EXPERIENCE WITH PHAEOCHROMOCYTOMA

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Most physicians and surgeons have encountered single cases of phaeochromocytoma, but we have been fortunate in assisting with the care of eight patients with this condition within a period of eight years. This paper draws attention to some of the more important features in the diagnosis and management, but no attempt is made to review all the preceding literature or to discuss all the possible modes of presentation.

The hypertension which may persist after removal of a phaeochromocytoma is of particular interest, its mechanism presumably being different from that of the pre-operative paroxysmal or persistent hypertension. Renal biopsy specimens were obtained in six cases and the presence or absence of renal lesions has been correlated with the post-operative progress of the patients.

Case Reports

Case 1
Male 17 years. No. 42362/53. Admitted 27.11.53.

History. 10 years: severe paroxysmal headaches occasionally accompanied by palpitations, retrosternal discomfort, lower abdominal pain and nausea. One year: frequent epistaxis and breathlessness on exertion. Family history of neurofibromatosis.

On Examination. Numerous coffee-coloured patches on skin, neurofibromata on tongue and back. Pulse rate 70 to 90/min. B.P. 190/120 to 220/170 mm. Hg. Tortuous retinal arteries with nipping of retinal veins.


Operation (20.12.53). Left adrenal exploration by left transthoracic approach. Phaeochromocytoma found above left kidney. Intravenous benzodioxane given when tumour handled. Blood pressure fell to 175/140 when tumour was removed, but then rose again to 195/150. Because of this a left-sided sympathectomy with section of the splanchic nerves and removal of the celiac ganglion was performed, after which blood pressure fell to 115/100 with subsequent rise to 140/120.

Progress. Since operation has remained well. Catechol amine excretion normal. Only occasional and slight albuminuria. ECG has improved. Blood pressure 140/90 to 160/120. Reserpine 0.25 mg. thrice daily begun in March 1960. Last seen in May 1962; blood pressure then 140/100 mm. Hg.

Case 2

History. Three months: severe paroxysmal headaches. One month: failing vision.

On Examination. Numerous coffee-coloured skin patches. Pulse rate 120/min. B.P. 230/160 mm. Hg. Pupils dilated. Bilateral papilledema, many large exudates, but only a few haemorrhages. Almost complete blindness.


Operation (1.1.55). Bilateral adrenal exploration through separate dorsal incisions: no tumour found. (6.1.55) Laparotomy: phaeochromocytoma found deep to inferior mesenteric vessels and duodeno-jejunal flexure lying in the angle between left renal vein and the aorta. Intravenous benzodioxane given while tumour handled. After removal of the tumour intravenous noradrenaline required for 14 hours to maintain blood pressure at normal levels.

Progress. Since operation has remained well except for quite severe visual impairment. Blood pressure 105/75 to 130/80. Catechol amine excretion normal. Urine usually free from albumin. Last seen in February 1962; blood pressure then 130/75 mm. Hg.

Case 3
Female 51 years. No. 12823/56. Admitted 21.4.56.

History. For 17 years, at about two-yearly intervals, severe paroxysmal headaches associated with giddiness, blurred vision, apprehension, chattering of teeth, sweating, nausea and vomiting.

On Examination. Pulse rate 80 to 100/min. Blood pressure 170/100 to 300/150 mm. Hg. Fundi normal.

Investigations. Urine: normal. Blood urea normal. Maximum urinary urea: 13.8 g./l. Benzodioxane tests: two positive, two negative (when blood pressure 210/110) and one equivocal. Urinary catechol amines: noradrenaline 322 µg., adrenaline 48 µg. in 24-hour specimen. Intravenous pyelography with presacral oxygen insufflation showed a large lobulated mass above left kidney.

Operation (27.4.56). Left adrenal exploration through lateral incision. The mass above left kidney proved to be
the spleen. Further exploration through an anterior incision and an ectopic tumour found anterior to inferior cava to right of head of the pancreas. Intravenous benzodiazoxide required during handling of tumour. After removal intravenous noradrenaline required for 2 days to maintain blood pressure at normal levels. Small left hemithorax and partial collapse of left lower lobe post-operatively.

Progress. Since operation catechol amine excretion normal. Renal function has improved (maximum urinary urea 19.2 g./l.); ECG has improved. Blood pressure remained normal for two months after operation, but then rose to 245/120. Treated with reserpine 0.25 mg. thrice daily. Blood pressure then 160/80 to 210/140. Last seen in June 1962; blood pressure then 160/80 mm. Hg.

Case 4

Female 39 years. No. 15990/57. Admitted 15.5.57.

History. Two years before admission: hypertension first noted (blood pressure 210/120 mm. Hg). Eight months before admission: three attacks within a month of tightness of chest, breathlessness, shakiness, sweating and pallor. Three months: paroxysmal headaches and vomiting. Two months: blurring of vision. Skin freckled since birth; skin nodules first noticed two years before.


Operation (17.5.57). Laparotomy. Phaeochromocytoma found in front of left renal vessels, but behind lower border of pancreas. After its removal blood pressure fell to 115/95, but later rose to 180/110.

