SIX CASES OF PHAEOCHROMOCYTOMA WITH UNUSUAL CLINICAL MANIFESTATIONS

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Phaeochromocytoma was described by De Courcy (1953) as "the great mimic" because it could present in many ways. This paper describes six cases in which the clinical features were unusual. In three the symptoms suggested primary renal disease. Persistent fever, episodes of profound shock, and convulsions with papilloedema were other misleading symptoms.

Case 1

A farmer aged 46 had been well until August, 1959, when he began to have attacks lasting from half an hour to three days in which he sweated profusely, his hands and feet felt cold, and he shivered. Sometimes exertion precipitated an attack. Afterwards there might be diarrhoea, frontal headache, and a feeling of weakness. There were no palpitations or feelings of anxiety.

On October 1 he had a severe attack of sweating and vomiting and lost consciousness. He was admitted to another hospital as an emergency case. He was stuporous and sweated profusely. Pulse rate was 60 and systolic blood-pressure 70 mm. Hg. The fundi were normal. There were rales at the lung bases.

Several hours later the B.P. rose to 190/130, and after a further half an hour was 200/160. The next day he was still drowsy. There was sweating over the forehead and trunk; the extremities were cold, cyanosed, and moist. The B.P. remained 190/140, the pulse rate had risen to 140, and a gallop rhythm was present over the praecordium. On October 3 the head and neck had become an intense plum colour. Next day he coughed up about 1 pint (570 ml.) of bloody fluid. A chest radiograph taken the same day revealed changes compatible with inhaled blood, a film four days later was normal, and in retrospect it seems that this was an episode of acute pulmonary oedema.

The urine on admission contained much albumin with moderate numbers of red and white blood cells, and a few hyaline and granular casts in the centrifuged deposit. These abnormalities decreased, and by October 19 the urine was normal. The blood urea on admission was 82 mg./100 ml. and two days later 85 mg., but it fell to 29 mg. by October 19. Excretory urography was then normal.

The patient steadily improved, being discharged home on October 22 symptom-free, the blood-pressure having fallen to 180/110.

He was seen periodically in the out-patient department, and remained symptom-free. On January 22, 1960, the B.P. was 200/120 and urinalysis revealed a trace of albumin. The blood urea was 30 mg./100 ml.; Hb 100%.

On February 27 he was readmitted complaining of frontal headache, recent deterioration in vision, and the passing of very little urine for several days. He complained of coldness of the extremities, and had vomited small amounts of fluid. He was sweating, and the facies was again of a striking red parboiled hue; this colour persisted for several days. The pulse rate was 80; the B.P. 100/80. Forty-eight hours after admission the B.P. had risen to 210/130 and remained high.

No urine was voided during the first 12 hours in hospital. Next day 880 ml. was passed (specific gravity 1015) and the output increased steadily until three days after admission, when 3,700 ml. was passed. After this the urinary output fell to normal. On admission the urine contained much albumin and numerous hyaline and granular casts, and a few red blood cells were present in the centrifuged deposit. The albuminuria rapidly decreased, and two days later only a trace was present. The haemoglobin level two days after admission was 130% with a red blood cell count of 6,300,000 c.mm. Blood urea on admission was 125 mg./100 ml., next day 290 mg., and on March 3 (five days after admission) 170 mg.

A diagnosis of phaeochromocytoma was made. Intravenous phentolamine caused a fall in B.P. from 210/120 to 160/80 in 30 seconds; it rose again to 230/120 within three minutes. He was transferred to the Bristol Royal Infirmary on March 5. On admission his appearance was unchanged; the legs were cyanosed and cold, and a small ischaemic ulcer was present on the right fourth toe. B.P. was 250/170. The optic fundi were normal.

Investigations.—Hb 101%; E.S.R. 18 mm. in first hour; plasma non-protein nitrogen (N.P.N.) 112 mg./100 ml. Catechol amine excretion was 3,600 μg./24 hours (normal, less than 180 μg./24 hours). Perirenal insufflation of carbon dioxide (March 11) revealed a large right suprarenal mass. On March 9 he had a fit, with sweating and pale cold extremities. The B.P. was too high to record, but 20 minutes later was 280/180. Phentolamine 5 mg. intravenously reduced the B.P. to 120/80 in eight minutes, but 15 minutes later it had risen to 180/110. Subsequently the B.P. level was controlled by phenoxybenzamine 10 mg. intramuscularly three-hourly. On March 15 a laparotomy was performed and the right adrenal gland, which contained a tumour weighing 130 g., was removed. Histologically the tumour was typical of a phaeochromocytoma.

Noradrenaline and hydrocortisone were given for 24 hours after the operation. On the day of operation the patient received a transfusion of 1 pint (570 ml.) of blood. On the first post-operative day the Hb was 49% and 2 pints (1,140 ml.) of packed cells was given, followed by a further 2 pints on March 18. On April 7 the Hb was 73%. There was no evidence of heavy loss of blood at operation or of bleeding afterwards. The B.P. was 170/100 on discharge from hospital, and the ischaemic ulcer on the toe had healed. The blood urea was 44 mg./100 ml.

