, and was accompanied by constant oozing; 5 pints (2.8 litres) of blood had been transfused by this stage. Further dissection of the tumour led to arterial bleeding, and a sudden fall of blood pressure to unrecordable levels. Blood and dextran were rapidly infused, and the tumour was removed. Further profuse bleeding occurred when the clamps on the renal vein were removed. The blood pressure again fell to unrecordable levels, but was restored by blood and plasma. Nephrectomy was then performed, and later the spleen was removed because of injury during retraction. By the time the abdomen was finally closed the blood pressure had been restored to 110/86. The pulse throughout had been regular apart from occasional extrasystoles, and the rate varied between 72 and 92. The operation lasted seven hours. While the patient was being moved to the recovery room he suddenly became blue and pulseless. Cardiac resuscitation measures failed. At necropsy the lungs were oedematous. The heart weighed 600 g. and showed left ventricular hypertrophy. The tumour was cystic, extra-adrenal, and weighed 350 g.

Patients with Paroxysmal Hypertension

Only two patients with a normal blood pressure and paroxysms of hypertension had been operated on in this series. One example is given below.

Case 8

A 34-year-old housewife had had attacks of slow palpitations, pallor, and throbbing headaches after her first pregnancy, but she had undergone three subsequent pregnancies without attacks. She could precipitate the attacks by carrying her baby under her left arm. Her blood pressure normally was 110–120/70–80 mm. Hg, but massage of a mass in the left hypochondrium would produce a rise to 200/120 within two minutes. The tumour was extra-adrenal, lying behind the lesser sac, and produced mainly adrenaline. Preoperative preparation was given with phenoxybenzamine only. Before induction of anaesthesia the blood pressure was 90/70 and

pulse rate 130. The blood pressure rose to 190/120 during manipulation of the tumour and the pulse rate fell to 55. The blood pressure fell to 75/50 when the tumour was removed, rising rapidly to 100/80, a level at which it was maintained unaided.

Discussion

The case reports cited above well exemplify the problems involved in the surgical removal of a phaeochromocytoma. These are not merely concerned with control of the blood pressure, which is subject to considerable elevation during induction of anaesthesia and to violent fluctuations during dissection of the tumour, with sudden fall after its removal. Equally important is control of the heart rate, which is determined by the type of amine secreted and may be increased by premedication and induction as well as by handling of the tumour and by loss of blood. Cardiac arrhythmias produced by sensitization of the myocardium to the anaesthetic agent by catecholamines are also a hazard. Hypovolaemia caused by long-continued arteriolar constriction intensifies the hypotensive effect of loss of blood. Each is discussed in turn.

1. Control of Blood Pressure before and during Operation

Most patients with a phaeochromocytoma respond to the ganglion-blocking drugs or to bretylium and guanethidine by a fall of blood pressure, though theoretically a rise of pressure might be anticipated, since these drugs potentiate the pressor effect when infused with noradrenaline in normal subjects (Geffen and Ross, 1956; Laurence and Nagle, 1963). In practice this pressor effect seems to occur only with the intravenous administration of the hypotensive agents, and not when they are administered by mouth, presumably because the plasma concentration achieved is lower. These substances are not effective in controlling the blood pressure during removal of the tumour.

The hypothesis of α - and β -receptors put forward by Ahlquist (1948) to explain the differing actions of adrenaline and noradrenaline on various tissues suggested that a rational approach for the control of blood pressure and heart rate in this disease could be formulated. α -Receptors are responsible for vasoconstriction in all vascular beds, and hence their stimulation results in hypertension. β -Receptors mediate relaxation of arterial smooth muscle, and are also responsible for the inotropic and chronotropic effects of catecholamines on the myocardium (see Table).

