PHAEOCHROMOCYTOMA

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Fränkel²⁷ described the first case of phaeochromocytoma; further case reports accumulated slowly until by 1944 Mackeith was able to find 165 in the literature.⁵⁰ By 1953 the figure had reached 255,³¹ and by January 1957, 626.⁶ Apgar and Papper¹ remark on the difficulty in compounding accurate statistics because of multiple reports on single cases. They cite examples which were reported in four or five papers.

These tumours occur in both white and coloured people; they are very rarely familial, eight kinships being recorded up to 1959.³³ They are not uncommon in children;^{19, 75} but are most often found in adults, women being affected a little more frequently than men. Phaeochromocytoma has also been found in dogs and cattle.³⁸

Pathology

The majority of these tumours are found in the adrenal, the right gland being involved more frequently than the left. Barbeau *et al.*⁶ found that 45 cases of bilateral tumour had been described up to January 1957, making an incidence of approximately 7 per cent. The incidence of multiple tumours is, however, more common than this, for phaeochromocytoma also occurs in other tissues derived from the neural crest such as the organs of Zuckerkandl and the sympathetic ganglia. Such tumours are most often found in the upper abdomen, either singly or in association with an adrenal tumour, but they may occur lower down, for example, in the urinary bladder⁴⁹ and very rarely in the chest and neck.^{11, 61}

There is an enormous variation in size, the weight ranging from 3 to 2,100 g.,¹⁸ but the appearance is comparatively uniform (Fig. 1). The tumours tend to be spherical or oval, though they are frequently bossed at various points. They are usually well encapsulated and in those arising in the adrenal it is usually possible to see a remnant of cortical tissue at one pole of the tumour.

The cut surface is plum coloured or greyish-

red; haemorrhagic and cystic areas are common and there is rarely some calcification.

Histology

The tumour cells are polygonal or spheroidal, resembling the cells of the normal adrenal medulla, but great variation in size and shape occurs and giant cell forms are common. The chromaffin reaction is of variable intensity and is unreliable if the tumour is fixed in formalin prior to treatment with bichromate. To some extent the name of this reaction is misleading, for as Brines and Jennings¹³ observe, any oxidizing substance will give a brown colour with adrenaline.

The architecture of tumours is also variable, but the most common picture is of alveolar cell masses separated by delicate connective tissue stroma. Usually the tumour cells merge into the remnant of cortical tissue, but sometimes the two are separated by a fibrous capsule.

Malignant Change

About 10 per cent. of cases are reported as malignant, mainly on the basis of histological signs such as capsular and vascular invasion by the tumour cells. Goodall and Symington³¹ observed the infrequency of metastases in cases where the tumours had these histological features and they doubted whether such tumours should be classified as truly malignant. The favourable clinical progress of many patients from whom such tumours are removed suggests that 10 per cent. is too high an estimate for malignancy. Russell and Rubinstein,⁷² from whose book the above notes on pathology are largely drawn, lean also to the view of Goodall and Symington³¹ and they remark that although several of their series of 18 tumours showed capsular invasion or intravascular deposits of cells, only one case had metastases; the cells of these metastases were primitive, but the bulk of cells in the bilateral primary adrenal tumours were of the adult phaeochrome type and only a few nests of primi-

FIG. 1.—Section across a typical phaeochromocytoma.

tive cells were found collected beneath the capsule and vascular connective tissue of the right adrenal tumour.

Pharmacology

Vulpian⁷⁹ demonstrated colour changes in watery extracts of adrenal glands which we can now assume to have been due to oxidation products of adrenaline. Adrenaline remained undiscovered until 1894 when its pressor effect was demonstrated by Oliver and Schäfer.⁵⁹ Twenty-eight years elapsed before Labbé, Tinel and Doumer⁴⁴ suggested that adrenaline was secreted by phaeochrome tumours to cause the hypertensive syndrome which they described so well, but proof of the connection between a high circulating level of adrenaline and the occurrence of clinical attacks was not forthcoming until 1937.⁹ The presence of another pharmacologically active catechol amine, noradrenaline, though synthesized along with adrenaline by Stolz⁷⁶ in 1904, was not proved until 1949 when it was found by Holton in phaeochromocytoma⁴⁰ and in large amounts in the urine of patients with these tumours by Engel and von Euler.²¹ The latter authors observed that the relative proportions of adrena-

line and noradrenaline were approximately the same in tumours and in urine. This is important inasmuch as ectopic tumours usually secrete only noradrenaline and the presence of large amounts of adrenaline in urine therefore suggests that the tumour is situated in the adrenal. The converse is not true in that the presence of excess noradrenaline alone in the urine does not rule out the adrenal as the site of the tumour.