The patient has been followed up in the out-patient department of the Royal Cornwall Infirmary for 18 months since operation and has remained symptom-free. The B.P. varies between 200/120 and 190/100. The urine contains a trace of albumin but no granular casts. The blood urea is normal.

Case 2

A 48-year-old carpenter was admitted to hospital as an emergency case on October 3, 1959. Three days previously he woke with a severe headache. He had sweated, felt feverish, and later began to vomit; vomiting continued until admission. During the two days before admission the urine was scanty and a dark orange-red colour.

On admission he was ill, pale, and sweating, but fully alert. Temperature 99.6° F. (37.6° C.), pulse 128 and regular. The B.P. was 200/150. The heart sounds were normal and there was no heart failure. Several soft exudates were seen in the fundi.

Next day he became drowsy and euphoric and the temperature rose to 103.4° F. (39.7° C.). He remained very ill for the next three days, the pulse being 120 to 150, and the B.P. varying between 130/110 and 170/130. On

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the third day in hospital a striking plethora of the head and neck was noted.

For the first two days urine flow was scanty, the volumes being 580 and 650 ml. for 24 hours. It contained 2 g. of albumin per litre and there were 30–40 granular and hyaline casts per low-power field. Culture was sterile. On the third day 1,150 ml. of urine was passed and a moderate diuresis followed, the maximum volume being 3,580 ml. six days after admission. The albuminuria decreased to 0.25 g./litre on the third day in hospital, and thereafter varied from 0 to 0.5 g./litre. The first specimen of urine examined contained 0.5 g. of sugar and occasionally 0.25 g./100 ml. afterwards.

Hb was 128% ; the white count and E.S.R. were normal. The plasma non-protein nitrogen was 193 mg./100 ml. two days after admission. The plasma sodium, potassium, chloride, and bicarbonate were within the normal range. The plasma non-protein nitrogen and haemoglobin levels fell steadily during the first 14 days in hospital (Table I).

TABLE I.—*Haemoglobin and Plasma Non-protein Nitrogen Levels in Case 2 After First Admission to Hospital*

	Haemoglobin (%)	Plasma Non-protein Nitrogen (mg. 100 ml.)
Day of admission ..	128	—
3rd day	—	193
4th ,, ...	126	214
5th ,, ...	110	172
10th ,, ...	98	53
14th ,, ...	88	31

A diagnosis was made of acute renal failure secondary to pyelonephritis. He was given penicillin (1 mega unit six-hourly) and streptomycin (0.5 g. twice weekly) for 10 days ; the pyrexia persisted and so sulphafurazole was substituted ; later a course of nitrofurantoin was given. The pyrexia was unaffected likewise by this, but gradually settled spontaneously six weeks after admission.

The B.P. was labile, varying between 160/90 and 190/140 throughout the stay in hospital. Renal function continued to improve, and before discharge the specific gravity rose to 1025 during a water-deprivation test. He left hospital on November 20.

On December 21 he was symptom-free. The B.P. was 190/120, the urine normal. In March, 1960, however, he had developed angina on effort. He was pale ; there was an atrial gallop and the B.P. was 220/160. The optic fundi were normal. He was readmitted on April 10 for further investigation. Half-hourly B.P. measurements made over 24 hours with an automatic B.P. recorder (Davies and Shaw, 1962) showed that the systolic pressure varied between 160 and 220, and the diastolic between 110 and 140. An electrocardiogram showed changes of left ventricular hypertrophy. Intravenous pyelography was normal, blood urea 20 mg./100 ml., and urea clearance 81% of normal function. Treatment with bretylium and chlorothiazide led to a slight fall in B.P.

A pyrogen test for pyelonephritis (Pears and Houghton, 1958) was carried out and was negative, so a phaeochromocytoma was suspected. A 24-hour specimen of urine contained 6,000 μg. of catechol amines. Bretylium was then stopped and a second estimation was 5,300 μg./24 hours. Phentolamine (5 mg. intravenously) resulted in a fall in B.P. from 215/130 to 170/110 within three minutes.

On direct questioning the patient then admitted episodes of headache, palpitations, and pallor. He explained that he had attended hospital for these symptoms in 1948. No abnormality had been found on examination, and the B.P. was 140/90. He had been reassured convincingly, and he accepted the symptoms as part of his normal life and so had never complained of them again.

A retroperitoneal insufflation with carbon dioxide was undertaken on May 26 to confirm side of the tumour. *X*-ray films of the renal areas showed enlargement of the right suprarenal gland—about 2 by 1½ in. (5 by 3.8 cm.). A prophylactic dose of 5 mg. of phentolamine was given beforehand. However, on return to the ward after this procedure the patient was pale and sweating, the pulse was rapid, and the B.P. 230/155. After a further dose of phentolamine (5 mg. intravenously) the B.P. fell to 190/145 ; by next morning it had risen to 280/180, so he was given phentolamine 20 mg. t.d.s. orally and phenoxybenzamine 10 mg. three-hourly orally. On this the B.P. stayed between 150 and 200 systolic and 115 and 150 diastolic. Phenoxybenzamine alone was given four-hourly next day and six-hourly for the next two days.