Progress. Since operation catechol amine excretion normal. Fundi have improved considerably, albuminuria has diminished. Five months after operation blood pressure had risen to 210/160, so treatment with mcamylin and reserpine was started. Later mcamylin was discontinued and chlorothiazide was given with the reserpine. Last seen February 1960; blood pressure then 190/100 mm. Hg.

Case 5


History. 15 years: dull aching in left loin and frontal headaches which gradually became more frequent and more severe. For 10 years: headaches accompanied by constricting sensations in upper abdomen, rapid palpitations and feelings of shakiness. Eight years: attacks of profuse sweating precipitated by exertion, warm surroundings or hot drinks. One year: blurring of vision.


Investigations. Urine: up to 1/5th vol. albumin. Blood urea, urea concentration test and serial blood sugars normal. BMR + 39%. Radioactive iodine test normal. Benzodioxane and phenolamine tests positive. No response to hexamethionium bromide 40 mg. i.m. ECG: left ventricular preponderance. Urinary catechol amines: noradrenaline 2,800 μg., adrenaline 615 μg. in a 24-hour specimen. Intravenous pyelography with presacral oxygen insufflation showed masses above both right and left kidneys, the right kidney being displaced downwards.

Operations. (2.7.57) Right adrenal exploration by transthoracic approach. Large tumour above right kidney extending behind vena cava: this was removed in two parts, with no fall in blood pressure. Left side of abdomen then explored through mid-line abdominal incision and an ectopic tumour was found lying in left para-aortic area and removed. Another large tumour was found above and in front of left kidney, but it was decided to defer its removal until a later date. Second operation (16.7.57) after cortisone 50 mg. b.d. for two days: remaining tumour removed by transthoracic route. Intravenous noradrenaline required for four days after operation to maintain blood pressure at normal levels.

Progress. After second operation developed paranoid delusions which persisted for two weeks. Then developed right chylos and left serous pleural effusions which gradually reabsorbed.

Progress. Since operation: catechol amine excretion normal. Albuminuria has ceased. Blood pressure 130/90 to 170/110. ECG has improved. Five months after operation tachycardia and triple rhythm were still present and the BMR was still raised (+35%), but 13 months after operation the heart sounds and pulse rate were normal and the basal metabolic rate was within the normal range. Last seen in July 1962; blood pressure then 100/70 to 110/110 mm. Hg.

Case 6

Male 29 years. No. 42834/51. Admitted 7.10.57.

History. Four years: excessive sweating in warm atmospheres. One year before: hypertension (blood pressure 180/120 mm. Hg) first discovered.


Operation (22.10.57). Left adrenal exploration by transthoracic approach. A large phaeochromocytoma was found above left kidney. Intravenous noradrenaline required for four hours after operation.

Progress. Symptom-free since operation. BMR raised (+32%) five weeks after operation, but normal seven months after operation. Albuminuria has ceased. Electrocardiogram has returned to normal. Blood pressure never above 120/90. Last seen May 1962; blood pressure then 110/75 mm. Hg.

Case 7

Male 60 years. No. 31584/57. Admitted 16.10.57.

History. A few hours before admission: transient right hemiplegia, hemianesthesia, and aphasia which had recovered almost completely by time of admission. No other symptoms.

On Examination. Mildly ‘thyrotoxic’ appearance. Slight generalized increase in skin pigmentation. Pulse
intravenously on eighth post-operative day and continued by mouth for 12 days. Severely disoriented for 17 days after operation.

Progress. Since operation has remained well except for residual visual impairment. Retinal appearances have improved. Catechol amine excretion normal. Albuminuria has ceased. Blood pressure 120/70 to 130/80. Last seen July 1962; blood pressure then 120/70 mm. Hg.

Clinical Features

Symptoms

The characteristic symptoms of phaeochromocytoma, which include paroxysmal headaches, visual disturbances, sweating, and feelings of apprehension, are now well known, having been fully reviewed by Macketh (1944), Pickering (1955), and Wright (1960) among others. The relative frequency of individual symptoms have, however, varied in different series (Howard and Barker, 1937; Smithwick, Greer, Robertson and Wilkins, 1950).

It is perhaps not so widely appreciated that such symptoms may have been present for a considerable time before the patient seeks medical advice. Thus Allen (1940) described one patient in whom symptoms had been present for 16 years, and Hamilton, Litchfield, Peart and Sowry (1953) another who had had symptoms possibly for as long as 20 years. Nor must it be forgotten that occasionally the condition may be completely symptomless.

The symptoms complained of by the patients described here are listed in Table 1. Of these the commonest were severe paroxysmal headaches, visual disturbances, and sweating attacks. In seven patients symptoms had been present for 2 weeks, 3 months, 8 months, and 4, 10, 15 and 17 years respectively. One patient had had no symptoms of any kind until he was brought to hospital having had transient aphasia and hemiplegia.