Concept of Alpha- and Beta-adrenergic Receptors. Effects Mediated by the Two Types of Receptor

<i>Adrenergic Receptors</i>	
α -Receptor	β -Receptor
Vasoconstriction of all vascular beds especially skin	Vasodilatation of all vascular beds especially skeletal muscle
Contraction of nictitating membrane	Relaxation of uterus
" " dilator pupillae	" " intestinal smooth muscle
" " orbital smooth muscle	" " bronchial " "
" " spleen	Positive inotropic responses of heart muscle
" " uterus	Positive chronotropic responses of heart muscle
" " piloerector muscles	
Relaxation of intestinal smooth muscle	
<i>Antagonists</i>	
Phentolamine Phenoxybenzamine	Dichloroisoprenaline Pronethalol Propranolol

Substances which block the α -receptors have been used for many years in this disease. Piperoxan hydrochloride (benzodioxane), dibenamine, tolazoline hydrochloride (Prisol, Priscoline), phentolamine (Rogitine, Regitine), and phenoxybenzamine (Dibenzylamine, Dibenzylamine) have been used successively in the management of patients with phaeochromocytoma for the control of the blood pressure before and during operative

removal of the tumour. Phentolamine is a short-acting blocking agent which must be given repeatedly by intravenous injection or by continuous infusion during handling of the tumour (Grimson, Longino, Kernodde, and O'Rear, 1949). It abolishes some of the excessive swings of blood pressure, but control is far from perfect, as has been shown above. Despite the limitations of this drug its use is still advocated in recent papers (Glenn and Mannix, 1963; Crandell and Myers, 1964; Baker, Swindell, and Rollins, 1964; Kirkendall, Liechty, and Culp, 1965).

Phenoxybenzamine, on the other hand, has a much longer period of action and is much more effective in its clinical use. It may be given intravenously or orally. If full α -receptor blockade is required it is preferably given intravenously. Oral administration is satisfactory in the control of symptoms and blood pressure in patients awaiting operation or in whom the tumour cannot be found at laparotomy. For preoperative preparation we have given phenoxybenzamine intravenously. The dose was originally assessed on a weight basis, 1 mg./kg. body weight, following the recommendation of M. Nickerson (personal communication, 1960). In our most recent patients, when the tumour has been located before operation, 100 mg. of phenoxybenzamine has been given on each of three days immediately preceding operation, and 50 mg. on the morning of operation also seems desirable. When the tumour has not been located before operation less than complete α -receptor blockade is preferred, since location of the tumour is facilitated if a rise of blood pressure results from squeezing the tumour during surgical exploration of the abdominal cavity or thorax.

When complete antagonism of α -receptors is achieved the vascular compartment is fully dilated, so that the blood pressure is solely dependent upon cardiac output and blood volume. The blood pressure will therefore fall rapidly whenever bleeding occurs. The pressure will also fall if blood pools in the lower extremities. The patient must be warned of the liability to faint on standing, and should be kept in bed after phenoxybenzamine has been given intravenously.

2. Blood Pressure after Removal of the Tumour

Since the vascular compartment is fully expanded under the complete influence of adrenergic α -blocking agents, no fall of blood pressure results when catecholamines are no longer entering the circulation after clamping of venous effluent from the tumour and its removal. We have experienced no difficulty with hypotension from this cause in our patients. Hypotension in these circumstances denotes insufficient filling of the vascular system and is properly corrected by the administration of blood. Apprehension that antagonism of α -receptors would lead to irrecoverable hypotension after removal of the tumour (Crandell and Myers, 1964) is unfounded in practice.

If, by accident or by design, antagonism of α -receptors is incomplete there will be a fall of blood pressure when the tumour is removed, the extent of which will be determined by the degree of antagonism achieved and by the degree of filling of the circulation. Provided it is definite that hypovolaemia is not present, the blood pressure can be restored by the intravenous administration of noradrenaline, which will still be effective, as blockage of its receptors is incomplete. On the only occasions when noradrenaline has been given postoperatively to patients who have received phenoxybenzamine there have been no indications for its use other than the inbred reaction of a house-physician to give pressor drugs when the systolic pressure falls below 100 mm. Hg. Blood would have been much more appropriate as therapy on these occasions.

3. Tachycardia

When α -receptors are blocked with phenoxybenzamine or phentolamine catecholamines can still act on the β -receptors,

resulting in an increase in heart rate. This effect occurs irrespective of whether the predominant catecholamine secreted by the tumour is adrenaline or noradrenaline.

Tachycardia can be an alarming feature of patients under the influence of complete adrenergic α -blockade after they have received premedication, particularly if atropine is used. Hyoscine appears to be more satisfactory for this purpose. Increase in heart rate also occurs immediately after induction of anaesthesia and particularly during handling of the tumour.