Before this hypertensive attack the urinary output had varied from 1,100 to 2,100 ml./day, usually being about 1,500 ml. On the day of the hypertensive attack the output was 1,000 ml., on the following day 700 ml., and it then increased to 1,000 to 1,300 ml. a day for three days, 1,800 ml. on the fifth day, and 4,200 ml. on the sixth day after the attack. No albuminuria was present before the carbon dioxide insufflation, but within 24 hours the urine contained much albumin, and there were red and white blood cells and granular casts in the deposit. The urinary abnormalities were transitory, the albuminuria being reduced to a trace in two days and the casts disappearing after a week.

On the morning after the hypertensive attack began the patient felt ill, and that evening vomited about a pint (570 ml.) of fluid which contained some altered blood. Next day the complexion changed from a deathly pallor to dark red in colour, and this persisted for two days.

The plasma N.P.N. and haemoglobin levels rose after the crisis, and large volumes of fluid (3.5–4 l. daily) were given both orally and intravenously. The levels are shown in Table II.

TABLE II.—*Haemoglobin and Plasma Non-protein Nitrogen Levels in Case 2 After Hypertensive Crisis During Second Admission to Hospital*

	Haemoglobin (%)	Plasma N P.N. (mg. 100 ml.)
Before crisis	100	20
1 day after crisis ..	140	77
3 days ,, ,, ..	125	57
6 ,, ,, ,, ..	90	30

The phaechromocytoma was removed 10 days after the hypertensive crisis. When the tumour was isolated from the circulation there was a marked fall in B.P., which was controlled by transfusing blood and noradrenaline. Noradrenaline infusions were stopped next day and the B.P. remained approximately 140/90.

The urinary catechol amines were normal both four days and four months after operation (60 and 30 μg./24 hours), as were the blood urea and urinalysis. The B.P. rose after discharge from hospital, and was 190/110 in the outpatient department on July 20, and again in October, 1960.

The tumour was 5 by 2.5 cm. in section, weighed 26 g., and was yellow-brown in colour with small haemorrhagic areas. On histological examination it was typical of a phaeochromocytoma.

Case 3

A housewife aged 22 had acute nephritis at 5 years of age. At 19, in her first pregnancy, she developed hypertension, and a caesarean section was performed at 32 weeks. The child was stillborn. Two miscarriages at three months during the next year led to a trachelorrhaphy. At this time the B.P. was 115/60. Shortly afterwards the fourth pregnancy began, and the B.P. was again raised. She was kept in bed from 24 to 37 weeks, when a caesarean section was successfully carried out, a live male child being delivered.

After the delivery the hypertension persisted (diastolic pressure 130–150 mm. Hg). Investigations revealed no albuminuria, deposit normal, and culture sterile. Urinary output of W.B.C.s 160,000/hour, with no rise after intra-

venous pyrogen. Maximum urine concentration 1027, blood urea 30 mg./100 ml., intravenous and retrograde pyelography normal.

Renal biopsy showed slight hypertensive changes in arteries, but no other abnormality. Catechol amine excretion was below 50 μg./24 hours (four specimens examined). A diagnosis was made of latent glomerulonephritis after the episode of acute nephritis in childhood.

Bretylium (up to 300 mg. t.d.s.) had little effect. On guanethidine 10 mg. daily the B.P. was usually 120/85.

In November, 1960, the fifth pregnancy began, and at the third month the B.P. was again 170/130 and albuminuria was present. She was admitted to hospital for termination of pregnancy and sterilization, which were duly carried out. On her return to the ward she became cold, pale, and sweated, and the systolic pressure fell to 60 mm. Hg. The pulse was 120 and regular. A gradual improvement followed transfusion of 2 pints (1,140 ml.) of blood.

This post-operative collapse once again raised the suspicion of a phaeochromocytoma. Repeated catechol amine excretions were 360, 540, 1,140, 1,440 μg./24 hours. Two estimations of vanilmandelic acid (3-methoxy-4-hydroxy-mandelic acid) excretion were 18 and 19 mg./24 hours. Urinary catechol amines assayed biologically were 1 μg./ml., of which 80% was adrenaline.

At laparotomy an ectopic phaeochromocytoma the size of a small hen's egg was removed. Its site was to the right of the midline and below the level of the right adrenal gland. The main drainage vein crossed the midline and entered the left renal vein. Both adrenal glands were normal in appearance.

Blood-volume studies were carried out eight days before and 13 days after removal of the phaeochromocytoma. At operation about 300 ml. of blood in excess of the estimated loss had been transfused. Red-cell volume was measured by tagging with ^{51}Cr and plasma volume by Evans blue dye. The results are shown in Table III and discussed below.

