CLINICAL AND PATHOLOGICAL DETAILS OF TWO CASES OF PHAEOMOCYTOMA IN CHILDHOOD

BY

M. J. ROBINSON and ALAN WILLIAMS

From the Royal Children's Hospital, Melbourne

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Hypertension due to the presence of a tumour of the adrenal medulla was first described by Labbé, Tinel and Doumer in 1922. Four years later such a tumour was successfully removed by Roux (1926). The literature concerning phaeochromocytoma in childhood was recently reviewed by Daeschner, Moyer and Able (1954). They were able to find only 16 recorded cases of active phaeochromocytoma in children under the age of 14 years, to which number they added one further case. Three cases have been recorded since then (Negri and Pugno Vanoni, 1954; Mégevand and Ferrier, 1954; Popper and Theron, 1954).

We record the clinical notes, including diagnosis and operative management, of two children aged 8 and 10 years respectively in each of whom a phaeochromocytoma was discovered and successfully removed. The investigation of hypertension detected on routine physical examination led to the diagnosis and removal of the tumours. This was followed in each case by a reversion of blood pressure to normal levels, and alleviation of symptoms. The nature of the tumours was confirmed by histological studies and hormone assays.

Case Reports

Case 1. A.L., a boy aged 8 years and 7 months was perfectly well until about two years before admission when it was first noticed that he sweated profusely. The sweating was not related particularly to the environmental temperature, but was more pronounced at night. Frontal headaches began six months before admission. These occurred once or twice weekly, usually early in the morning and lasted several hours.

Two months later puffiness and redness of both hands and wrists were noticed. The lower extremities had never shown vasomotor changes. One month before

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Fig. 1.—Drawing of the ocular fundi in Case 1 showing bilateral papilloedema, flame-shaped haemorrhages, and exudate. There is a well developed macular star in the right ocular fundus.
admission the boy complained of progressive difficulty of vision and of a grey shadow before his eyes. Over the past few weeks he had been excessively thirsty and wanted additional salt with his meals. There had been no urinary symptoms or nocturia.

On examination he was a cooperative, intelligent boy of normal physical development. The heart was slightly enlarged, the impulse being located 3½ in. from the mid-sternal line. The aortic second sound was accentuated. Both femoral arteries were easily palpable. The blood pressure was 200/160 mm. Hg.

Retinoscopy showed bilateral papilloedema with a large amount of exudate and scattered haemorrhages. There was a well defined macular star in the right fundus. The vessels were tortuous and thickened (Fig. 1).

The only other significant findings on physical examination were swollen red hands and wrists. The skin over the hands was coarse and dry, but pitting on pressure was not possible.

Laboratory Tests. Repeated urine tests showed traces of albumin but no sugar. The specific gravity of the urine ranged between 1.010 and 1.025 and microscopy revealed an occasional hyaline cast only. The blood urea was 44 mg. per 100 ml. and urea clearance and concentration tests showed normal function. An intravenous pyelogram was normal.

Radiological examination of the thorax showed very slight cardiac enlargement but the electrocardiogram was normal. The haemoglobin level was 15·5 g. per 100 ml., and leucocytes 12,850 per c.mm. with a normal differential cell count. Wassermann and Kahn tests were negative. The fasting blood sugar was 112 mg. per 100 ml.

Phentolamine Test. An intravenous infusion was set up and approximately one hour later, when the blood pressure was stable, 2·5 mg. of phentolamine ('regitine', Ciba Ltd.) in 10 ml. of saline was injected slowly and produced a fall of approximately 40 mm. Hg in both systolic and diastolic pressures (Fig. 2).

Urine Assay. Confirmation of the diagnosis of phaeochromocytoma was obtained by biological assay of a 24-hour specimen of urine which was found to contain 300 μg. per litre of pressor amine.*

Radiology. The tumour was demonstrated by combining retroperitoneal air insufflation and angiography. This procedure was performed under general anaesthesia and the blood pressure controlled by phentolamine. This investigation demonstrated an enlarged right adrenal shadow. On the left side no adrenal shadow was visible.

From the time the diagnosis was considered until operation was performed, the boy was maintained on oral phentolamine, 20 mg. six-hourly. This enabled a constant blood pressure of 160/120 mm. Hg to be maintained, and relieved much of his sweating, headache and giddiness. However, he developed a tolerance to oral phentolamine and the dosage had to be increased to 30 mg. four-hourly.

For three days before operation he was given cortisone, 20 mg. orally, each day.