Some of the symptoms produced by a phaeochromocytoma may lead to an erroneous diagnosis of an anxiety state, especially if the patient is examined during a normotensive phase. Alternatively, hyperthyroidism may be suspected, and this suspicion may sometimes be strengthened by the 'thyrotoxic' appearance of the patient, and in some cases by the increased basal metabolic rate where this is estimated.

It is very important to realize that while in hospital under observation patients may no longer experience the symptoms for which they sought medical advice, because such precipitating factors as physical exertion or hot stuffy surroundings may no longer be encountered. But even in the absence of symptoms the blood pressure, if re-

80/min. Blood pressure 210/120 to 280/150 mm. Hg. Very slight weakness of right arm and leg. Numerous white exudates, but only a few small hæmorrhages.

Investigations. Urine: up to 1/5th vol. albumin. Blood urea normal. Maximum urinary urea 18.6 g./l. BMR +16%. Radioactive iodine test normal. Radiograph of chest: slight enlargement of heart. Benzo-dioxane and phenolamine tests positive. No response to hexamethonium bromide 40 mg. i.m., or to mecamylamine 2.5 mg. combined with reserpine 0.25 mg. thrice daily. ECG: gross left ventricular preponderance. Urinary catechol amines: noradrenaline 935 μg., adrenaline 350 μg. in 24-hour specimen. Intravenous pyelography with preserial oxygen insufflation showed large spherical mass above right kidney.

Operation (1.11.57). Right adrenal exploration by transthoracic approach. Very large tumour found above right kidney. Intravenous noradrenaline required for four days after operation; Cheyne-Stokes respiration when blood pressure allowed to fall below 150/80.

Progress. Has remained physically well since operation, but there has been a gradually increasing confusion and impairment of memory, and when last seen in June 1961 there were well-marked signs of dementia. BMR still raised (+82%) three months after operation, but normal in September 1959. Catechol amines normal. Albuminuria has diminished considerably (slight haze); urea concentration test unchanged. ECG has improved. Blood pressure 160/85 to 220/140. Last seen June 1961; blood pressure then 170/85 mm. Hg.

Case 8


Operation (2.5.58). Left adrenal exploration by transthoracic approach. Large tumour found lying above left kidney. Intravenous noradrenaline required for five days after operation, then discontinued, then required again for a further five days. Hydrocortisone given

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No. of Cases</th>
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<tbody>
<tr>
<td>Headache</td>
<td>6</td>
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<tr>
<td>Visual disturbances</td>
<td>5</td>
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<td>Sweating</td>
<td>4</td>
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<td>Feelings of apprehension</td>
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<tr>
<td>Nausea and vomiting</td>
<td>3</td>
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<td>Dyspnea</td>
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<tr>
<td>Palpitations</td>
<td>2</td>
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<td>Chest pain</td>
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<td>Abdominal pain</td>
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<td>Epistaxis</td>
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<td>Giddiness</td>
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<td>Tachycardia</td>
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<td>Loten pain</td>
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corded frequently, will usually be found to fluctuate widely.

**Hypertension**

It is now generally recognized that in cases ofpheochromocytoma a persistently raised blood pressure is found at least as often as paroxysmal hypertension. Sustained hypertension was found in 11 of 18 cases described by Howard and Barker (1957), half of the 152 cases reviewed by Mackeith (1944), and four of the six cases of Pickering (1955).

In all eight patients in this series the blood pressure was markedly and persistently elevated and rose to even higher levels at times. Such rises in blood pressure were not always accompanied by any of the symptoms of which the patients complained.

In only three patients has the blood pressure become normal and remained so since operation; the remainder are still hypertensive, though in every case the blood pressure is lower than before operation. The systolic pressure has been most affected.

Hypertension that is sustained is not necessarily irreversible as is shown by Cases 2, 6 and 8 of this series. However, in some patients with sustained hypertension removal of the pheochromocytoma does not lower the blood pressure permanently. One explanation for hypertension which persists after operation is that secondary hypertensive vascular changes in the kidneys are responsible, and this possibility will be discussed more fully later.

**Retinal Changes**

Severe retinopathy with papillædema was present in three patients; severe retinopathy without papillædema in two; and minimal retinal changes in two. In one patient the retinae were normal.

In three patients the retinal exudates were considered to be disproportionately large and numerous when compared with the haemorrhages present. While this may have been purely fortuitous, it is possible that such a picture is the result of vaso-spastic changes associated with the intermittent release of catechol amines into the circulation. We can find no record of this observation having been made previously.

In all patients papillædema and/or retinopathy regressed following operation, though two of those who had papillædema have been left with quite severe visual impairment.

**Neurofibromatosis**

It is now well recognized that neurofibromatosis has a definite association with pheochromocytoma. In two of the patients described here both neurofibromata and pigmented patches were present, one of these patients having a family history of neurofibromatosis. Another patient had multiple pigmented patches but no neurofibromata.

It is important to recognize minor degrees of this condition, and the slight generalized increase in skin pigmentation, seen in another three of our patients, may possibly represent a *forme fruste* of the disease, and when encountered in patients with hypertension should suggest the possibility of pheochromocytoma.