TABLE III.—*Blood-volume Studies in Case 3 Before and After Removal of Phaeochromocytoma*

	Before Operation	After Operation
Total blood volume ..	3·03 litres	3·47 litres
Red blood cell volume ..	1·11 ,,	1·34 ,,
Plasma volume ..	1·92 ,,	2·13 ,,
Total body haematocrit	36·6%	38·6%
Venous haematocrit ..	42·7% (corrected for trapped plasma)	40·8%
Ratio total body/venous haematocrit	0·86	0·945

Occasional palpitations over the three years with possibly a tendency to sweat unduly had been the only symptoms suggestive of a phaeochromocytoma. In keeping with the presence of such a tumour was a loss of 2 stone (12.7 kg.) in weight over the previous two years.

Case 4

A housewife aged 48 had suffered from attacks of abdominal pain, headache, and vomiting for several months. She was admitted to hospital as an emergency case three days after the onset of one of these attacks. On admission she was pale and looked ill. There was slight tenderness in the right hypochondrium. The pulse was 100, B.P. 120/80; a few rales were present at the right base. Her general condition improved but vomiting continued intermittently. A cholecystogram revealed several small gall-stones, and a cholecystectomy was carried out two weeks after admission. The gall-bladder contained a few small stones but the wall was not grossly thickened.

After operation vomiting continued intermittently, and six days post-operatively she broke out in a cold sweat. The B.P. was 220/110, pulse 140 and regular. She then stated that she had had many similar attacks, sometimes associated with asthma and blood-stained frothy sputum. Nine hours after this attack the B.P. fell to 90/50.

A few days later a similar attack of palpitation, sweating, and vomiting occurred shortly after a meal. The pulse was 180 and regular, B.P. 190/110. After phentolamine 3 mg. intravenously the B.P. fell within two minutes to 100/70.

On October 25, 1955, Mr. W. M. Capper removed a left adrenal tumour via a transverse upper abdominal incision. The tumour weighed 22.5 g. and was typical of a phaeochromocytoma histologically. On bioassay the noradrenaline content was 100.6 μg./g.

After operation a noradrenaline drip was maintained for 48 hours. Convalescence was interrupted by the development of a left pleural effusion. On discharge from hospital she was symptom-free, B.P. normal.

Four years later she was well, B.P. 155/80.

Case 5

A youth of 15 sustained a fractured skull in a road accident at the age of 4 years, and had been unconscious for 17 days. There were no sequelae. At 10 years of age he developed fainting attacks and nocturnal restlessness, for which he was referred for a neurological opinion. No physical abnormality was found. At 12 years of age a severe iron-deficiency anaemia associated with splenomegaly responded to treatment with oral iron. Since that time he had noted excessive sweating, polydipsia, and polyuria.

In May, 1956, at the age of 15, he began to have severe frontal headaches, more severe on the right side and lasting from one to several hours. The attacks were sometimes associated with vomiting, and on one occasion two months after the onset he had two left-sided convulsions associated with incontinence of urine.

On admission to hospital following these fits he was conscious though lethargic. The B.P. was 190/140, and no abnormality was detected in the central nervous system. The cerebrospinal fluid was clear and the pressure 130 mm. of water. The protein content was 95 mg./100 ml., cell count normal. Ten days later there was a further left-sided fit, and papilloedema was noted on the right. A cerebral tumour was suspected, and he was transferred to a neurosurgical unit. Relevant clinical findings were B.P. 240/190, pulse 140 and regular, bilateral papilloedema with venous engorgement and marked arterial spasm, no haemorrhages or exudates. Right sixth-nerve palsy, with slight left sixth-nerve weakness was noted. Ventriculography revealed no significant abnormality.

The patient's general condition began to deteriorate, and he became apathetic, lethargic, and cachectic. The B.P. remained between 235/200 and 180/150, and pulse between 120 and 140. A gallop rhythm was noted. Frequently he broke out into a sweat. A macular star was now present in the right eye.

A 24-hour sample of urine was found to contain 3,000 μg. of noradrenaline by biological assay. He was transferred to the Bristol Royal Infirmary, and at laparotomy a tumour was found in the left adrenal weighing 35 g. Analysis revealed 880 μg. of noradrenaline and 66 μg. of adrenaline per g. of tumour tissue.

After operation noradrenaline was given by intravenous drip for several hours. The B.P. then remained approximately 130/110 for several days, falling to 120/95 after 14 days. The polydipsia and polyuria disappeared after operation.

At follow-up four months later he looked well and had gained 2 stone (12.7 kg.). The visual acuity had improved. On *x*-ray examination the heart was smaller and there was less evidence of L.V. strain on the electrocardiogram. Extensive fine exudates were present, mainly in the right fundus; the disks were normal. B.P. was 120/65. Urinary noradrenaline excretion was normal. Four years later vanilmandelic acid excretion was 1.8 mg./24 hours.

Case 6

A housewife of 29 years had had three normal pregnancies. At the 12th week of her fourth pregnancy the B.P. was 120/80. In the fourth month of pregnancy she developed severe headaches and sweating attacks, and, later, blurring of vision. When next seen by her doctor at the sixth month the B.P. was 180/140, and she was sent into hospital. On admission the size of the uterus corresponded with a 24-weeks pregnancy. There was no oedema, albuminuria, or glycosuria. The fundi showed papilloedema, haemorrhages, and exudates. The pulse was 128 and regular, B.P. 180/130, and blood urea 15 mg./100 ml.