Operation. At operation under thiopentone, tubocurarine chloride, nitrous oxide and oxygen, the right adrenal gland was exposed via a right transthoracic extraperitoneal approach and a tumour palpated in its substance. This was enucleated following ligation and division of its blood vessels.

Manipulation during excision of a phaeochromocytoma results in large quantities of adrenaline and noradrenaline being liberated into the circulation with the consequent development of sudden and profound hypertension. Removal of the tumour is usually followed by sudden circulatory failure presumably due to deprivation of the large quantities of vasoconstrictor hormone to which the patient has been accustomed. In this patient during manipulation of the tumour, a total of 4·75 mg. of phentolamine was intermittently injected, and, following the initial level of 190/160 mm. Hg, at no stage did the blood pressure exceed 240/170 mm. Hg. When the

*[Throughout this paper the pressor amine content is expressed in terms of nor-adrenaline.
vessels to the tumour were clamped the blood pressure rapidly fell to 80/60 mm. Hg and the infusion of intravenous nor-adrenaline was immediately begun, the rate of flow being adjusted to maintain a systolic pressure greater than 100 mm. Hg. This required between 6 and 10 ìg. of nor-adrenaline per minute. By the end of the operation, the blood pressure was constant at 115/80 mm. Hg and the nor-adrenaline was stopped. The variations of the blood pressure and measures to control them are illustrated in Fig. 3.

The post-operative period was uneventful. Headaches and sweating completely disappeared and his vision had greatly improved. In the few weeks before his discharge from hospital the systolic pressure fluctuated between 125 and 135 mm. Hg and the diastolic between 84 and 95 mm. Hg. The blood urea following operation was 24 mg. per 100 ml. A 24-hour specimen of urine contained 40 ìg. per litre of pressor amine, a normal value. Three months after operation the papilloedema and haemorrhages had almost completely resolved, and the exudates were much reduced (Fig. 4).

**PATHOLOGY.** The tumour, together with its surrounding rim of adrenal cortex, weighed 22 g. Traversal revealed a solid pink tissue of uniform appearance throughout. Within 15 minutes of its surgical removal portions of tissue were placed in formalin, Regaud’s fluid, and in osmic acid vapour.

Histological preparations showed that the tumour had a dense fibrous capsule, which separated it from adrenal cortical tissue. Traversing the tumour were numerous fibrous septa, the spaces between which were occupied by groups of cells with indistinct outlines (Fig. 5). The majority of cells consisted of nuclei surrounded by a varying amount of cytoplasm and by clear spaces. The nuclei varied in size, many being large and containing prominent nucleoli. Multinucleated cells containing two to four nuclei were present but not numerous. No differentiated nervous tissue or ganglion cells were seen in numerous sections prepared. The tumour was extremely vascular, many thin-walled vessels being present in fibrous septa and amongst the cells so that they often formed the walls of the vessel.

The formalin in which tissue was fixed became pale brown within 24 hours. Material fixed in Regaud’s fluid rapidly became dark brown and in sections stained with haematoxylin and eosin numerous dark brown granules were seen. These granules were, however, best demonstrated by Sevki’s modification of Schmorl’s Giemsa stain (Pearse, 1953) after which they became bright green (Fig. 6). Their osmiophilic nature was seen in material fixed by osmic acid, and from which fats were extracted. Fat globules within tumour cells was demonstrated by this method and also by frozen sections from formalin stained with Sudan III. The high fat content did not appear to account entirely for the vacuolated appearance of the cells seen in sections of paraffin-embedded tissue.

The pressor amine content of the tumour was 1,370 ìg. per g. of tissue.

**Case 2.** G.B., a boy aged 10 years and 9 months, was well until about eight months before admission to hospital when his parents noticed increasing pallor. About this time he complained of headaches. These occurred about once a week, usually situated over the vertex and lasted from one to eight hours. Occasionally the headaches were associated with vomiting. Sweating was noticed only occasionally and then usually at night.
At no stage had he complained of visual disturbances, or symptoms referable to the renal system.

His private doctor found hypertension and a cardiac bruit and referred the boy to hospital for investigation.

On examination, the abnormal physical findings were confined to the cardiovascular system. The heart was enlarged, the impulse being located 4 in. from the mid-sternal line in the fifth left intercostal space. A triple rhythm was audible over the whole of the precordium and a blowing diastolic bruit down the left border of the sternum. The blood pressure was 180/130 mm. Hg. All major arteries of the lower limbs were readily palpable. The ocular fundi were normal.