**Mental Changes**

In this series two patients became mentally deranged for short periods after operation. The explanation for this is not clear, but it might have been due to the sudden lowering of the level of circulating catechol amines, or to the fall in blood pressure. In one patient (Case 7) there has been a gradual progressive impairment of memory and intellect since operation. But in view of the patient's age, and his previous stroke, it is difficult to blame this directly on the removal of the pheochromocytoma. However, this was the patient who developed Cheyne-Stokes respiration when his blood pressure was allowed to fall below 150/80 mm. Hg after operation; and it is possible that the moderate fall in blood pressure since operation has been sufficient to aggravate pre-existing cerebral ischaemia due to cerebral atherosclerosis.

**Other Signs**

Tachycardia, either intermittent or persistent, was seen in seven patients; fever in two; and cold cyanosed extremities in one. In the four patients in whom it was carried out, pressure over the kidneys produced no alteration in blood pressure. Three patients were examined for postural hypotension with negative results.

**Investigations**

**Urine**

Albuminuria was found in seven patients, and in all it either ceased or diminished considerably after operation even when hypertension persisted. Glycosuria, which was slight and intermittent, was found in only one patient and ceased after operation.

**Renal Function Tests**

Impairment of renal function as judged by the urea concentration test was present in two of the five patients in whom the test was performed. In one impairment was slight and has remained unchanged since operation; in the other impair-
ment was moderate, but renal function has now returned almost to normal.

**Basal Metabolic Rate and Radioactive Iodine Uptake**

The basal metabolic rate was estimated in three patients and was raised in all. Surprisingly it did not return to normal immediately after operation but was still raised 5 months after operation in Case 5; 5 weeks after operation in Case 6; and 3 months after operation in Case 7; even though the post-operative excretion of catechol amines was normal in each case, as was the radioactive iodine test of thyroid function, before and after operation. In all three patients the basal metabolic rate eventually fell to normal.

**Response to Hypotensive Drugs**

Hypotensive drugs (either hexamethonium bromide by intramuscular injection, or a combination of mecamylamine and reserpine by mouth) were given to five patients, and in all the response was poor. This was also noted in a case described by Tulloh (1952); and in any case of hypertension which responds poorly to hypotensive drugs the possibility of a phaeochromocytoma should be borne in mind.

**Electrocardiograms**

Electrocardiograms were recorded in four patients and showed the changes of left ventricular preponderance. Since operation serial tracings have shown a gradual return of the electrocardiographic pattern towards normal.

**Response to Adrenolytic Drugs**

A phentolamine test was performed on three patients and was positive in all. A benzodioxane test was performed on five patients. In four of these it was positive, and in the fifth the test was performed five times: three times elsewhere, with two positive and one equivocal result, and twice at the London Hospital (when the blood pressure was at its lowest observed level) with negative results.

In some patients with phaeochromocytoma (e.g. Case 3 of this series; and Cases 1 and 4 of Hamilton and others, 1953) benzodioxane tests have given negative results even though the patients were hypertensive at the time of the tests. The reason for this is uncertain, but Goldenberg (1954) has suggested that in such patients the tumours have become inactive, so that they no longer secrete catechol amines in significant amounts, and that the hypertension is due to some other mechanism uninfluenced by adrenolytic drugs. This may be so in some patients (and then presumably the diagnosis can only be made by radiographic studies or exploratory operation); but in the patients we have mentioned (Case 3 of this series; and Cases 1 and 4 of Hamilton and others, 1953), all of whom had sustained hypertension, paroxysmal rises in blood pressure and a significantly raised excretion of catechol amines bore witness to the activity of the phaeochromocytoma.

In such cases it is possible that the blood pressure is raised to and sustained at a certain level by secondary mechanisms, and that rises in blood pressure above this level are due to the intermittent release of catechol amines by the tumour. In these circumstances a phentolamine or benzodioxane test might be expected to be positive only if carried out when the blood pressure had risen to the higher levels in response to the release of catechol amines. And it may follow that a negative phentolamine or benzodioxane test in a hypertensive patient proved by other means to have a phaeochromocytoma indicates that the level of blood pressure at the time of the test is independent of circulating catechol amines and will not be reduced permanently by operation. This suggestion is supported by the findings in Case 3 of this series. In this case the blood pressure before operation varied between 170/100 and 300/150 mm. Hg. A benzodioxane test was negative on two occasions when carried out with the blood pressure at 210/110. Following operation the blood pressure fell temporarily, but later rose to 245/120.

Though not remarked upon in this context there were similar findings in cases described by Hamilton and others (1953). In the first of these cases (Hamilton’s Case 1) the patient’s blood pressure before operation varied between 180/110 and 200/140 mm. Hg. A benzodioxane test was performed when the blood pressure was 185/125 and was negative. For ten months after operation the blood pressure was 160/120, but it later rose to 230/130. The second patient (Hamilton’s Case 4) has a pre-operative blood pressure which varied between 200/120 and 230/150 between attacks and rose to 300/200 during attacks. At the beginning of the benzodioxane test the mean blood pressure reading was 224/140 and the test was negative. Seven weeks after operation, following a temporary drop, the blood pressure was 240/140.