A diagnosis of toxaemia of pregnancy was made, and treatment with amylobarbitone and later mecamylamine was started. On mecamylamine (1.25 g. daily) the average B.P. was 140/100. Postural hypotension developed and more sweating. A phaeochromocytoma was then suspected, and phentolamine (5 mg. intravenously) led to a fall of B.P. from 150/120 to 70/50 within four minutes. Excretion of catechol amine was 5.5 mg./24 hours. A perirenal insufflation of air demonstrated a rounded shadow above the left kidney. Next day the patient developed acute pulmonary oedema. Four days later at laparotomy a phaeochromocytoma of the left adrenal gland was removed. The B.P. thereafter remained between 110/78 and 140/100. She went into labour spontaneously at 35 weeks, and was delivered of a live female child weighing 5 lb. 4 oz. (2,380 g.). At follow-up examination six months after delivery the B.P. was 125/80. Visual acuity was normal, but many retinal scars remained. (This case has been fully reported by Bennett and Mather (1959).)

Discussion

Phaeochromocytoma classically presents with attacks of hypertension associated with pallor, sweating, tachycardia, and vomiting. One or more of these features were present in each of the six cases; sweating was common to them all and in several led to the correct diagnosis. However, in the cases reported here other symptoms were also present, and these led to initial diagnoses of gall-stone colic, toxaemia of pregnancy, cerebral tumour, glomerulonephritis, and renal failure attributed to chronic nephritis and chronic pyelonephritis. It is of interest to consider how some of these symptoms may have been produced.

Interference with Kidney Function

Urinary abnormalities and changes in renal function in phaeochromocytoma are well recorded. Howard and Barker (1937) found albuminuria in 9 out of 18 cases, and Green (1946), in a review of 37 cases of phaeochromocytoma with persistent hypertension, found altered renal function in 24, and in 2 of these there was a raised blood urea. After operation renal function usually improved. There may be retention of urine (Baird and Cohen, 1954), and other cases have been mistakenly diagnosed as chronic nephritis (Kremer, 1936; Fertig, Taylor, Corcoran, and Page, 1951). In one of the earliest records of phaeochromocytoma (Labbé, Tinel, and Doumer, 1922) there were episodes of oliguria, albuminuria, and renal failure following hypertensive attacks similar to those described in our Cases 1 and 2. Complete renal failure, however, seems to be uncommon in phaeochromocytoma because Graham (1951) recorded death in uraemia in only 3 out of 207 cases reviewed.

Uraemia in subjects with phaeochromocytoma and persistent hypertension can be due to nephrosclerosis. In the acute hypertensive attack, dehydration associated with vomiting may also result in uraemia (Pickering, 1955). Neither of these explanations is satisfactory in the two cases reported here. Thus nephrosclerosis (though possibly present) could not alone account for the profound changes in renal function, because both our patients recovered completely. In Case 1 dehydration from vomiting may have contributed to the oliguria and uraemia but could not have caused the heavy albuminuria. In Case 2 dehydration was not the cause of the uraemia, because before the patient's first admission his vomiting, though frequent, had been of small amounts and he was not dehydrated. Moreover, in his second attack of uraemia he vomited little more than 1 pint (570 ml.).

The probable explanation of these episodes of renal failure is the effect that noradrenaline and adrenaline are known to have on kidney function. Richards and Plant (1922) found that adrenaline perfused through a rabbit's kidney led to a rise in perfusion pressure and to swelling of the kidney. They attributed these observations to efferent arteriolar constriction. This mechanism was demonstrated in man by Chasis, Ranges, Goldring, and Smith (1938), who found that adrenaline caused a fall in renal plasma flow with a rise in filtration fraction. Similar observations have since been made by others (Ranges and Bradley, 1943; Churchill-Davidson, Wylie, Miles, and de Wardener, 1951; Berne, Hoffman, Kagan, and Levy, 1952; Moyer and Handley, 1952). Moyer and Handley also noted that as the rate of infusion was increased there was a further fall in renal plasma flow, glomerular filtration rate, and maximum tubular reabsorption of glucose, which they attributed to the exclusion from the circulation of entire nephrons. Likewise, in dogs, Corday and Williams (1960) found evidence of a renal "shut-down." In phaeochromocytoma Wilkins, Greer, Culbertson, Halperin, Litter, Burnett, and Smithwick (1950) demonstrated a reduction in renal plasma flow in a hypertensive attack, and Van Epps, Hyndman, and Greene (1940) recorded a fall in urea clearance from 90% to 53% during a similar episode.

In our Cases 1 and 2 the attacks of oliguria and uraemia occurred during hypertensive crises, and it would therefore seem that they were caused by noradrenaline and adrenaline released from the tumour. Such a mechanism would account for the reversibility of the renal failure and the transient albuminuria (Starr, 1926; Chesley, Markowitz, and Wetchler, 1939). If renal vasoconstriction persists long enough the tubules may become necrotic; it is possible that this occurred in Case 2 during the first episode of oliguria in view of the subsequent diuresis.

