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STUDIES IN PHAEOCHROMOCYTOMA: I. PATHOLOGICAL ASPECTS.

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Phaeochromocytoma is the term applied to a tumour of the medulla of the adrenal gland. Usually it causes hormonal changes in the body similar in effect to the administration of excessive dosage of adrenaline-like substances. In most cases this tumour is pathologically benign but it may produce fatal results if untreated.

Inadequate criteria and incomplete descriptions prevent the identification of the first recorded case with certainty. The earliest typical description of the tumour now known as phaeochromocytoma is probably that of Fränkel (1886) who found bilateral adrenal tumours at autopsy in a girl of eighteen years who collapsed suddenly and died. Recognition thereafter was slow and only about 160 cases are found in the literature up to 1947: since then almost 120 cases have been recorded. There is some difficulty in giving exact numbers, as several cases have been reported on more than one occasion by different authors; thus a single case has been recorded in five different papers (Engel *et al.*, 1942; Hyman & Mencher, 1943; Mencher, 1944; Colston, 1947; Calkins & Howard, 1947), and another in four (Goldenberg *et al.*, 1947; Snyder & Vick, 1947; Cahill, 1948; Ganem & Cahill, 1948). The first recorded successful operation for removal of such a tumour was carried out by Roux (1926), followed closely by Mayo (1927). The first successful preoperative diagnosis and operation was by Pincoffs (1929).

The clinical entity of phaeochromocytoma is now well-recognised but, in spite of the increasing number of reports, the condition probably occurs much more frequently than is recognised. It may be encountered in all branches of medicine and diagnosis may be difficult even in the presence of typical adreno-sympathetic attacks: many cases escape recognition because they do not fulfil the criteria usually associated with the disease. When persistent hypertension is present, the case may be mistaken for essential hypertension, although adrenergic blocking drugs are of considerable help in distinguishing the two conditions. Much is known about

the preoperative and operative treatment of patients with phaeochromocytoma, but the control of post-operative hypotension still remains one of the outstanding problems in the surgery of this condition.

This review is based on twelve cases studied personally by the authors in Glasgow Royal Infirmary between the years 1944 and 1952. Two were diagnosed clinically, seven were found incidentally at post-mortem examination and three were sent from allied hospitals as biopsy or post-mortem specimens.

Early diagnosis is very important for this tumour can be removed surgically with the prospect of complete cure while, if no treatment is given, death is almost inevitable.

HISTOLOGICAL METHODS.

The histological methods used have been described in detail in a previous article (Blacklock *et al.*, 1947). Only relevant clinical and histological data are given of Cases 1 to 6 which have been reported fully elsewhere (Blacklock *et al.*, Cases 1 to 6).

CASE REPORTS.

Case 1. A male, aged 21, had a history typical of the adreno-sympathetic syndrome which is characterized by paroxysmal attacks of hypertension. Between attacks, the blood pressure was normal but rose during paroxysms to 260/120. Biochemical findings were within normal limits. A tumour of the right adrenal gland was removed at operation using the lumbar extraperitoneal route. The patient developed marked post-operative hypotension which did not respond to adrenaline, plasma, blood transfusions and Eucortone. He died 62 hours after operation.

The adrenal tumour measured 8 × 6 cm. and weighed 86 g. Microscopically, it was a classical large alveolar type of phaeochromocytoma. A positive chrome reaction was obtained. At post-mortem the heart (400 g.) showed concentric hypertrophy of the left ventricle. In the kidneys, there was splitting of the internal elastic lamina in the arcuate arteries and the walls of some afferent arterioles were partly hyalinized and the lumen narrowed. The glomerular capillaries were thickened but only a few glomeruli fibrosed.

Case 2. A female, aged 37, had a history typical of the adreno-sympathetic syndrome, with paroxysmal attacks of hypertension when the blood pressure varied from 148/78 to 220/115. Following an attack, albumin was present in the urine and the serum potassium elevated, from 24.6 mg.% to 33.5 mg.%. She was adequately pre-medicated, did not develop a paroxysmal attack during the removal of the tumour of the right adrenal and no post-operative hypotension occurred. She is alive 9 years after the operation.