The concentration of noradrenaline in tumours usually ranges from 1 to 8 mg./g., but much smaller and larger concentrations have been recorded. Adrenaline is never present to the exclusion of noradrenaline,²⁵ but may equal or slightly exceed the output of noradrenaline. Wright⁸⁴ found differences in the relative concentrations of adrenaline and noradrenaline in each of three tumours removed from the same patient, and there was in particular a higher proportion of adrenaline to noradrenaline in a nodular portion of one of these tumours as compared with the surrounding tissue in the same tumour. No cytological differences were noted between these two areas, but it is of some interest that capsular invasion was present in the tissue surrounding the nodule.

There is some evidence to suggest that adrenaline and noradrenaline are not only stored in separate granules in the phaeochrome cells but that the two substances may even be stored in separate cells.³⁵ Proof of this idea must await histochemical techniques specific for N-methylation.

Studies with isotopically labelled precursors of biologically active catecholamines show that adrenaline is formed rapidly in the normal adrenal but is stored for some considerable time. In patients with phaeochromocytoma the turnover is much more rapid. It is suggested that the size of a tumour is to some extent determined by the ability of its cells to methylate noradrenaline and to store adrenaline.⁷⁴

Recently two substances chemically related to the pressor amines have been isolated from tumours; 3-hydroxytyramine (Dopamine) was found in one out of 35 tumours examined chromatographically by Manger *et al.*⁵⁵ who related it to post-mortem changes in an embalmed specimen, but it was also found in each of two fresh tumours examined by Weil-Malherbe⁸¹ and in one tumour examined by McMillan.⁵² 3-hydroxy-tyramine was the predominant catechol-amine present in McMillan's tumour and it is of interest that this tumour was locally invasive. Weil-Malherbe also found dihydroxy-phenyl-alanine (Dopa) in both of his tumours.

The finding of Dopa and Dopamine in phaeochromocytomata supports the theory of biosynthesis of adrenaline from tyrosine put forward by Blaschko in 1939¹² (Fig. 2).

The practical significance of these findings is that they provide a possible explanation for the physiologically inactive phaeochromocytomata which have not infrequently been described. It seems possible that such tumours are unable to carry the synthesis of catechol-amines further than 3-hydroxy-tyramine. Although 3-hydroxy-tyramine does not appear to exert any dramatic physiological effects, evidence is accumulating that it has a physiological role other than that of a mere intermediary in catechol-amine metabolism.

Within the last three years some of the breakdown products of pressor amines have been isolated from urine and tumours. Armstrong and McMillan² and Axelrod⁴ demonstrated the presence of 3-methoxy,4-hydroxy-mandelic acid (V.M.A.) in urine and showed that it is generally increased in cases of phaeochromocytoma. These workers also isolated dihydroxy-mandelic acid (D.M.H.) from urine, thus showing that one catabolic pathway for adrenaline is by deamination followed by O-methylation. It seems more probable, however, that the more important breakdown route is by a reversal of these processes,

FIG. 2.—Main pathway of formation of catechol-amines (Blaschko, 1959).

i.e. by O-methylation to the 3-methoxy,4-hydroxy derivatives (normetanephrine and metanephrine) followed by deamination to V.M.A. (Fig. 3). Normetanephrine occurs in normal urine and was isolated for the first time in tumour tissue by Sjoerdsma *et al.*⁷⁴

Clinical Features of Phaeochromocytoma

Paroxysmal Hypertension

Intermittent secretion of pressor amines causes a most characteristic chain of symptoms by which the presence of phaeochromocytoma may be inferred. Attacks usually begin with feelings of intense anxiety; palpitation, precordial distress, headache and nausea quickly follow. Vomiting is common and profuse sweating usual. Palpitation may be slow or rapid and there is some correlation in this respect with the relative proportion of adrenaline and noradrenaline being secreted, the heart being quickened by adrenaline and slowed by noradrenaline.

FIG. 3.—Metabolism of adrenaline and noradrenaline (Armstrong and McMillan, 1959).

The two important signs are rise in blood pressure, which may exceed 300/180, and pallor of the face and extremities. Pallor serves to distinguish these attacks from superficially similar attacks seen in more common conditions such as anxiety states in subjects with labile blood pressure, menopausal hot flushes and hypoglycaemic states, in all of which there is a tendency for facial flushing. This sign also serves to distinguish rarer conditions which may mimic very closely the paroxysms associated with phaeochromocytoma. Respiratory obstruction, whether organic, as in oesophageal carcinoma with laryngeal involvement,⁷⁸ or hysterical,⁷⁷ may cause attacks of paroxysmal hypertension and similar attacks have been observed by Pickering⁶² in patients with aortic incompetence who suffer from angina pectoris at rest. In all these conditions the face tends to be flushed; it must be noted, however, that in phaeochromocytoma the face may be almost always flushed in between paroxysms of hypertension owing to reactive hyperaemia.