Changes in Blood Volume

The high haemoglobin levels observed during hypertensive episodes may likewise be explained on the basis of the effects of noradrenaline and adrenaline on the circulation. Thus Kaltreider, Meneely, and Allen (1942) and Finnerty, Buchholz, and Guillaudeu (1958) have shown that these substances cause a contraction in plasma volume and an increase in the venous haematocrit. The rapidity with which the haemoglobin rose in Case 2 (from below normal to 140% within 24 hours of the onset of a hypertensive attack) suggests such a decrease in plasma volume.

Plethora of the head and neck, observed during the hypertensive attacks in Cases 1 and 2, has previously

been described (Labbé *et al.*, 1922). Graham (1951) and Pickering (1955) pointed out that flushing of the skin may occur after hypertensive attacks. Lever, Mowbray, and Peart (1961) have shown in man that a transient increase in skin blood flow occurs at the end of a noradrenaline infusion and coincides with a flush of the skin which is often seen at this time. It seems possible that such an increase in skin blood flow, together with the high venous haematocrit present at the same time, was responsible in these patients for their intense facial rubor. Plethora was noted in both cases in which interference in renal function was observed. In the case reported by Labbé *et al.* similar changes in renal function were associated with such a plethora.

Post-operative Shock

Post-operative shock following removal of the tumour is usually attributed to the sudden deprivation of vasoconstrictor substances. However, Brunjes, Johns, and Crane (1960) have suggested that post-operative shock in phaeochromocytoma is due to a chronic decrease in blood volume resulting from the prolonged effect of vasoconstriction. Pre-operatively in two cases they found a diminution in total blood volume due to a reduction in red-cell volume. They also found a reduction in the ratio of total body haematocrit : venous haematocrit reading to 0.68 and 0.77 (normal 0.91). This they attribute to the effect of widespread vasoconstriction, with a resultant increase in the number of small vessels in which the haematocrit level is lower, as first suggested by Hahn, Bale, and Bonner (1942). After operation the blood volume and haematocrit ratio returned to normal. Brunjes *et al.* suggest that with the release of vasoconstrictor tone at operation the chronic reduction in blood volume is unmasked and causes the oligaemic shock to appear. They further suggest that treatment of this shock by blood transfusion is more rational than by further infusion of noradrenaline.

Blood-volume studies were carried out in only one patient in this series (Case 3). At operation the amount of blood transfused was 300 ml. in excess of estimated loss ; the measured blood volume rose by 440 ml. above the pre-operative level, with an increase in both the plasma volume and red-cell volume. The ratio of total body haematocrit : venous haematocrit rose from 0.86 to 0.945. These changes after operation are much less than those noted by Brunjes *et al.* ; in our patient, however, excretion of catchol amines was less than in other cases. Further studies of alterations in blood volume before and after operation are necessary to guide us in the proper management of post-operative shock in these cases.

Hypotensive Attacks

Hypotensive attacks may occur in phaeochromocytoma apart from that after operation. Usually these attacks follow an episode of hypertension (as in Case 4), but occasionally a patient may present in a state of severe shock (as in Case 1) or become severely shocked after admission to hospital, having previously been normotensive. Such cases present much difficulty in diagnosis and may be mistaken for cardiac or abdominal catastrophes (Gilliland and Daniel, 1951 ; Jelliffe, 1952). Occasionally the blood-pressure level fluctuates widely, and in the case recorded by Terry, Tobin, and O'Connor (1958) varied between 290/140 and 80/0 many times within 24 hours and was controlled only by a continuous infusion of phentolamine.

Hypotension may be associated with infusions of noradrenaline ; thus Blacket, Pickering, and Wilson (1950) showed in the rabbit that hypotension occurred after continuous infusion of L-adrenaline and L-noradrenaline, and Green *et al.* (1948) reported hypotension after a long infusion of adrenaline in man. Likewise Lever *et al.* (1961) found in man, dogs, and rabbits that during an intravenous infusion of noradrenaline for one to two hours an initial rise in blood-pressure was followed by a decline during the infusion and a fall below the baseline after the infusion had been stopped. They thought that the production of a circulating vasodilator substance was the most likely explanation of these findings. It seems more than likely that the hypotensive episodes which occur in the course of phaeochromocytoma are of a similar nature.

Fever

Pyrexia may be a feature of phaeochromocytoma and was present at some time in two of the cases in the present series. In Case 2 the fever was continuous and rose to 103° F. (39.4° C.). Occurring together with renal failure, it was wrongly attributed to pyelonephritis and led to a delay in the correct diagnosis.