These effects of the unopposed action of catecholamines on the β -receptors can be blocked by dichloroisoprenaline (Moran and Perkins, 1958; Powell and Slater, 1958), but this substance itself has sympathomimetic activity. It has also been reported to cause myopathic changes in cat muscle (Zaimis, 1965). It has been used successfully to control arrhythmias during operative removal of a phaeochromocytoma (Riddell *et al.*, 1963). Pronethalol has only slight sympathomimetic activity (Barrett, 1965) and has been demonstrated to be an effective β -blocking agent in animals (Black and Stephenson, 1962; Black, Duncan, and Shanks, 1965) and in man (Dornhorst and Robinson, 1962). It has unfortunately been incriminated as a carcinogen in mice, producing thymic and other tumours (Paget, 1963), and has now been withdrawn.

Propranolol, so far as is known, is devoid of carcinogenic activity (Tucker, Alcock, and Baker, 1965) and has no intrinsic sympathomimetic activity (Black *et al.*, 1965). Clinically it is a more useful β -receptor antagonist, as it has a much wider therapeutic ratio. It is given by mouth on the preoperative days when phenoxybenzamine is given. An initial dose of 20 mg. is given and the subsequent dosage is adjusted to produce the desired pulse rate; this may require as much as 120 mg. Propranolol can also be given intravenously, slowly, in doses of 1 to 5 mg. when the pulse rate rises during operation. This results not merely in a fall of heart rate but also usually in a rise of blood pressure (Prichard and Ross, 1966).

Though this β -receptor antagonist controls the tachycardia resulting from simultaneous blockade of adrenergic α -receptors, it should not be used to control the tachycardia of bleeding, which responds to adequate replacement by blood. It should be noted that the degree of β -blockade which controls the tachycardia produced by α -blockade will reduce but not abolish the tachycardia of haemorrhage. Tachycardia therefore becomes a less sensitive indicator of the amount of blood loss in patients under adrenergic blockade.

4. Anaesthetic Agents

The hydrocarbon anaesthetic agents, such as cyclopropane, trichlorethylene, and halothane, stimulate the release of catecholamines from stores in tissues, including those in chromaffin tumours. Thiopentone does not have this action (Crandell and Myers, 1964). In the case of cyclopropane this may occur with normal arterial PCO_2 levels, but with halothane catecholamines increase only when there is CO_2 retention (Black, Linde, Dripps, and Price, 1959). These anaesthetic agents also sensitize the myocardium to the effects of catecholamines on excitation and conduction, leading to arrhythmias such as ventricular tachycardia, coupled beats, and multifocal extrasystoles. Diethyl ether also releases catecholamines, and its administration often results in tachycardia, but not in ventricular arrhythmias. Thiopentone causes myocardial depression and hypotension. In the present series fall of blood pressure has followed the administration of thiopentone even though this has been injected slowly. This hypotensive phase has always been followed by a rebound of blood pressure above its original level.

When complete blockade of α - and β -receptors has been attempted a considerable fall of blood pressure may follow the administration of thiopentone—for example, when the patient (Case 7) was given 500 mg. of thiopentone his blood pressure fell from 110/76 to 60/? mm. Hg. Even the admin-

istration of 125 mg. to another patient produced a fall from 100/70 to 70/?. Great care is therefore essential when anaesthesia is induced with thiopentone in the presence of β -blocking agents.

Many of the problems in the management of patients with phaeochromocytoma can be removed by the use of ether anaesthesia (Crandell and Myers, 1964), but this precludes the use of cautery, and most surgeons prefer to have cautery available when removing these very vascular tumours.

Halothane has been used as an anaesthetic agent during this operation, but despite the use of phentolamine wide fluctuations of blood pressure occurred (Murphy, Prior, and Joseph, 1964). Etsten and Shimosato (1965) used halothane with controlled ventilation and showed that plasma levels of adrenaline and noradrenaline fell with the introduction of halothane and that squeezing the tumour did not provoke an excessive rise of pressor amines. Ventricular extrasystoles may occur with halothane anaesthesia if atropine is given in the presence of CO_2 retention (Johnstone and Nisbeth, 1961). Halothane may have a place in the anaesthetic management of these patients provided ventilation is adequate and monitoring of arterial PCO_2 and venous pressure is performed.