Attacks may occur spontaneously, but patients frequently notice precipitating causes; commonest of these are changes in posture such as bending over and lateral flexion of the trunk.⁶⁶ Almost all case histories refer to a tendency for attacks to be provoked by lying on one side; this usually proves to be the side opposite to that on which the tumour is situated. Attacks may be precipitated by hyperpnoea,⁵⁶ possibly due to the massaging action of the diaphragm, and occasionally by the act of swallowing when an intrathoracic tumour is present.¹¹ Horn⁴² described the case of

a 41-year-old Negro in whom attacks seemed to be precipitated by food or drink, but as the patient also had a duodenal ulcer it is difficult to be certain to which cause the symptoms were attributable. Occasionally emotional stress causes attacks. Attacks are particularly prone to occur for the first time during pregnancy; when they begin during labour the consequences may be very serious.^{7, 32, 37} Lumb and Gresham⁴⁹ describe a case of phaeochromocytoma of the urinary bladder which gave rise to attacks of paroxysmal hypertension after micturition in warm weather. This rare site for the tumour has apparently been described only twice before.^{64, 85}

Genito-urinary symptoms may occur irrespective of the site of the phaeochromocytoma for male patients may complain of impotence and the sudden outpouring of catecholamines may interrupt the act of micturition. Wright⁸⁴ found a high concentration of catecholamines in a large volume of urine passed by a woman with a phaeochromocytoma who had not urinated for the previous 18 hours.

The history of paroxysmal hypertension may be very long indeed, as long as 20 years for instance. One peculiar feature about such histories is that there may be long periods of freedom from symptoms. Such remissions from symptoms do not necessarily imply that attacks of hypertension no longer occur, in fact one of the well recognized forms of presentation of phaeochromocytoma is the discovery of labile blood pressure in the complete absence of symptoms. There does seem to be a possibility, however, that the activity of some tumours may diminish for con-

siderable periods; this is likely in view of the marked tendency of these tumours to undergo haemorrhagic necrosis and cyst formation. There are no authentic cases to show that the disease is ever self-limiting in this way, but the onset of malignant change in a tumour must occasionally affect its ability to produce biologically-active catechol-amines. Mandl⁵⁴ cites the case of a 28-year-old woman who had symptoms suggestive of paroxysmal hypertensive attacks since childhood. The attacks gradually diminished in severity and were absent at the time when laparotomy disclosed a large malignant phaeochromocytoma. She had a third child after the operation; apparently functionless metastases appeared at the age of 30 and she died a year later.

Fixed Hypertension

A fair proportion of patients present for the first time with persistent hypertension; they may not admit to any symptoms suggestive of phaeochromocytoma even on close questioning. The hypertension may be of 'benign' or 'malignant' type. The onset of malignant hypertension associated with phaeochromocytoma may be devastating and patients can go blind from retinopathy in a very few weeks.⁶⁷ Such cases are of great theoretical interest, for although they have all the clinical features of malignant hypertension it is rare for arteriolar necrosis to be found either in the kidneys or other organs and the patient may be completely cured by removal of the tumour. Cases in which arteriolar necrosis occurred are, however, described.^{17, 63, 80}

Sudden death from cerebral vascular accident may occur in patients with phaeochromocytoma; death is occasionally due to a state of irreversible shock which may come on quite suddenly without antecedent symptoms, but more often follows a paroxysm of hypertension. When such a catastrophe overtakes a patient with no previous symptoms there may well be suspicion of poisoning.⁴¹ The clinical features are those of profound shock with low blood pressure and severe pulmonary oedema. Death occurs within a few hours. At post-mortem examination massive haemorrhage into the tumour may be found,⁴⁶ though there may be no gross changes in it.⁶⁸ Irreversible shock sometimes follows removal of a phaeochromocytoma,^{8, 54} but also may occur after operations for unrelated conditions.¹⁰

Associated Symptoms and Signs

Clinical diagnosis of phaeochromocytoma in the absence of a history of attacks of hypertension is very difficult, but occasionally, helpful signs are present. The most important of these is a palpable

abdominal tumour. It may be possible to observe a rise in blood pressure when such a tumour is palpated, but even if no tumour is palpable massage of one or other loin may also be associated with rise in blood pressure. Ransom *et al.*⁶⁶ describe a patient who had a large left subcostal tumour which could be palpated without a rise in blood pressure occurring, however this patient could voluntarily produce a paroxysm of hypertension by lateral flexion of his trunk. The occurrence of haemorrhagic necrosis in a phaeochromocytoma may give rise to local discomfort, fever and high polymorphonuclear leucocytosis.

Other endocrine abnormalities are frequently associated with phaeochromocytoma; the most important of these is a thyrotoxic appearance; this is not usually very marked, the eyes have a slight 'staring' quality, the thyroid is uniformly slightly enlarged and there may be considerable wasting. The basal metabolic rate is then almost always raised, but uptake of ¹³¹I is usually within normal limits.

Glycosuria with impaired sugar tolerance is common; frank diabetes mellitus with diabetic symptoms is much less common. Freedman *et al.*²⁸ describe four cases of phaeochromocytoma occurring in diabetics and demonstrated improved sugar tolerance after removal of the tumours. They discovered two more possible cases of phaeochromocytoma by screening for excess catechol-amines the urine from 144 carefully selected diabetics with hypertension.