Metabolic Effects

Patients with phaeochromocytoma are often thin. The average weight of 23 of the 24 patients with phaeochromocytoma and persistent hypertension reported by Kvale, Roth, Manger, and Priestley (1957) was 121.8 lb. (55.3 kg.), and 11 of these weighed under 113 lb. (51.3 kg.). Patients with paroxysmal hypertension in the same series were also usually thin but not as thin as patients in whom hypertension was persistent. In commenting on their 50 cases the authors state that " the tumours seem to be peculiar to thin people especially those with persistent hypertension," and, in referring to the low weight of the group with persistent hypertension : " this seems to exclude the obviously obese patient with hypertension, for to our knowledge phaeochromocytomas are not likely to occur in this group." In our Cases 1, 3, and 5 the patients had lost weight and Cases 1 and 5 were even gaunt and cachectic. In Case 2, however, the patient weighed 135 lb. (61.2 kg.) and was moderately obese. Thus the association of phaeochromocytoma, obesity, and persistent hypertension may occasionally occur.

Diabetes is present in 10% of cases, and a further 9% have a reduced glucose tolerance (Freedman, Moulton, Rosenheim, Spencer, and Willoughby, 1958). When glycosuria is accompanied by weight loss, tachycardia, sweating, and anxiety the resemblance to thyrotoxicosis may be close. In this series only one patient (Case 2) had glycosuria.

Diagnostic Investigations

Various pharmacological tests are available for confirming the presence of a phaeochromocytoma. Intravenous phentolamine for patients with persistent hypertension, and histamine stimulation with subsequent phentolamine administration for those with a normal pressure, are useful screening tests (Roth, Flock, Kvale, Waugh, and Ogg, 1960). However, false-positive and false-negative results occur in a variety of circumstances, and, moreover, the histamine provocation test may induce dangerously high blood-pressure. An increase in urinary catechol amine excretion (Engel and von Euler, 1950 ; Burn, 1953) is of great diagnostic

value; however, normal levels of excretion have been recorded in the presence of a phaeochromocytoma (Litchfield and Peart, 1956) and in our Case 3 excretion in four 24-hour samples was normal two years before the diagnosis was finally established. Vanilmandelic acid excretion may possibly have been increased at this time, but facilities for its estimation were not then available. Increased excretion of this metabolite has been reported in phaeochromocytoma in the presence of normal catechol amine excretion (Sandler and Ruthven 1960; Gitlow, Mendlowitz, Khassis, Cohen, and Sha, 1960).

Perirenal insufflation with air or carbon dioxide has been used to locate the phaeochromocytoma. However, in two of our cases in which this investigation was performed dangerous hypertensive crises followed shortly afterwards. It is doubtful, therefore, whether the information gained by this procedure outweighs the risk it entails.

At operation a transverse upper abdominal incision enables both adrenals to be readily explored and the incision can then be prolonged to either side, depending on the site in which the tumour is found.

Summary

Six cases of phaeochromocytoma are described. In three the picture suggested primary renal disease; in the others toxaemia of pregnancy, gall-stone colic, and cerebral tumour were initially diagnosed. Weight loss, fever, vomiting, hypotensive episodes, facial plethora, and post-operative oligaemic shock are among other features encountered.

Interference with renal function in phaeochromocytoma is discussed, and it seems likely that this is due to the high level of circulating vasoconstrictor substances.

In one case urinary catechol amine excretion was at first within the normal range.

Perirenal insufflation with air or carbon dioxide as a means of locating the tumour proved a danger to life in two patients.

Four of the six patients were transferred to the Bristol Royal Infirmary from other hospitals; in spite of the perplexing symptoms in all of these four cases the diagnosis of phaeochromocytoma was made before admission to this hospital. We are grateful to Dr. J. D. Hardy, of the Royal Cornwall Infirmary, Truro; Dr. Gordon Mather, of Southmead Hospital, Bristol; and Dr. D. H. Davies and Mr. W. M. Capper, of the United Bristol Hospitals, for permission to publish cases under their care.