The tumour of adrenal measured 6.5 × 5.5 × 3.5 cm. and weighed 70 g. Microscopically, it was a large alveolar type of phaeochromocytoma (Fig. 20) showing a typical positive chrome reaction. An important feature of this case was the presence of mature phaeochromocytes in the lumen of thick-walled veins in the tumour (Fig. 21).

Case 3. A male, aged 39, had many features of the adreno-sympathetic syndrome, although the case was considered one of malignant hypertension. During the hypertensive attacks he was giddy when assuming the erect position after stooping ; he had attacks of pain in the neck radiating up to the occipital region ; occasionally he lost consciousness ; his blood pressure rose to 240/130, and his urine contained a trace of albumin. During his stay in hospital he became disorientated and mentally confused, and frequently screamed. He died while under investigation and during the two days previous to his death the blood pressure did not exceed 100/30.

At post-mortem (12 hours after death) a small, fairly sharply defined, greyish-white tumour, 1 cm. in diameter, was present in the medulla of the upper pole of the left adrenal. The microscopic structure was that of a small alveolar type of

phaeochromocytoma similar to that shown in Figs. 12 and 13. The tissue was not specially fixed for the chromaffin reaction and post-chromatization was unsatisfactory. The heart (620 g.) showed marked hypertrophy of the left ventricle and in the kidneys there was irregularity of the cortical markings. The branches of the renal arteries in the substance of the kidney were prominent, but kidney sections were not available for histological examination.

Case 4. A female, aged 56, was admitted on account of periostitis complicated by hepatic abscess ; she died 9 days after admission. Her blood pressure was normal on the six occasions on which it was examined and there were no features suggestive of adreno-sympathetic syndrome and this case appeared to fall into the asymptomatic group.

At post-mortem (5 hours after death) a well-encapsulated tumour, 3 × 2 × 0.5 cm., was present in the medulla of the right adrenal gland. Microscopically, the phaeochromocytoma was of the small alveolar-type. The cells in some alveoli gave a positive chrome reaction, while those in adjacent alveoli were negative (Fig. 1). Many cells seen at the periphery of the tumour closely resembled the ganglion cells of a ganglio-neuroma. The heart (250 g.) appeared normal. In the kidneys there was slight thickening of the afferent arterioles and complete sclerosis of a few glomeruli. Arteriosclerotic changes were present in the interlobular arteries.

Case 5. A male, aged 73, with a carcinoma of prostate died in hospital from pulmonary embolus. At no time were features characteristic of the adreno-sympathetic syndrome noted. His blood pressure was persistently elevated (220/110) and albumin was present in the urine.

At post-mortem (18 hours after death) a spherical tumour, 1.5 cm. in diameter and weighing 8 g., was present in the middle of the right adrenal. The growth was fleshy in consistence and pale red in colour. Microscopically, the adrenal tumour was a small alveolar type of phaeochromocytoma but failed to give a positive chrome reaction. The heart (490 g.) showed left ventricular hypertrophy. There was splitting of the internal elastic lamina of the arcuate and interlobular arteries of the kidneys. A few glomeruli were fibrosed.

Case 6. A female, aged 34, complained of progressive weakness and breathlessness of six months' duration and of a dragging pain in the left abdomen relieved in most instances by lying down. Menstruation, hitherto regular, ceased a month after the onset of these symptoms. The blood pressure was 128/74 and repeated questioning failed to show any feature of the adreno-sympathetic syndrome. A palpable mass in the left flank was explored and the left kidney with a large tumour attached to its upper pole was removed. Her convalescence was uneventful and menstruation returned one month later. There was a steady improvement in her physical capacity interrupted after 9 months by marked dyspnoea due to a large left-sided blood-stained pleural effusion. This was followed by pain in the left hypochondrium, invasion of the left rectus muscle by tumour growth and, when she died 13 months after operation, the growth occupied the whole of the left side of the abdomen and the medial portion of the right hypochondrium. Repeated blood pressure readings until the time of her death were normal. Permission for post-mortem examination was refused.