A further endocrine abnormality which is said to occur is Addison's disease due, presumably, to destruction of both adrenal cortices by bilateral tumours. This must be very rare indeed since some cortical tissue usually survives on the surface of a phaeochromocytoma. It seems possible that the pigmentation seen in some of the alleged cases of Addison's disease in phaeochromocytoma is really due to neurofibromatosis (*vide infra*).

McGavack *et al.*⁵¹ cite such a case in which there was advanced cachexia due to malignant phaeochromocytoma with metastases, and patchy pigmentation over face and trunk (B.P. 122-85/82-70). At necropsy there were multiple secondary growths from a large primary phaeochromocytoma in the right adrenal, the left adrenal being normal.

Adrenal cortical hyperfunction appears to be a rare concomitant of phaeochromocytoma.^{16, 58}

The association of neurofibromatosis with phaeochromocytoma is becoming increasingly well recognized. Rosenthal and Willis⁶⁹ reported such a case and mentioned five others appearing in the literature up to that time. Glushien, Mansuy and Littman²⁹ found 11 more cases published after 1936; they added another of their own in addition to reporting two cases of

FIG. 4.—Minimal clinical evidence of neurofibromatosis in a 17-year-old boy with a left-sided phaeochromocytoma. (The dressing on the back covers area of biopsy of skin nodule.)

phaeochromocytoma associated with angiomatosis retinae. They were able to find only one other case in the literature showing the latter association. They predict that other neurocutaneous syndromes such as the Sturge-Weber syndrome and tuberose sclerosis will in due course be reported in association with phaeochromocytoma. These authors made the interesting observation that in cases of neurofibromatosis the phaeochromocytoma lay on the left side in 16 out of 21 cases, whereas in general phaeochromocytoma more commonly affects the right adrenal. Davies *et al.*²⁰ found that three out of ten cases admitted to the London Hospital since 1947 had proven neurofibromatosis. Two of the patients had multiple skin lesions, but the third, a young man aged 17 (Fig. 4) had only one or two skin nodules, a nodule in the tongue and a few café-au-lait patches on the skin. These authors comment on

increased skin pigmentation in four more of their cases and they believe that the commonly accepted incidence of 10 per cent. considerably underestimates the association between neurofibromatosis and phaeochromocytoma. The finding of hypertension in patients with neurofibromatosis should lead to a careful search for phaeochromocytoma. Rare cases have been described in which neurofibromata of the intercostal nerves have caused notching of the ribs and a wrong diagnosis of coarctation of the aorta has been made.

Diagnosis

Catechol-amine Estimation in Urine

Engel and von Euler²¹ showed that large amounts of noradrenaline and sometimes adrenaline are excreted in the urine of patients with phaeochromocytoma and further studies in the last decade have fully justified their view that

this is a reliable way of confirming the diagnosis. Reviewing their experience of 35 cases of phaeochromocytoma, von Euler and Ström²⁵ found that in all cases showing clinical signs of a secreting tumour the catechol-amine secretion is increased. They give the normal noradrenaline output for 24 hours as 20-40 $\mu\text{g.}$; 32 out of 35 cases of phaeochromocytoma excreted amounts of noradrenaline exceeding 300 $\mu\text{g.}$ in 24 hours, and the lowest values they recorded in cases of proven tumour were 104 and 109 $\mu\text{g.}$ For practical purposes they regard a daily excretion in 100-200 $\mu\text{g.}$ as the lower limit of noradrenaline excretion in an actively secreting tumour. An exceptional case in which the pressor amine content of three separate 24-hour specimens of urine was normal was described by Litchfield and Peart;⁴⁷ hypertensive attacks occurred during the collection of each of these specimens. Cases such as these must be very rare indeed and it would be unfortunate if the general validity of urine catechol-amine estimations were to be questioned on these grounds.

In defining the limits of normality for catechol-amine estimation some allowance must be made for the method used. Biological assay is more sensitive than most chemical methods, but less specific. Specificity for both biological and chemical methods of assay is enhanced by preliminary purification of the urine. This is commonly done by adsorption on aluminium oxide columns and elution of the pressor amines with acid, the eluate being subjected to biological assay or, after suitable treatment, to fluorimetry.^{22, 36, 60, 82} Wright⁸³ employs a less tedious method of purification of urine before fluorimetric estimation. Because in this method only small volumes (5 ml.) of urine are used, technical errors are magnified in assessing 24-hour output, and Wright concedes an upper limit of normal of 200 $\mu\text{g.}$ noradrenaline per 24 hours by his method. Fig. 5 shows serial specimens of urine from two patients with phaeochromocytoma assayed by this method. The need for 24-hour specimens is clearly shown by the normal levels of catechol-amine excretion in several of the individual specimens of urine passed by one of these patients.

Fortunately, in most cases of phaeochromocytoma the output of pressor amines is so great that comparatively crude chemical methods suffice as screening tests.^{15, 39, 53} Much more sensitive are the biological methods devised by Moulton and Willoughby⁵⁷ and Floyer,²⁶ in which the pressor effects of minute quantities of untreated urine are measured in cats and rats respectively.