This is an important point and emphasizes the necessity, in cases of suspected phaeochromocytoma, of recording the blood pressure frequently for several days before carrying out a phentolamine or benzodioxane test so that it may be performed when the blood pressure is in its higher range.

These tests may prove to have a prognostic value, for in a case of phaeochromocytoma with
sustained hypertension a negative phenolamine or benzodioxane test may indicate that operation will not reduce the blood pressure to normal permanently.

Of course, not all patients who remain hypertensive after removal of a phaeochromocytoma have negative phenolamine or benzodioxane tests before operation. Indeed, some (e.g. Case 7) react with a fall in blood pressure to normal levels or below. This is difficult to explain if, as has been postulated, some degree of hypertension is due to some secondary mechanism uninfluenced by adrenolytic drugs; for one might expect the blood pressure to fall to that level which is subsequently found to persist after operation, but no lower; and the same could be said about the fall in blood pressure which occurs when a phaeochromocytoma is removed at operation.

It may be that when the blood pressure is raised by circulating catechol amines above the level for which the secondary mechanism is responsible, an abrupt fall in the blood level of catechol amines or a sudden inhibition of their effect causes a temporary paralysis of vascular tone with a resultant fall in blood pressure to very low levels.

Localization of Tumours

Tumours may be localized by intravenous pyelography with presacral oxygen insufflation, and by aortography. Intravenous pyelography with presacral oxygen insufflation was carried out in five cases, and intravenous pyelography alone in one case. The tumour was correctly localized by these procedures in four cases, but in one what appeared radiographically to be a tumour proved at operation to be the spleen, and an ectopic tumour was found which had not been visualized radiographically. In another case, in which there were multiple tumours, an ectopic tumour was not seen on the pre-operative X-rays.

In two patients the urgency for operation was such that exploratory laparotomy was carried out without preliminary investigation by intravenous pyelography with presacral oxygen insufflation. Aortography was not used in this series but would have been of value.

Surgical Management

When patients are too ill to undergo full radiological examination, or the results of such examination are equivocal, the best course is to do a laparotomy. If para-aortic tumours are found, they can be removed through this incision. Tumours in the left adrenal can be removed either through the laparotomy incision or after turning the patient and making a transthoracic exposure of the adrenal. The decision rests on the size and vascularity of the tumour. If a tumour is found in the right adrenal the patient must be turned and the tumour removed by a transthoracic approach. In some cases these tumours are wrapped around the inferior vena cava. If this vessel is torn during dissection, it can only be repaired through a transthoracic approach.

In these series the tumours had good planes of cleavage. These were very vascular and even slight pressure caused a rise in blood pressure. The importance of obtaining complete haemostasis at operation cannot be overemphasized. The state of the patient in the post-operative hypotensive phase is indistinguishable from that produced by post-operative bleeding. It is therefore essential to prevent this complication.

Handling the tumour must be as gentle as possible to reduce the amount of catechol amine squeezed into the circulation. This is best achieved by using as direct an approach as possible by making an adequate incision. Even with these precautions, a rise in blood pressure follows palpation of the tumour. The possibility of multiple tumours must be remembered; the other adrenal and the para-aortic area should be palpated at the time of operation. The rise in blood pressure can be used as a guide to the presence and site of the tumours, especially when the abdomen has to be explored through a transthoracic incision.

Anaesthetic Management

In considering the anaesthetic management of these cases, attention must be given to four factors: (i) the pre-operative condition of the patients; (ii) unusual reactions of the patients to anaesthetic drugs; (iii) the acute changes in circulation and blood pressure occurring during the operation when the tumour is handled and when the venous drainage from it is occluded; and (iv) the effect of the surgical technique used on the post-operative course.

The patients in this series were ill and generally poor subjects for anaesthesia. Apart from the hypertension the most significant feature to the anaesthetist was the extreme apprehension of the patients. Those who had paroxysmal attacks feared them and this dread was mirrored in their attitude to the operation. This called for pre-operative sedation to alleviate anxiety and to prevent an exhausting paroxysmal attack before the anaesthetic.

The possible reactions to anaesthesia peculiar to the disease are two. Certain anaesthetic drugs may provoke an attack. Ether releases adrenaline into the circulation and any difficulties arising in the induction of anaesthesia would be magnified by the hypertension: d-tubocurarine may stimu-
late the release of histamine. Many of these patients respond to minute doses of histamine by a release of catechol amines.

Certain anaesthetic agents, notably halogen-substituted hydrocarbons and cyclopropane, may cause serious disturbances of cardiac rhythm in the presence of circulating adrenalin. As such a release is inevitable during the removal of the pheochromocytoma, these drugs are contra-indicated.

The special problems posed by the surgical procedures involved in removing a pheochromocytoma are: (i) that any pressure on the tumour or on structures surrounding it leads to a discharge of catechol amines into the circulation. This causes a hypertensive reaction somewhat modified by anaesthesia, but nevertheless severe; and (ii) that ligation of the veins of the tumour deprives the body of its excessive supply of catechol amines, and profound hypotension ensues.