Laboratory Tests. Repeated urine tests showed an occasional trace of albumin but no sugar. Several urine specimens were normal on microscopy. The blood urea was 28 mg. per 100 ml. A concentration-dilution test, a urea clearance test and an intravenous pyelogram gave normal results. Radiological examination of the thorax revealed slight cardiac enlargement. An electrocardiogram showed left axis deviation and slight left ventricular hypertrophy. The haemoglobin was 17·2 g. per 100 ml., leucocytes 10,800 per c.mm. and the differential white cell count normal. Wassermann and Kahn tests were negative, and a glucose tolerance was normal.

Phentolamine Test. After 3 mg. of phentolamine intravenously, the blood pressure fell from 170/100 mm. Hg to 150/50 mm. Hg in eight minutes.

Urine Assay. A 24-hour specimen of urine contained 400 µg. of pressor amine per litre.

Radiography. Under general anaesthesia, combined retroperitoneal air insufflation and angiography was performed and tomogram films taken. No definite conclusion was reached, but the films suggested the possibility of a left adrenal tumour. During angiography, the blood pressure immediately rose to 230/140 mm. Hg. This promptly returned to the previous level when 1 mg. of phentolamine was injected intravenously.

Throughout this period of investigation, the blood pressure remained fairly constant at 160/110 mm. Hg. Oral phentolamine was not given. Cortisone, 25 mg. daily, was given for three days before operation.

Operation. Operation was performed under thiopentone-sodium, gallamine, nitrous oxide and oxygen. The left adrenal gland was exposed via a left trans-thoracic approach following resection of the tenth left rib. The left adrenal gland was normal, so the incision was enlarged and the abdomen then explored. A mass was found infiltrating the left psoas muscle at the junction of the aorta and the left common iliac artery. This mass was removed with difficulty, there being no suggestion of any plane of cleavage.

The blood pressure was controlled in a similar manner to that in Case 1. Blood pressure readings were taken at least every two minutes (Fig. 7).

The post-operative course was complicated by a left lower lobe pneumonia which responded to chemo-
therapy. Following operation the blood pressure rose again to 160/110 mm. Hg, but just before discharge from hospital was 140/100 mm. Hg. In addition the boy had lost his headaches and was much improved. Urinary nor-adrenaline assay before discharge gave a normal value (16 µg. per litre).

Variations in the clinical signs and symptoms will vary with the relative amounts of these substances secreted. Adrenaline is responsible for changes in metabolism but the absence of hyperglycaemia and glycosuria in the above cases supports Cahill’s (1948) contention that these changes are not frequently found in children with phaeochromocytomas. The secretion of nor-adrenaline is responsible for the hypertension with which these children present. From recorded cases, and our two, the hypertension in such children appears to be constant rather than paroxysmal. Although the hypertension in Case 1 had reached the malignant phase, removal of the tumour still resulted in reversion of all signs and symptoms.

The use of phentolamine appears to be safe and affords valuable evidence of the presence of a phaeochromocytoma. Further and conclusive evidence is afforded by analysis of urine for catechol derivatives. This is done by biological assay and, although time consuming, is warranted in such cases. Pre-operative localization of the tumour may be possible as is demonstrated in Case 1 above. Successful localization of adrenal tumours by presacral air injection has been recorded on many occasions. It appears, however, impossible to localize the extra-adrenal phaeochromocytoma pre-operatively and from the recorded cases it is apparent that a high proportion of such tumours in children are situated in sites other than the adrenals. Thus, including our two cases, in six of the 21 children tumours of extra-adrenal chromaffin tissue have been responsible wholly or partly for the hypertension and accompanying symptoms. This differs from the situation in adults where the literature suggests 10–15% of phaeochromocytomas are extra-adrenal (Goldenberg, Snyder and Aranow, 1947: Brines and Jennings, 1948). These tumours were in the retroperitoneal tissue near the adrenals, or intimately associated with the abdominal aorta and vena cava, situations in which chromaffin tissue may normally be found in the foetus or infant (Coupland, 1952; Kohn, quoted by Goldenberg et al., 1947).