Blood Catechol-amine Levels

Blood catechol-amine levels are of diagnostic value only during hypertensive crises or in

FIG. 5.—Rate of urinary excretion of catechol-amines in two cases of phaeochromocytoma.

- A. Continuous high excretion.
- B. Intermittent high excretion.

patients who are constantly secreting an excess of these substances. The Mayo Clinic group find these estimations useful in conjunction with the provocative histamine test.⁴³ Some argument exists as to the normal plasma catechol-amine level, but most workers now agree that this lies below 6 $\mu\text{g./l.}$ whatever the method of estimation used.

Estimation of the Breakdown Products of Pressor Amines

The fact that only about 4 per cent. of infused noradrenaline appears in the urine may well account for low urinary excretion figures in some cases of phaeochromocytoma. The recent discovery that one of the end-products of catechol-amine metabolism, 3-methoxy,4-hydroxy-mandelic acid (V.M.A.), appears in large amounts in the urine of patients with phaeochromocytoma,³ gives grounds for hope that an unequivocal diagnostic tool is now available. These workers give the normal urine content of V.M.A. as 1.5-3.5 $\mu\text{g./mg.}$ of creatinine. In eight cases of phaeochromocytoma the values ranged from 9 to 90 $\mu\text{g./mg.}$ creatinine. The figures for a few patients moribund from various causes fell in the intermediate range from 3.5 to 9, but otherwise the distinction between normal and abnormal values was sharp. Estimation of V.M.A. and other breakdown products of adrenaline and noradrenaline depends at present on preliminary separation by paper chromatography and as this technique is not very suitable for screening large numbers of urines a specific chemical test is awaited with interest.

Drug Tests: Adrenolytic Agents

15-20 mg. piperoxan ('Benzodioxane')³⁰ or 5-10 mg. phentolamine ('Regitine')⁴⁸ given intravenously to patients with hypertension due to phaeochromocytoma produce a sharp fall in blood

pressure. Sometimes the fall in blood pressure is enough to cause alarming symptoms. False positive results particularly tend to occur in uraemic patients; such patients often have slightly raised blood catechol-amine levels.⁶⁵ False positive tests may also occur in patients who are taking sedatives or narcotics and such drugs should be withheld for 48 hours before these tests are made. In contrast to piperoxan, phentolamine is said not to produce pressor responses in patients with benign essential hypertension.

Provocative Tests

25-50 mg. histamine-base intravenously usually causes a large rise in blood pressure with or without accompanying symptoms.⁷¹ This test should be reserved for normotensive patients who give a history suggestive of phaeochromocytoma and phentolamine should be to hand to abort the attack if necessary.

10-20 mg. Mecholyl subcutaneously³⁴ and 400 mg. tetra-ethyl ammonium bromide intravenously⁴⁵ may also be used to provoke attacks.

Kvale *et al.*⁴³ reviewing the Mayo Clinic experience of 8,873 pharmacological tests done on 7,993 patients in the 11 years prior to their publication report no serious side reactions. It is true that fatalities arising in connection with these tests are very rare and possibly coincidental, but the amount of vascular damage caused by individual hypertensive attacks is not easy to determine. Wright⁸⁴ witnessed the appearance of fresh retinal haemorrhages in a patient who voluntarily produced a hypertensive attack by lying on his right side. In view of the rapidity with which patients can become completely blind or develop permanent neurological disorders it does not seem justifiable to apply any of these drug tests unless facilities for urinary catechol-amine estimation are not available.

Localization of the Tumour

Features in the history, the clinical examination and the relative amounts of noradrenaline and adrenaline secreted in the urine may all help in the localization of the tumour.

Radiographic examination is usually needed for precise localization. Plain films of the abdomen may show a soft tissue shadow due to the tumour. Rarely a rim of calcified tissue may outline the tumour sharply. Intravenous pyelography frequently shows abnormal downward displacement of the kidney on the affected side.

Peri-renal air insufflation and aortography are dangerous in this condition, but pre-sacral air insufflation is safe and may give most helpful information (Fig. 6). Ectopic tumours are not always easy to visualize and may be encountered

unexpectedly at operation. Chest X-rays are indispensable for demonstrating the presence of intrathoracic primary phaeochromocytoma or metastases, and incidentally for giving information about heart size and pulmonary congestion.

A special technique applied successfully by von Euler *et al.*²⁴ in three cases of phaeochromocytoma is selective catheterization of the vena cava at various levels with estimation of pressor amines in the blood samples so obtained. This technique also gave useful information in a case of primary intrathoracic phaeochromocytoma with functioning lung metastases.¹¹

Treatment

The treatment of phaeochromocytoma is surgical, but as preliminary investigations may take some time it may be necessary to temporize with medical measures. Richardson *et al.*,⁶⁷ confronted with a case of fulminating malignant hypertension resulting in almost complete blindness in a young man, were able to obtain partial control of blood pressure and relief of symptoms for several days by intermittent intravenous infusion of piperoxan. Tolerance to this drug developed rapidly and enormous doses were required prior to successful operation. Bannon and Allen⁵ had a similar experience in a case of malignant phaeochromocytoma with metastases which were presumed to be functioning after removal of the primary tumour. They found that for long-term usage Dibenylene was superior to other adrenolytic drugs.