If the blood pressure is recorded frequently and carefully during the operation the first of these reactions may be helpful in locating the site of the tumour, especially when it is ectopic. Excessive hypertension, which may cause acute left ventricular failure or a cerebrovascular accident, must be prevented by a gentle surgical approach aided by profound relaxation and, if necessary, by the use of adrenolytic drugs.

When the veins of the tumour are ligated the blood pressure falls precipitously, so much so that it is difficult to follow with a stethoscope and sphygmomanometer, each beat being at a lower pressure than its predecessor. If unchecked the fall in blood pressure may endanger the circulation to vital structures, particularly in patients who have become accustomed to a high blood pressure. Hypotension is treated by the intravenous infusion of noradrenaline which is begun as soon as the pressure begins to fall. The concentration of the noradrenaline solution used will depend on the response of the patient and his fluid requirements. In this series the concentration of noradrenaline varied from 4 mg./l. to 16 mg./l.

Post-operative care is particularly directed to the adequacy of the circulation, the noradrenaline infusion being continued for several days if necessary.

Respiratory management is also most important, particularly if the surgical approach has been transpleural.

The premedication varied in detail from case to case, but in the main relied on phenothiazine drugs to counteract the apprehension. Chlorpromazine has the additional advantage of an adrenolytic action. Promethazine has been given as an antihistamine, and, relying on the cover this provided, d-tubocurarine has been used as the relaxant in the subsequent anaesthesia. The premedication has been completed with pethidine as a basal analgesic and atropine or scopolamine as an anticholinergice. Although on theoretical grounds atropine is best avoided, because it potentiates the pressor action of circulating noradrenaline (Swan, 1949), it was used in some of the cases without ill effect.

The anaesthetic has been thiopentone, nitrous oxide and oxygen with d-tubocurarine as a relaxant. Full respiratory exchange has been maintained by using intermittent positive-pressure respiration in both the abdominal and trans-thoracic approaches. Curare was chosen as the relaxant in order to depart as little as possible from the standard routine we were at that time using for thoracotomies and to produce profound relaxation which would limit the pressure exerted on the tumour during its exposure.

The release of histamine produced by the injection of curare reveals itself by a cutaneous 'triple response'. This is seen if the injection is made extravenously, or if the drug is driven back into the capillary bed because the injected vein is obstructed. These errors were avoided and promethazine was given in premedication as an antihistaminic. There were no severe paroxysms of hypertension associated with this use of curare, although two patients showed a moderate rise in blood pressure during the induction of anaesthesia.

Once the patient has been intubated and controlled-respiration established the most important task for the anaesthetist is to follow the rapid changes in blood pressure. And it is better to delegate the ventilation of the patient to an assistant than to risk the failure of an inexperienced assistant to observe significant changes in blood pressure. If during the exploration severe bouts of hypertension occur they must be controlled by the use of an adrenolytic drug, such as phenolamine or benzodioxane. This was only found necessary in the first three cases of this series, for in the others although rises in pressure were encountered they did not reach pre-operative peak levels.

Noradrenaline infusion was necessary to maintain an adequate blood pressure after clamping the veins of the tumour in all but one case (Case 5) in which the pressure did not fall significantly until the third tumour was removed at the second operation. A saline infusion was started during the induction of anaesthesia so that noradrenaline could be given without delay when needed. As previously mentioned, a noradrenaline infusion may have to be maintained after operation for as
long as ten days until the vascular bed has accommodated itself to the new conditions.

If a transthoracic approach is used it is important that the lung should be fully expanded before the chest is closed, and in all cases at the end of the operation full respiratory power must be restored by antagonizing the residual curare. For this we have used atropine, 1 mg., followed by neostigmine, 2.5 mg., without causing any disturbance of cardiac rhythm.

Pathological and Chemical Examination of Tumours

All the tumours had the characteristic histological features of pheochromocytoma; in only one (Case 5) was there histological evidence of invasion of the capsule by tumour cells.

The weights of the tumours and their catecholamine contents are given in Table 2.

Renal Histology (J. H. R.)

Seven specimens from six patients were available: six were obtained at the time of removal of the tumours, including specimens from the right and left kidneys in the patients who had bilateral tumours (Case 5), and one was taken, percutaneously, three weeks after operation (Case 4). Sections, cut 5 to 6 microns thick, were stained with haematoxylin and eosin, a combined elastic and Van Gieson's stain, by the periodic-acid-Schiff method or with Heidenhain's azan and, in some instances, with phosphotungstic acid haematoxylin. (See Table 3).

Case 2 (Operation specimen SD 2/55)

Very occasional glomerular capsular adhesions and prominence of polymorphonuclear leucocytes in a few glomerular capillaries. Very slight hypertrophy of interlobular arteries.

Case 4 (Needle biopsy specimen DH 2878/57)

The glomeruli were enlarged with apparent increase of endothelial cells, some capsular adhesions and thickening of Bowman's capsules. Tubules were normal. Slight patchy interstitial fibrosis present. Medial hypertrophy of glomerular arterioles. No interlobular arteries present in the small specimen (Figs. 1 and 2).