Unfortunately, the biopsy specimen was not received until 24 hours after surgical removal. The left kidney and adrenal tumour weighed 1,200 g., the adrenal growth measured 28 × 22 × 14 cm., and was surrounded by a thick fibrous capsule. On section it was composed mainly of large yellow-green areas of necrosis and areas of haemorrhage ; only a few areas of fleshy tissue were present at the periphery of the tumour.

Recently, additional material from the tumour was examined microscopically and points of interest may now be added to those reported previously (Blacklock *et al.*, Case 6). In particular the diversity of the histological picture can be stressed. The major portion of the tumour displayed a solid trabecular arrangement, interspersed with a few capillaries and thick-walled veins, but without any alveolar formation. The cells showed a slight degree of pleomorphism ; the cell borders were distinct and the cytoplasm finely granular and eosinophilic rather than basophilic in character. Nuclear pleomorphism was not marked. The nuclei were generally vesicular, a few hyperchromatic, and mitoses were present in many of them. Numerous multinucleate giant-cells were scattered throughout (Fig. 2). Large alveoli separated by vascular sinusoidal spaces were seen only in small parts of the tumour. A prominent basement membrane was present in most cells, which wer

finely granular, basophilic in character, and showed cellular and to a lesser extent nuclear pleomorphism. The nuclei were rather hyperchromatic, although a few were vesicular (Fig. 3). Nearer the periphery of the tumour the cells showed an abrupt change. Groups of cells were separated by a fibro-vascular tissue and produced an alveolar arrangement. The cells showed marked nuclear and cellular pleomorphism and their cytoplasm was distinctly granular (Fig. 4).

The chrome reaction and bio-assay for adrenaline were negative on account of the long period (24 hours) which elapsed between operation and examination. The only noteworthy feature seen in the kidney was reduplication of the internal elastic lamina of the arcuate artery.

Case 7. A male, aged 39, was admitted on 3rd March, 1951, with the complaint of headache of four years' duration. There was excessive sweating of some months and dimness of vision in the right eye for fourteen days. Left ventricular hypertrophy was present. The blood pressure was 205/140 and remained at about this level during his entire period in hospital. There was persistent tachycardia varying from 100 to 130 per minute. The ocular fundi showed the changes of hypertensive neuro-retinopathy. Albumin and glucose were present constantly in the urine. He was in poor condition on admission and gradually deteriorated and died.

At post-mortem (24 hours after death) a circular tumour, 6.25 cm. in diameter and weighing 80 g., replaced the left adrenal (Fig. 5). When fixed in dichromate solution it did not give the typical dark brown appearance but developed a dull grey colour. It was very vascular and two cystic spaces, 1 cm. in diameter, were present in the centre of the growth. Microscopically, the features were typical of the large alveolar type of phaeochromocytoma. A thin fibrous capsule completely surrounded the tumour which was composed of cellular trabeculae broken up by sinusoidal spaces and thin-walled blood capillaries to form large alveoli (Fig. 6). The cells were mature phaeochromocytes with prominent cell membranes and finely granular basophilic cytoplasm (Fig. 7). The chrome reaction was negative. There was marked cellular and nuclear pleomorphism and at places strange bizarre nuclear forms were present (Figs. 8 & 9). The sinusoidal spaces were lined only by tumour cells which were present also in the lumen together with erythrocytes. The left ventricular hypertrophy was confirmed. No renal material was available to us.

Case 8. A female, aged 63, was admitted on 9th April, 1950, with severe headaches and weakness of the limbs of 24 hours' duration. The pain came on suddenly while shopping. After admission she vomited and lumbar puncture revealed increased pressure, but no blood in the cerebro-spinal fluid. A week later a transient left hemiplegia developed. Her blood pressure throughout was in the region of 220/110. Nine weeks later she was able to go to a convalescent home. Two days after admission she developed epileptiform seizures and gradually lapsed into coma. Her blood pressure fell and she died ultimately with marked circulatory failure. No localizing signs were present in the central nervous system.