5. Prevention of Arrhythmias

Adrenergic β -receptor antagonists protect the myocardium from the tendency of hydrocarbon anaesthetics and cardiac glycosides to produce arrhythmias and substantially increase the amounts of catecholamines or of hydrocarbon anaesthetic that can be given before arrhythmias appear (Schull, Berry, and Villarreal, 1961; Murray, McKnight, and Davis, 1963; Vaughan Williams and Sekiya, 1963). Pronethalol is effective against ventricular arrhythmias (Harrison, Braunwald, Glick, Mason, Chidsey, and Ross, 1964; Cohen, Effat, Goodwin, Oakley, and Steiner, 1964) and has been used to protect against arrhythmias during operative removal of a phaeochromocytoma (Riddell *et al.*, 1963). Pronethalol antagonizes arrhythmias produced by cardiac glycosides (Stock and Dale, 1963; Vaughan Williams and Sekiya, 1963). β -Receptor antagonists must be used with caution in view of the report by Stock and Dale (1963) that heart failure can be precipitated by their administration. However, Gillam and Prichard (1965) report the case of a 71-year-old woman with angina in whom heart failure was precipitated by 10 mg. q.d.s. of propranolol by mouth. After treatment with digoxin and chlorothiazide she tolerated propranolol in a dose of 50 mg. q.d.s. without ill effect. Although we have given propranolol intravenously in a dose of 20 mg. repeated three times over a period of two hours in the preparation of a patient for laparotomy for post-operative intestinal obstruction (Prichard and Ross, 1966), care must be exercised when propranolol is given intravenously and minimal doses are used initially.

Patients with phaeochromocytoma should not be treated with β -receptor antagonists in the absence of blockade of the α -receptors, since the vasoconstrictor α -effects of adrenaline will be left unopposed by the vasodilator β -effects and a dangerous rise of blood pressure may occur. A history of asthma is also a contraindication (McNeill, 1964).

Cardiac glycosides likewise sensitize the myocardium to the action of catecholamines and should be avoided in the pre-operative period. Sudden death has also been reported in a patient treated with quinidine when phenoxybenzamine was given (Moser, Watkins, Morris, Prandoni, and Mattingly, 1953).

6. Hypovolaemia

Reduction of circulating plasma volume results from the prolonged infusion of adrenaline (Kaltreider, Meneely, and

Allen, 1942) and noradrenaline (Finnerty, Buchholz, and Guillaudeu, 1958). Patients with a phaeochromocytoma may also have a reduced circulating plasma volume and sometimes also a reduced red-cell volume (Brunjes, Johns, and Crane, 1960). This hypovolaemia is an important factor contributing to the hypotension that follows removal of the tumour in the patient not prepared preoperatively by adequate α -receptor blockade. Some authors recommend restoration of the blood volume by transfusion before operation, others during the early part of the operation. We follow the latter course, but also give phenoxybenzamine for three days before operation to permit circulatory readjustment to occur before operation.

7. Haemorrhage

Haemorrhage can be very considerable during removal of a large vascular tumour (the record size seems to be 3.6 kg.). This loss of blood must be made good because the blood pressure of patients under complete, or nearly complete, adrenergic blockade is particularly vulnerable to loss of blood. For this reason blood transfusion is started early in the operation, and replacement should exceed measured blood loss by at least half a litre. Pre-existing hypovolaemia should have been corrected by preoperative treatment with phenoxybenzamine.

Our experience of patients who have been given both α - and β -adrenergic blocking agents has convinced us that measurement of central venous pressure is highly desirable throughout operation. Venous pressure, together with arterial blood pressure, recorded by auscultation, provides a reliable indicator of the balance between venous return and cardiac output (Sykes, 1963). A fall of both venous and arterial pressures indicates a low circulating blood volume, which must be corrected by the administration of blood. Rise of venous pressure when arterial pressure is falling suggests overtransfusion.