Case 5 (Operation specimens SD 3331/57 and 3580/57)

The right and left specimens were similar in their histological characteristics. No enlargement of the glomeruli, but some appeared to have increased numbers of endothelial cells with occasional capsular adhesions. About one-third of the glomeruli were shrunken with thickened Bowman's capsules. Focal atrophy and dilatation of tubules was present and there was slight patchy increase of interstitial tissue with a few associated chronic inflammatory cells. The glomerular arterioles and interlobular arteries showed medial hypertrophy, but no degenerative changes (Figs. 3 and 4).

Case 6 (Operation specimen SD 5399/57)

The glomeruli were normal apart from occasional capsular adhesions and an unusual prominence of polymorphonuclear leucocytes in the capillaries. The tubules and blood vessels, up to the size of interlobular arteries, were normal, but there was slight periglomerular and perivascular increase of interstitial tissue.

Case 7 (Operation specimen SH 5715/57)

Most of the glomeruli were large with increased numbers of endothelial cells and increased 'intercapillary' material. There were capsular adhesions and polymorphonuclear leucocytes were prominent in the capillaries. A few glomeruli were shrunken with partially hyalinized tufts and thickening of Bowman's capsules. There was focal atrophy and dilatation of tubules with eosinophil casts in the lumina and focal collagenous increase of interstitial tissue with a few associated chronic inflammatory cells.

There was cellular hypertrophy of the glomerular arterioles and marked medial hypertrophy of the inter-

<table>
<thead>
<tr>
<th>Case</th>
<th>Weight of Tumour g.</th>
<th>Weight of Tumour g.</th>
<th>Catecholamine Content µg. per g.</th>
<th>Catecholamine Content µg. per g.</th>
<th>Catecholamine Content µg. per g.</th>
<th>Catecholamine Content µg. per g.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Not recorded</td>
<td></td>
<td>Adrenaline</td>
<td>Noradrenaline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>35.9</td>
<td></td>
<td>45</td>
<td>151</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>36.6</td>
<td></td>
<td>123.6</td>
<td>779.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>57.0</td>
<td></td>
<td>Not estimated</td>
<td>Not estimated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>225.0</td>
<td></td>
<td>1,230</td>
<td>1,880</td>
<td>1,088</td>
<td>975</td>
</tr>
<tr>
<td>6</td>
<td>144.5</td>
<td></td>
<td>Nodular portion: 1,600</td>
<td>Surrounding tumour: 472</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>70.0</td>
<td></td>
<td>59</td>
<td>1,570</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>475.0</td>
<td></td>
<td>Not estimated</td>
<td>Not estimated</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>268.7</td>
<td></td>
<td>672</td>
<td>2,030</td>
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<td></td>
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</tbody>
</table>

The estimations in cases 2, 3 and 6 were carried out by Dr. H. Weil-Malherbe, and those in cases 5 and 8 by Dr. J. T. Wright.
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age when First Seen</th>
<th>Renal Function</th>
<th>Papilloedema</th>
<th>Blood Pressure Preoperatively (mm. Hg.)</th>
<th>Blood Pressure Postoperatively (mm. Hg.)</th>
<th>Duration of Postoperative Follow-up</th>
<th>Summary of Renal Biopsy Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>M</td>
<td>20</td>
<td>Blood urea normal</td>
<td>+</td>
<td>Persistently raised up to 230/160</td>
<td>NORMAL Up to 130/80</td>
<td>5 yrs. 2 mths.</td>
<td>Normal glomeruli. Very slight hypertrophy of interlobular arteries.</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>39</td>
<td>Blood urea normal</td>
<td>+</td>
<td>Persistently raised 210/120–250/150</td>
<td>RAISED 190/100 with hypotensive drugs</td>
<td>2 yrs. 9 mths.</td>
<td>Hypercellular glomeruli with capsular adhesions. Medial hypertrophy of arterioles</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>35</td>
<td>Blood urea and urine concentration normal</td>
<td>o</td>
<td>Persistently raised 220/110–260/150</td>
<td>RAISED 130/90 150/110</td>
<td>5 yrs. 0 mths.</td>
<td>Ischaemic scarring with focal atrophic glomerular lesions and medial hypertrophy of interlobular arteries.</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>29</td>
<td>Blood urea and urine concentration normal</td>
<td>o</td>
<td>Persistently raised 180/120–220/140</td>
<td>NORMAL Up to 120/90</td>
<td>4 yrs. 7 mths.</td>
<td>Minor glomerular lesions. Normal vessels.</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>60</td>
<td>Blood urea normal. Urine urea concentration 18.6 g./l.</td>
<td>o</td>
<td>Persistently raised 210/120–280/150</td>
<td>RAISED 160/85–220/140</td>
<td>3 yrs. 8 mths.</td>
<td>Focal atrophy or hypercellularity of glomeruli. Medial hypertrophy with subintimal fibrosis and hyalinisation of interlobular arteries.</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>47</td>
<td>Blood urea normal</td>
<td>+</td>
<td>Persistently raised 165/105–210/130</td>
<td>NORMAL 120/70</td>
<td>4 yrs. 3 mths.</td>
<td>Focal interstitial scarring with atrophic glomeruli, dilated tubules, arteriolar lesions and inflammatory infiltration ?pyelonephritis.</td>
</tr>
</tbody>
</table>