Anaesthesia

Apgar and Papper¹ were able to find some information on anaesthetic problems in only 41 out of 91 published reports of operation in cases of phaeochromocytoma. In reviewing this important subject they comment on the need for avoiding anoxia and carbon dioxide retention which may cause hypertensive crises prior to removal of the tumour. Cyclopropane should be avoided on the grounds that disturbances of cardiac rhythm may occur with this anaesthetic in the presence of high circulating levels of pressor amines. Curare has the theoretical disadvantage of a histamine-like action which could cause a release of pressor amines; good relaxation is important since adequate exposure and minimal handling of the tumour is essential for success and later workers have been able to use curare freely by administering an anti-histamine drug with other premedication.

Favourable reports attend the use of thiopentone, nitrous oxide and oxygen; ether may be used for continued anaesthesia despite experi-

FIG. 6.—Pre-sacral air insufflation with simultaneous intravenous pyelogram shows the presence of bilateral phaeochromocytoma. The presence of these was confirmed at operation, but an additional para-aortic tumour was also encountered.

mental evidence that it causes a rise in plasma catechol-amine levels.³⁷

Spinal anaesthesia is unsafe in this operation, but epidural anaesthesia supported by light general anaesthesia has been used successfully.¹⁴

The Operation

The operative approach is important. If the tumour is clearly located on one side, a renal incision undoubtedly offers the best exposure, but when the pre-operative studies leave some doubt regarding the site of the tumour or if the possibility of multiple tumours is entertained an abdominal approach is best used. Kvale *et al.*,⁴³ who have very considerable experience in this field, use a transverse high abdominal incision curving slightly upwards.

An experienced operating team is unlikely to be troubled by a hypertensive crisis occurring during operation, but it is as well to have a solution of phentolamine ready for intravenous injection. In any event, an intravenous drip transfusion of dextrose saline or blood is essential because as soon as the veins draining the tumour are ligated a sharp fall in blood pressure usually occurs; it is then necessary to give intravenous noradrenaline; a concentration of noradrenaline of 4 mg./l. is usually sufficient, but much larger

amounts may have to be given over a period of several days. Even so, it may prove impossible to resuscitate patients from post-operative shock; Beard *et al.*⁸ gave to a patient a noradrenaline solution containing 40 mg./l. at a rate of 40-60 drops per minute for about 15 hours without success; the patient having received 128 mg. noradrenaline at the time of his death.

Another hazard of operation is local haemorrhage since the vascular supply of these tumours may be very great and they are sometimes adherent to adjacent structures. Traumatic pneumothorax with subsequent effusion is common and occasionally chylous effusions occur owing to unavoidable section of the thoracic duct.

A more remote complication which occurred in two of the cases described by Davies *et al.*²⁰ was an acute schizophrenic episode coming on towards the end of the first week and lasting two weeks in one of the cases. In view of the importance of catechol-amine metabolism in cerebral function it is curious that the literature does not appear to contain other references to psychological disorders after removal of phaeochromocytoma.

An additional hazard is inherent in removal of bilateral tumours because it may be impossible to preserve any adrenal cortical tissue. Roth *et al.*⁷⁰ were able to remove, in single operations, bilateral

tumours from each of three siblings without untoward effect. Only one of these subjects required to be maintained on cortisone. As a general rule it would seem wiser to perform two-stage operations in such cases, giving cortisone cover for the second stage and continuing maintenance therapy if need be.

Results of Treatment

Complete removal of secreting tumour tissue results in cessation of hypertensive attacks. The noradrenaline content of the urine may remain slightly raised for some days and this is thought to be due to temporarily increased vasomotor activity.

There are many reports of successful relief of hypertension, even when this has been regarded as of chronic character. Unhappily, hypertension may persist in a number of cases. The mechanism is obscure, but the most likely explanation is that secondary hypertensive vascular changes in the kidneys are responsible. Failure to lower the blood pressure permanently by removal of the tumour does not preclude great improvement in hypertensive retinopathy, but continued visual impairment is common.

Residual hypertension may respond well to hypotensive drugs of the ganglion-blocking variety, whereas before operation these drugs are usually ineffective.