During compression of the tumour both venous and arterial pressures rise, as would be expected. Failure to replace loss of blood results in a fall of venous pressure as well as a fall of arterial pressure. Overtransfusion may not be accompanied by a rise of arterial pressure if the heart is failing, but is immediately detected by a rise of venous pressure. Hypotension was present throughout the latter part of the operation in Case 7 owing to uncontrollable blood loss on two occasions. The repeated uncontrollable haemorrhage resulting in an unrecordable arterial pressure was probably followed by overtransfusion, which eventually resulted in pulmonary oedema and death two hours after the end of the operation. This problem of uncertainty about the adequacy of the circulating blood volume is a very real one in patients under complete adrenergic blockade when the signs that normally indicate to the anaesthetist when and how much blood to give are lost. A baseline for venous pressure must be established before surgery begins and blood administered according to information given by changes in venous pressure, arterial pressure, and measured blood loss.

8. Adrenocortical Insufficiency

The possibility that the patient's sole adrenal gland may be removed with the phaeochromocytoma is remote, but should be borne in mind when hypotension occurs without other obvious cause a week or more after operation. Hypotension due to adrenocortical insufficiency has occurred 10 days after an unsuccessful operation when the tumour had been incorrectly located by perirenal oxygen insufflation (Ross, 1961).

9. Advantages of Partial α -Receptor Blockade

If full adrenergic blockade has been achieved by phenoxybenzamine, and hypovolaemia is absent, fall of blood pressure will not occur when the venous affluent from the tumour is

occluded. In practice it is an advantage if this degree of blockade is not achieved, allowing a slight fall of blood pressure to occur when the tumour is removed or a rise of pressure when the tumour is handled, since (1) bilateral or multiple tumours may be present—absence of a fall of blood pressure will draw attention to the possibility of the presence of a second tumour; (2) though a tumour may appear to have been located by radiographic or other means before operation, appearances are often deceptive—should no tumour be found in its anticipated site the surgeons can search elsewhere; and (3) no pre-operative location of the tumour may have been made.

Conclusions

α -Blockade

The advent of drugs which antagonize adrenergic α -receptors has greatly simplified the operative management of these tumours and has made it far less hazardous. The advantages of its use are: (1) preoperative vasodilatation, which permits re-expansion of the contracted plasma volume; (2) control of blood pressure and symptoms arising from this; it also has a soporific effect, so that the patient comes to the anaesthetic room placid and relaxed; (3) the rise of blood pressure that follows induction of anaesthesia is reduced, as are the abrupt swings of blood pressure during handling and dissection of the tumour; and (4) since the patient no longer has a contracted circulating volume, removal of the tumour is not followed by an abrupt fall of blood pressure and it is unnecessary to infuse noradrenaline.

β -Blockade

β -Blockade during the preoperative and operative management of patients with phaeochromocytoma appears to us to be indicated: (1) to control tachycardia, usually aggravated by α -blockade, and (2) when arrhythmias are produced by α -blockade.

The administration of a β -blocking agent to a patient under α -blockade causes a rise of blood pressure, which in turn necessitates administration of more α -blocker (Prichard and Ross, 1966). Premedication and induction of anaesthesia in the patient under α -blockade can produce a serious increase in heart rate, which can be controlled by β -blockade. It is desirable to test the patient's sensitivity to propranolol administered orally on the days before operation when an α -blocking agent has been given. The patient is given an appropriate dose of propranolol—for example, 40 mg.—when the premedication is given on the morning of operation.

During operation propranolol is given intravenously (5 mg. slowly over five minutes) if manipulation of the tumour produces tachycardia or arrhythmias.

Isoprenaline could, theoretically, be administered if β -blockade has been excessive, as the blockade of propranolol is competitive.

Complete (or almost complete) blockade by both α - and β -blocking agents appears to add difficulties to the surgical and anaesthetic management of the case in that (1) the patient becomes more sensitive to the hypotensive effect of thiopentone, which should be given slowly and in small dosage until the desired degree of anaesthesia is attained; (2) venous oozing is more pronounced when α -adrenergic agents are given, and this adds a hazard to the operative procedure; (3) the patient becomes very sensitive to the hypotensive effect of haemorrhage, since vasoconstriction is prevented by α -blockade, but this encourages prompt blood replacement—there is evidence in dogs that propranolol may reduce coronary flow after haemorrhage (Parratt and Grayson, 1966; Redding and Rees, 1966); and (4) the tachycardia of haemorrhage is more readily apparent

because haemorrhage produces an early fall of blood pressure when compensatory vasoconstriction is prevented by α -blockade.