**FIG. 1.**—Case 4. Hematoxylin and eosin. × 130. Hypertrophy of glomerular arteriole.  

**FIG. 2.**—Case 4. Hematoxylin and eosin. × 55. Thickening of Bowman’s capsule. Interstitial fibrosis.
lobular arteries with subintimal fibrosis and hyaline degeneration, but no fibrinoid necrosis (Fig. 5).

**Case 8 (Operation specimen SD 2219/59)**

One-sixth of the glomeruli were hyalinized: a few had shrunken tufts with thickened capsules and were associated with interstitial fibrosis. The remainder were normal apart from occasional capsular adhesions. There was patchy tubular atrophy and dilatation in the areas of interstitial fibrosis, with focal dense chronic inflammatory cell infiltration. Some glomerular arterioles were hypertrophied with occasional subintimal hyalinization; no interlobular arteries seen.

The lesions described were most marked in the areas of chronic inflammatory cell infiltration, suggesting that chronic pyelonephritis was responsible.

**Comment**

The changes described in the specimen from Case 8 were probably due to chronic pyelonephritis. The vascular and parenchymal lesions in the other cases were indistinguishable from those found in the kidneys of patients with essential hypertension and there were no features which could be considered characteristic; Heptinstall (1954), for example, has described such lesions in renal biopsy specimens from patients undergoing sympathectomy for severe hypertension. Silva and Sommers (1958), in a study of nine renal biopsy specimens from patients with pheochromocytoma, found hypertrophic lesions to be more marked in the larger renal arteries than in arterioles, the reverse of findings in essential hypertension (Sommers, Kelmar and Smithwick, 1958). They also described local dilatation of glomerular 'root capillaries' ascribed to the jet effect of blood released from hypertrophied afferent arterioles. These features were not seen in the present series. It would appear that the lesions in the specimens of Silva and Sommers were, on the whole, less advanced; they described ischemic glomerular changes with arteriolar fibrosis in only one patient, who had been known to have persistent hypertension for eight years prior to the removal of the pheochromocytoma and who was the only patient in their series to have hypertension persisting after operation (150/90 mm. Hg).

There is no reason why the renal parenchymal lesions associated with pheochromocytoma should differ fundamentally from those occurring with essential hypertension if it is assumed that they are due solely to the rise in blood pressure. It is possible, however, that the catechol amines from the tumour produce vasoconstriction differing in its localization from that due to the unknown vasoconstrictor mechanism responsible for essential hypertension. Such a difference might be reflected structurally in the early renal vascular lesions as suggested by Silva and Sommers but may not be apparent in more advanced stages.
Three of the patients had papilledema but fibrinoid necrosis and endarteritis fibrosa of the renal arterioles, the acute and healed lesions of malignant hypertension, were not seen in any of the specimens. Such lesions may be difficult to find in large sections of the kidneys of patients dying with early malignant hypertension and their absence in these cases could be explained by the small size of the biopsy specimens. The lack or paucity of arteriolar necrosis with phaeochromocytoma has been noted before (e.g. Pickering, 1954) and may be another manifestation of the particular vascular constriction action of noradrenaline.

The table shows the relationship between the features in the biopsy specimens and the post-operative persistence of hypertension. The renal lesions in two of the three patients whose blood pressure returned to normal after operation (Cases 6 and 2) were negligible and they were most severe in Case 7, whose post-operative hypertension has been most persistent. Cases 5 and 4 are intermediate between these two extremes with regard to the severity of both their renal lesions and their post-operative blood pressure.

The persistent hypertension which follows removal of a phaeochromocytoma must have a different origin from the original hypertension. The observations on these biopsy specimens suggest that a renal mechanism is responsible. The persisting hypertension in these patients is analogous to the hypertension of rats produced by unilateral renal artery constriction, which is maintained when the hypertensive vascular lesions have developed in the ‘untouched’ kidney, although the constriction is relieved (Wilson and Byrom, 1939, 1941; Floyer, 1951). In such animals removal of the ‘untouched’ but damaged kidney restores the blood pressure to normal, indicating that the hypertension must have been renal in origin and is not dependent on hypertensive vascular lesions which may be found in other organs.

Summary

The clinical details and post-operative progress of eight patients who underwent operation for removal of phaeochromocytoma are outlined, and the experience gained in the diagnosis and management of this condition is discussed.

We are grateful to Lord Evans, Professor Clifford Wilson, Dr. A. E. Clark-Kennedy and Mr. G. C. Tresidder for permission to publish, and to Dr. J. T. Wright and Dr. H. Weil-Malherbe for undertaking the catechol amine estimations.

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