At post-mortem (22 hours after death) a greyish tumour, 2.5 × 2 cm., was present in the upper pole of the right adrenal gland and lay under the right lobe of the liver (Fig. 10). Microscopically, a thin fibrous capsule separated the adrenal tumour from the normal portion of the gland. The growth was extremely vascular and consisted of large dilated sinusoidal spaces which broke up the cellular trabeculae, but the alveoli so formed were not so large as in the previous case (Case 7). The cells once more were mature phaeochromocytes with granular basophilic cytoplasm (Fig. 11). There was nuclear and cellular pleomorphism and bizarre nuclear forms. A few areas were haemorrhagic but not necrotic.

The heart (360 g.) showed hypertrophy of the muscle of the left ventricle and the coronary vessels were normal. The kidneys (right 80 g., left 80 g.) were small and the capsule stripped with some difficulty leaving an irregular finely granular surface. The cortex was diminished in size and the renal vessels arteriosclerotic and rather prominent on section. Microscopically, the changes of essential hypertension were noted in the kidneys. Naked-eye the pancreas was normal, but microscopic examination showed hyalinization of the interlobular arterioles with no significant changes in the islet tissue. An irregular area of softening, 1.5 cm. in diameter, was present in the sub-cortical region of the brain about the middle of the right temporal lobe. The vessels in the circle of Willis were arterio-sclerotic and atheromatous.

Case 9. A female, aged 52, was in a fairly deep coma on admission. She was a long-standing diabetic under treatment with diet and insulin. She lived alone and for two or three days had been ill with vomiting, anorexia and drowsiness. She had had neither food nor insulin. On admission the pulse was of low tension and poor quality (130/min., B.P. 100/50). The eyeball tension was low, air-hunger was present and acetone was noted in the breath. The temperature on admission was 97°F. but rose to 102° prior to death. No details of ophthalmoscopic examination were given. The urine contained albumin, was orange to Benedict's test and strongly-positive to Rothera's and Gerhardt's tests. The blood sugar was 500 mg.% on admission. She did not respond to treatment and there was no lowering of blood sugar below 400-500 mg.%. Terminally she became oedematous with moist sounds throughout her lungs.

At post-mortem (27 hours after death) a growth, 3 × 2.5 cm. in size and weighing 25 g., was present in the substance of the left adrenal. The tumour had a greyish haemorrhagic appearance and was surrounded by yellow cortical tissue. Microscopically, the adrenal tumour had an ill-defined capsule which separated it from the remnants of compressed adrenal cortex. The tumour cells were small in size, had no obvious cell membranes and showed only a slight degree of nuclear pleomorphism. The cytoplasm was finely granular and basophilic in character and in some parts the trabeculae of cells were separated by large sinusoidal spaces and formed small alveoli. In other parts the cells, although still grouped in small alveoli, were separated by loose bands of fibrous tissue but without any evidence of sinusoidal spaces (Fig. 12). A negative chrome reaction was obtained. Part of the tumour was necrotic and the blood vessels at the periphery of this area were dilated and thrombi present in the lumen. A small cortical adenoma was present outside the capsule at one pole of the tumour. The features seen in this tumour were essentially those found in the small alveolar group, except for the presence of sinusoidal spaces in portions of the growth. No abnormalities were seen in the other adrenal.

The heart (400 g.) showed considerable hypertrophy of the left ventricle. The coronary vessels appeared healthy and no abnormalities were seen in the valves. The kidneys (right 240 g., left 230 g.) were increased in size, showed a fine granularity of the surface, and prominent renal vessels were seen on section. Microscopically, the lesions present were those of the exudative type of diabetic glomerulo-sclerosis. Pancreas: No abnormalities were noticed in the islets of Langerhans following haematoxylin and eosin staining. This material was unsuitable for α and β islet cell examination.

Case 10. A female, aged 52, was admitted in a semi-comatose condition. She had had a cerebral catastrophe four years previously and since then had been unable to use her right arm and leg or to speak clearly. Examination showed a middle-aged woman perspiring profusely. Knee and ankle jerks were absent and pulsation could not be obtained over the left dorsalis pedis and posterior tibial arteries. The left leg and lower half of thigh were cold. The temperature was 101°F., pulse 140 and respirations 32/min. Blood pressure recordings were not available. Urine: Reaction acid, sugar orange, albumin ++, trace of acetone.