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REFERENCES

1. APGAR, V., and PAPPER, E. M. (1951), *A.M.A. Arch. Surg.*, **62**, 634.
2. ARMSTRONG, M. D., and McMILLAN, A. (1957), *Fed. Proc.*, **16**, 146.
3. ARMSTRONG, M. D., and McMILLAN, A. (1959), *Pharmacol. Rev.*, **11**, 394.
4. AXELROD, J. (1957), *Science*, **126**, 400.
5. BANNON, W. G., and ALLEN, E. V. (1952), *Proc. Mayo Clin.*, **27**, 459.
6. BARBEAU, A., MARC AURELE, J., LEBOEUF, G., BROUILLET, J., CARTIER, P., VITTE, B., MIGNAULT, G., and GENEST, J. (1958), *Un. med. Can.*, **87**, 165.
7. BENNET, M., and MATHER, G. (1959), *Lancet*, **i**, 811.
8. BEARD, E. F., BUTLER, D. B., and ROSENBERG, H. S. (1955), *Arch. intern. Med.*, **96**, 273.
9. BEER, E., KING, F. H., and PRINZMETAL, M. (1937), *Ann. Surg.*, **106**, 85.
10. BERGER, H. (1954), *Zbl. Chir.*, **29**, i, 14.
11. BJÖRK, V. O., LINDERHOLM, H., LUBLIN, H., PERNON, B., and TÖRNBERG, B. (1959), *Acta chir. scand.*, **116**, 411.
12. BLASCHKO, H. (1939), *J. Physiol.*, **96**, 50P.
13. BRINES, O. A., and JENNINGS, E. R. (1948), *Amer. J. Path.*, **24**, 1167.
14. BROMAGE, P. R., and MILLAR, R. A. (1958), *Canad. anaesth. Soc. J.*, **5**, 282.
15. BURN, G. P., and FIELD, E. O. (1956), *Brit. med. J.*, **ii**, 1152.
16. CAHILL, G. F. (1943), *Penn. med. J.*, **47**, 655.
17. CHAMOVITZ, J., and FANGER, H. (1949), *Amer. J. clin. Path.*, **19**, 243.
18. COHLE, R. R. (1950), *J. Missouri State Med. Ass.*, **47**, 590.
19. CONE, T. E., JR., ALLEN, M. S., and PEARSON, H. A. (1957), *Paediatrics*, **19**, 44.
20. DAVIES, D. M., RICHARDSON, J. E., and WRIGHT, J. T. (1960), in preparation.
21. ENGEL, A., and EULER, U. S. v. (1950), *Lancet*, **ii**, 387.
22. EULER, U. S. v., and HELLNER, S. (1951), *Acta physiol. scand.*, **22**, 161.
23. EULER, U. S. v., and FLODING, I. (1955), *Ibid.*, **33**, Supp. **118**, 57.
24. EULER, U. S. v., GEMZELL, C. A., STRÖM, G., and WESTMAN, A. (1955), *Acta med. scand.*, **153**, 127.
25. EULER, U. S. v., and STRÖM, G. (1957), *Circulation*, **15**, 5.
26. FLOYER, M. A. (1958), *Lancet*, **ii**, 1154.
27. FRANKEL, F. (1886), *Virchows Arch.*, **103**, 244.
28. FRIEDMAN, P., MOULTON, R., ROSENHEIM, M. L., SPENCER, A. G., and WILLOUGHBY, D. A. (1958), *Quart. J. Med. N.S.*, **107**, 307.
29. GLUSHIEN, A. S., MANSUY, M. M., and LITTMAN, D. S. (1953), *Amer. J. Med.*, **14**, 318.
30. GOLDENBERG, M., SNYDER, C. H., and ARANOW, H. (1947), *J. Amer. med. Ass.*, **135**, 971.
31. GOODALL, A. L., and SYMINGTON, T. (1953), *Glasg. med. J.*, **34**, 97.
32. GÖSSLER, A. (1953), *Zbl. Gynäk.*, **75**, ii, 1418.
33. GREENBERG, R. E., and GARDNER, L. I. (1959), *J. clin. Endocr.*, **19**, 351.
34. GUANERI, V., and EVANS, J. A. (1948), *Amer. J. Med.*, **4**, 806.
35. HAGEN, P. (1959), *Pharm. Rev.*, **11**, 361.
36. HAMILTON, M., LITCHFIELD, J. W., PEART, W. S., and SOWRY, G. S. C. (1953), *Brit. Heart J.*, **15**, 241.
37. HARDY, J. D., CARTER, T., and TURNER, M. D. (1959), *Ann. Surg.*, **150**, 666.
38. HEAD, K. W., and WEST, G. B. (1958), *J. comp. Path.*, **68**, 167.
39. HINGERTY, D. (1957), *Lancet*, **i**, 766.
40. HOLTON, P. (1949), *J. Physiol.*, **108**, 525.
41. HOLTZ, E. (1939), *Dtsch. Z. ges. gerichtl. Med.*, **32**, 94.
42. HORN, H. L. (1959), *Ann. intern. Med.*, **51**, 129.
43. KVALE, W. F., ROTH, G. M., MANGER, W. M., and PRIESTLY, J. T. (1956), *Circulation*, **14**, 622.
44. LABBE, M., TINEL, J., and DOUMER, (1922), *Bull. Soc. Méd. Hop. Paris*, **46**, 982.
45. LADUE, J. S., MURISON, P. J., and PACK, G. T. (1948), *Ann. intern. Med.*, **29**, 914.
46. LEHMAN, D. J., and ROSOF, J. (1956), *New Engl. J. Med.*, **254**, 474.
47. LITCHFIELD, J. W., and PEART, W. S. (1956), *Lancet*, **ii**, 1283.
48. LONGINO, F. H., GRIMSON, K. S., CHITTM, J. R., and METCALF, B. H. (1949), *Surgery*, **26**, 421.
49. LUMB, B. R. B., and GRESHAM, G. A. (1958), *Lancet*, **i**, 81.
50. MACKETH, R. (1944), *Brit. Heart J.*, **6**, 1.
51. MCGAVACK, T. H., BENJAMIN, J. W., SPEER, F. D., and KLOTZ, S. (1942), *J. Endocr.*, **2**, 332.
52. McMILLAN, M. (1956), *Lancet*, **ii**, 284.
53. McMILLAN, M. (1957), *Ibid.*, **i**, 715.
54. MANDL, W. von (1955), *Wien. med. Wschr.*, **105**, 516.
55. MANGER, W. M., FLOCK, E. V., BERKSON, J., BULLMAN, J. L., ROTH, G. M., BALDES, E. J., and JACOBS, M. (1954), *Circulation*, **10**, 641.
56. MORTIEL, E. J., and WHITTLE, J. P. (1945), *J. clin. Endocr.*, **5**, 396.
57. MOULTON, R., and WILLOUGHBY, D. A. (1955), *Lancet*, **ii**, 16.
58. NEFF, F. C., TICE, G., WALKER, G. A., and OCKERBLAD, N. (1942), *J. clin. Endocr.*, **2**, 125.
59. OLIVER, G., and SCHAFER, E. A. (1894), *J. Physiol.*, **16**, i.
60. PEKKARINEN, A., and PITKANEN, M. E. (1955), *Scand. J. clin. Lab. Invest.*, **7**, 1.
61. PHILLIPS, B. (1940), *Arch. Path.*, **30**, 916.
62. PICKERING, G. W. (1955), 'High Blood Pressure.' London: J. & A. Churchill Ltd.
63. PLATT, R., and DAVSON, J. (1950), *Quart. J. Med.*, **N.S.**, **19**, 33.
64. PUGH, R. C. B. (1956), *Proc. roy. Soc. Med.*, **49**, 710.
65. RAAB, W., LEPESCHKIN, E., STARCHESKA, Y. K., and GIGEE, W. (1956), *Circulation*, **14**, 614.
66. RANSOM, C. L., LANDES, R. R., and GADDY, C. G. (1958), *J. Urol.*, **79**, 368.
67. RICHARDSON, J. E., ROSS, J. H., and TURNBULL, L. (1955), *Lancet*, **ii**, 275.
68. RISER, M., PLANQUES, J., and RUFFIE, J. (1953), *Ann. Méd. Légale*, **33**, 257.