For these reasons we no longer advise complete α - and β -blockade, and find the operative management of these cases safer if adrenergic blocking agents are given as indicated on the basis of the criteria mentioned. β -Blocking agents should never be given without the previous administration of an α -blocking agent, as this may result in a severe elevation of blood pressure.

Suggested Procedure in Patients with Persistent Hypertension

1. While awaiting operation hypertension should be controlled with oral phenoxybenzamine, and tachycardia with oral propranolol.

2. *Day of operation minus three (D-3).*—Phenoxybenzamine 1 mg./kg. given intravenously in 250 ml. of 5% glucose in water over a period of one hour. The blood pressure will usually fall, after a delay of 30 to 60 minutes, to about 110/70 mm. Hg. Blood pressure is taken at five-minute intervals during infusion and half-hourly thereafter. The patient must be confined to bed during this procedure.

3. *D-2.*—Repeat phenoxybenzamine as above. Two hours after phenoxybenzamine has been given administer propranolol, 40 mg. by mouth. Follow the arterial blood pressure and pulse by 15-minute readings. If the pulse rate does not fall below 80 after two hours, give 80 mg. of propranolol, or more if necessary, to reduce the pulse rate to 80.

4. *D-1.*—Repeat phenoxybenzamine as above and continue the dose of propranolol required to reduce the heart rate to 80/min., readjusting if necessary.

5. *Morning of operation, one hour before induction.*—Pre-medication with papaveretum 20 mg. and hyoscine 0.4 mg. Unless blood pressure is above 160/100 mm. Hg, phenoxybenzamine is not given. If the blood pressure is higher than this 50 mg. of phenoxybenzamine is given intravenously. If phenoxybenzamine has been given on the morning of operation half the dose of propranolol previously required to lower the pulse rate to 80 beats per minute is administered. If no phenoxybenzamine has been given one-quarter of the dose of propranolol is given, provided the pulse rate is 100 or more. For pulse rates between 90 and 100 one-eighth of the dose is given. If less than 90 no propranolol preoperatively is recommended.

6. *During operation.*—Arterial pressure and pulse rate are recorded at two-minute intervals. An E.C.G. monitor is run continuously and frequent measurements are made of central venous pressure. Two intravenous infusions are set up. A supply of the following drugs for intravenous use must be available in the theatre: phentolamine, noradrenaline (8 μ /ml.), hydrocortisone, propranolol, sodium bicarbonate, and isoprenaline.

Summary

The high mortality of surgical removal of a phaeochromocytoma prompted the use of adrenergic blocking agents in preoperative and operative management. This paper details experience with the use of various α - and β -adrenergic blocking agents in 27 patients.

The short duration of action of phentolamine and the tachycardia it produces limits its usefulness as an α -blocker, and preference is given to phenoxybenzamine. This drug is given intravenously for three days before operation to control blood pressure and enable the blood volume to re-expand. Removal of the tumour is not promptly followed by hypotension provided α -blockade is adequate and blood loss is replaced. The use of noradrenaline is thereby avoided.

Tachycardia and arrhythmias are controlled by β -blockers given orally preoperatively, and intravenously with caution during operation. Initially pronethalol was used, but this has been superseded by propranolol. Complete α - and β -blockade is not advocated, and β -blockade must not be used without previous administration of an α -blocking agent.

Dangers of anaesthesia are outlined, especially the hypotensive effect of thiopentone in the presence of adrenergic blockade and the occurrence of arrhythmias with hydrocarbon anaesthetic agents. The response to haemorrhage is modified by these drugs; frequent arterial and venous pressure measurements and E.C.G. monitoring are essential for adequate blood replacement and prevention of overtransfusion.

A suggested procedure for the management of these patients is outlined.

Removal of a phaeochromocytoma still remains a potentially hazardous procedure, and its success depends largely upon the harmonious co-operation of a team comprising physician, pharmacologist, anaesthetist, and surgeon.

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