Multiple phaeochromocytomas are rare in adults, but in six of these 21 children more than one tumour was present. In one hypertensive child recorded by Hubble (1951) four phaeochromocytomas were found at necropsy. The failure of the blood pressure to return to normal after removal of a phaeochromocytoma necessitated further exploratory surgery in a child reported by Goldenberg et al. (1947). The symptoms subsided after removal of a second chromaffin tumour. The pre-operative use of phentolamine, together with the prevention of the post-operative fall in blood pressure by nor-

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**PATHOLOGY.** The tumour (weight 16 g.) was lobulated, of a uniform red-brown throughout and possessed a fibrous capsule which was incomplete in one area. Portions of tissue were fixed in a similar manner to the preceding case. In histological preparations a varied appearance was seen in different areas of the tumour. The major part presented an appearance similar to that of Case 1, namely, groups of ill-defined cells within fibrous tissue septa. Granules with staining reactions similar to the preceding case were present in these cells, as were the large irregular clear spaces which contributed largely to the difficulty in distinguishing cell boundaries. In a few areas clumps of smaller cells, with darkly staining nuclei and scanty non-vacuolated eosinophilic cytoplasm, were present. These were often arranged in palisade fashion and resembled nerve fibres, of which several well formed examples were present with the tumour. No ganglion cells were seen. No mitotic figures could be detected and there was no extension beyond the fibrous capsule.

The histological diagnosis was phaeochromocytoma. The pressor amine content of the tumour was 740 µg. per g.

**Discussion**

When seeking the cause of hypertension in a child, after excluding renal disease and coarctation of the aorta, it is logical to consider a phaeochromocytoma. Essential hypertension and pink disease remain diagnoses of exclusion.

Clinical features associated with the presence of a phaeochromocytoma are due to the secretion of adrenaline and nor-adrenaline by the tumour cells.

![Chart illustrating the control of blood pressure (Case 2) by the use of 'regitine' and nor-adrenaline during operative removal of the tumour.](chart.png)

(A denotes when tumour was palpated and B when tumour was removed.)

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*Image and text excerpt from a medical journal.*
adrenaline, appears to afford a degree of safety to these exploratory and sometimes repeated operations.

The macroscopic and histological appearance of the tumours removed in our cases conform with previous descriptions. Other authors have emphasized the variable macroscopic appearance, the indistinct outlines of cells grouped within their fibrous septa, and the staining reactions of granules within these cells in tissues which have been fixed rapidly after removal from the body. These granules were not demonstrated in all cells and in those which did contain granules their numbers varied. The staining reactions of the granules as recorded in Case 1, and which were similar in Case 2, are stated by Pearse (1953) to be due to oxidation of adrenaline precursor substances. As other cytoplasmic constituents may be oxidized with similar colour changes these reactions cannot be regarded as chemically specific for adrenaline, although their presence is usually regarded as characteristic of chromaffin tissue.

Malignant chromaffin tumours are rare and Willis (1953) doubts the accuracy of diagnosis of many tumours recorded as such. McGavack, Benjamin, Speer and Klotz (1942) present evidence of a malignant tumour of the adrenal medulla in a woman who died with numerous metastatic deposits. They accept seven other recorded cases as fulfilling the criteria for diagnosis of a malignant phaeochromocytoma. No such case has been recorded in childhood if, as suggested by these authors, the metastatic spread of tumours with a positive chromaffin reaction is used as the criterion of malignancy.

Summary

The clinical notes of two children with hypertension due to a phaeochromocytoma are reported. The main symptoms were severe sweating and headaches.

Remission of the hypertension and accompanying symptoms followed successful surgical removal of the tumours.

The tumours had the histological structure of phaeochromocytomas and biological assay of portions of both revealed a high nor-adrenaline content.

The value of phentolamine ('regitine') in the diagnosis of a phaeochromocytoma, and in controlling hypertension during the removal of such a tumour is illustrated.

The estimations of nor-adrenaline in urine and in tumour tissue were performed at the Baker Research Institute, Alfred Hospital, Melbourne. We express our gratitude to Dr. A. J. Barnett and Dr. G. A. Bentley of this Institute. For permission to record these cases we would like to thank Dr. R. Southby, Dr. S. W. Williams (physicians), Mr. J. G. Whitaker, Mr. R. N. Howard (surgeons), and Dr. M. McClelland (anaesthetist), who, as members of the senior medical staff of the Royal Children's Hospital, were responsible for the care of these children.

Addendum

Since the preparation of this paper the use of phentolamine in the diagnosis and management of phaeochromocytoma has been discussed by Helps et al. (Lancet, 2, 267, 1955).

In the same issue of this journal Richardson et al. record the reversal of malignant hypertension due to ectopic phaeochromocytoma, and Davis et al. describe a malignant phaeochromocytoma with functioning metastases.

References

Roux (1926). These, Lausanne. Quoted by Daeschner et al.