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69. ROSENTHAL, D. B., and WILLIS, R. A. (1936), *J. Path. Bact.*, **42**, 599.
70. ROTH, G. M., HIGHTOWER, N. C., BARKER, N. W., and PRIESTLEY, J. T. (1953), *Amer. med. Ass. Arch. Surg.*, **67**, 100.
71. ROTH, G. M., and KVALE, W. F. (1945), *Amer. J. med. Sci.*, **210**, 653.
72. RUSSELL, D. S., and RUBINSTEIN, L. J. (1959), 'Tumours of the Nervous System.' London: Arnold.
73. SJOERDSMA, A. (1959), *Pharm. Rev.*, **11**, 374.
74. SJOERDSMA, A., LEEPER, L. C., TERRY, L. L., and UDENFRIEND, S. (1959), *J. clin. Invest.*, **38**, 31.
75. SMID, A. C., and DUSHANE, J. W. (1955), *Amer. J. Dis. Child.*, **90**, 81.
76. STOLTZ, F. (1904), *Ber. dtsch. chem. Ges.*, **37**, 4149.

77. TYRER, J. H., EMMERSON, B. T., and MURPHY, K. J. (1959), *Quart. J. Med.*, N.S. **28**, 315.
78. VAQUEZ, H., and DONZELOT, E. (1926), *Pr. Méd.*, **34**, 1329.
79. VULPIAN, E. F. A. (1856), *C. R. Acad. Sci. (Paris)*, **43**, 663.
80. WASHINGTON, E. L., CALLAHAN, W. P., and EDWARDS, E. W. (1946), *J. clin. Endocr.*, **6**, 688.
81. WEIL-MALHERBE, H. (1956), *Lancet*, **ii**, 282.
82. WEIL-MALHERBE, H., and BONE, A. D. (1957), *J. clin. Path.*, **10**, 138.
83. WRIGHT, J. T. (1958), *Lancet*, **ii**, 1155.
84. WRIGHT, J. T., unpublished.
85. ZIMMERMAN, I. J., BIRON, R. E., and MACMAHON, H. E. (1953), *New Engl. J. Med.*, **249**, 25.