REFERENCES

Baird, I. McL., and Cohen, H. (1954). *Lancet*, **2**, 270.
Bennett, M., and Mather, G. (1959). Ibid., **1**, 811.
Berne, R. M., Hoffman, W. K., Kagan, A., and Levy, M. N. (1952). *Amer. J. Physiol.*, **171**, 564.
Blacket, R. B., Pickering, G. W., and Wilson, G. M. (1950). *Clin. Sci.*, **9**, 247.
Brunjes, S., Johns, V. J., and Crane, M. G. (1960). *New Engl. J. Med.*, **262**, 393.
Burn, G. P. (1953). *Brit. med. J.*, **1**, 697.
Chasis, H., Ranges, H. A., Goldring, W., and Smith, H. W. (1938) *J. clin. Invest.*, **17**, 683.
Chesley, L. C., Markowitz, I., and Wetchler, B. B. (1939). Ibid., **18**, 51
Churchill-Davidson, H. C., Wylie, W. D., Miles, B. E., and de Wardener, H. E. (1951). *Lancet*, **2**, 803.
Corday, E., and Williams, J. H. (1960). *Amer. J. Med.*, **29**, 228.
De Courcy, J. L. (1953). *Amer. J. Surg.*, **86**, 37.
Davies, D H., and Shaw, D. B. (1962). In preparation.
Engel, A., and von Euler, U. S. (1950). *Lancet*, **2**, 387.
Fertig, H. H., Taylor, R. D., Corcoran, A. C., and Page, I. H. (1951). *Ann. intern. Med.*, **35**, 1358.
Finnerty, F. A., Buchholz, J. H., and Guillaudeu, R. L. (1958). *J. clin. Invest.*, **37**, 425.
Freedman, P., Moulton, R., Rosenheim, M. L., Spencer, A. G., and Willoughby, D. A. (1958). *Quart. J. Med.*, **27**, 307.
Gilliland, I. C., and Daniel, O. (1951). *Brit. med. J.*, **2**, 275.
Gitlow, S. E., Mendlowitz, M., Khassis, S., Cohen, G., and Sha, J. (1960). *J. clin. Invest.*, **39**, 221.
Graham, J. B. (1951). *Int. Abst. Surg.*, **92**, 105.
Green, D. M. (1946). *J. Amer. med. Ass.*, **131**, 1260.
—— Johnson, A. D., Lobb, A., and Cusick, G. (1948). *J. Lab. clin. Med.*, **33**, 332.
Hahn, P. F., Bale, W. F., and Bonner, J. F. (1942). *Amer. J. Physiol.*, **137**, 717.
Howard, J. E., and Barker, W. H. (1937). *Bull. Johns Hopk. Hosp.*, **61**, 371.
Jolliffe, R. S. (1952). *Brit. med. J.*, **2**, 76.
Kaltreider, N. L., Meneely, G. R., and Allen, J. R. (1942). *J. clin. Invest.*, **21**, 339.
Kremer, D. N. (1936). *Arch. intern. Med.*, **57**, 999.
Kvale, W. F., Roth, G. M., Manger, W. M., and Priestley, J. T. (1957) *J Amer. med. Ass.*, **164**, 854.
Labbé, M., Tinel, J., and Doumer (1922). *Bull. Soc. méd. Hôp. Paris*, **46**, 982.
Lever, A. F., Mowbray, J. F., and Peart, W. S. (1961). *Clin. Sci.*, **21**, 69.
Litchfield, J. W., and Peart, W. S. (1956). *Lancet*, **2**, 1283.
Moyer, J. H., and Handley, C. A. (1952). *Circulation*, **5**, 91.
Pears, M. A., and Houghton, B. J. (1958). *Lancet*, **2**, 128.
Pickering, G. W. (1955). *High Blood Pressure*. Churchill, London.
Ranges, H. A., and Bradley, S. E. (1943). *J. clin. Invest.*, **22**, 687.
Richards, A. N., and Plant, O. H. (1922). *Amer. J. Physiol.*, **59**, 184, 191.
Roth, G. M., Flock, E. V., Kvale, W. F., Waugh, J. M., and Ogg, J. (1960). *Circulation*, **21**, 769.
Sandler, M., and Ruthven, C. R. J. (1960). In Ciba Foundation's *Adrenergic Mechanisms*, p. 42. Churchill, London.
Starr, I. (1926). *J. exp. Med.*, **43**, 31.
Terry, R. B., Tobin, J. R., and O'Connor, R. B. (1958). *Brit. med. J.*, **2**, 771.
Van Epps, E. F., Hyndman, O. R., and Greene, J. A. (1940). *Arch. intern. Med.*, **65**, 1123.
Wilkins, R. W., Greer, W. E. R., Culbertson, J. W., Halperin, M. H., Litter, J., Burnett, C. H., and Smithwick, R. H. (1950). Ibid., **86**, 51.

" The 120 ft. steel tower previously situated in the Mpanga Forest has now, with the generous help of funds from the World Health Organization, been moved to Zika Forest, which has the advantage of not only being very much nearer the Institute but of supporting a much larger population of mosquitoes. It has also been a very fruitful source of viruses in the past. Moreover, the proximity to main power lines has enabled the tower to have a permanent source of electric power, both for lights and for the operation of mechanical traps. A detailed study has been started on the naturally occurring activity-cycles of mosquitoes and other biting flies, similar to that previously carried out at Mpanga. One unexpected result is the finding that, while the mosquito *Aëdes africanus* shows its usual biting preference just after sunset in the forest canopy, which at Zika is at 60 ft., it shows another wave of activity just before sunrise at 80 ft., that is actually above the canopy. Although the pre-dawn burst of activity had already been demonstrated in the laboratory, its occurrence in nature above the forest canopy had to await the building of the tower before it could be directly observed. It is now possible to begin to fill in the complete picture for this species, and many apparent anomalies in previous records are thereby accounted for. In forest this species bites mainly at ground level by day. It apparently moves upward during the hour before sunset to produce a great wave of biting activity in the forest canopy during the hour after sunset. It remains in the canopy until just before dawn, when it apparently moves upwards again to a position above the canopy. After sunrise it is again found at ground level. *Ae. africanus*, already shown to be a highly important species as far as naturally occurring viruses are concerned, is thus in an 'ideal' position to pick up viruses from arboreal sleeping vertebrates, and to pass them to man during the day." (*East African Council for Medical Research Annual Report, 1960–61*, section on East African Virus Research Institute.)