No details of the post-mortem were available. Only a portion of 'a tumour connected to the left adrenal gland and material from the left kidney' were sent for examination.

Microscopically, the growth was separated from the remains of compressed adrenal cortex by a fibrous capsule. The cells of the tumour were arranged in small alveoli separated by loose fibrous tissue or small well-formed capillaries. In some parts the alveoli appeared to be lying free in a myxomatous medium which gave a negative Schiff reaction (Fig. 13). The cells resembled those seen in the previous case (Case 9). No cell borders were noticed, the cytoplasm was basophilic and a slight degree of nuclear pleomorphism was present. Thick-walled adrenal veins with prominent longitudinal muscle bundles were scattered throughout the growth and large thrombi were seen in many vessels. Sinusoidal spaces were not seen in any part of the growth. Three small extra-capsular adenomas were present. There was well-marked post-mortem change in the kidney. Only a few glomeruli were sclerosed and there was hyalinization only of a few afferent arterioles. The inter-lobular arteries were arterio-sclerotic.

Case 11. A male, aged 23, complained of severe headache and pain in the back a week before admission to hospital. Two days later he had two teeth extracted. The head and back pains continued and 8 hours before admission he collapsed and

became unconscious. He was very restless and irritable and had a positive Kernig's sign and nuchal rigidity. The cerebro-spinal fluid was under increased pressure and intimately mixed with blood; the centrifuged specimen showed xanthochromia. His condition gradually deteriorated and his temperature, which was normal on admission, rose to 106°F. and he died 48 hours after admission. When seen originally his blood pressure was 170/80 and subsequent readings were 155/95 and 130/95. Eyes: Disc margins were indistinct but no haemorrhages or exudate were noted. The blood urea was 24 mg.%.

At post-mortem (18 hours after death) a growth measuring 4 × 3.5 × 2 cm. and weighing 60 g. was present in the right adrenal gland. The tumour on section consisted of two circumscribed yellow nodules intimately associated with a dark grey background, which was found to consist of chromaffin tissue. The left adrenal weighed 10 g. and a small tumour, 1.5 cm. in diameter, was present in the upper pole. The growth was flesh coloured and haemorrhagic in places and surrounded by a yellow layer of cortex. Microscopically, the growth in the left adrenal was separated from the overlying cortex by a thin fibrous capsule. The tumour cells, as in Cases 3, 4, 5, 9 and 10, were arranged in small alveoli varying in size from 1 to 20 cells. They differed from those seen previously in the small alveolar type in that they consisted of mature phaeochromocytes, and resembled the cells seen in the large alveolar type (Cases 1, 2, 7 & 8). They had a distinct cell border, showed cell and nuclear pleomorphism and a granular basophilic cytoplasm. Bizarre nuclear forms were present. The alveoli were separated by fine fibrous strands (Fig. 14). Small capillaries were dispersed among the alveoli but sinusoidal spaces were not obvious. A small haemorrhagic area was present in one portion of the growth. A prominent feature in this tumour was the presence of thick-walled adrenal veins showing longitudinal muscle bundles. One vein was completely ensheathed by a layer of adrenal cortex in which the zona glomerulosa and zona fasciculata could be identified (Fig. 15). Small extra-capsular adrenal adenomas, similar to those seen in the normal adrenal gland were present on the surface of the growth. In the right adrenal the two yellow nodules noticed at post-mortem were typical adrenal cortical adenomas which merged gradually with adrenal medullary cells similar in appearance to those described in the left adrenal. In some parts only mature phaeochromocytes were present and in this portion a few haemorrhagic areas were seen. A mixture of adrenal medullary and cortical cells was found in other parts of the growth (Fig. 16), while adjacent areas consisted only of a pure cortical adenoma. Islands of phaeochromocytes separated by pale-staining mucoid-like material were noticed also in this case and thick-walled veins with prominent longitudinal muscle bundles were seen.

The heart (320 g.) showed hypertrophy of the left ventricle. The coronary vessels were healthy. The kidneys (right 140 g., left 140 g.) were normal macroscopically and microscopically. The pancreas likewise was normal. There was a subarachnoid haemorrhage which had originated in a small aneurysm of the communicating branch of the anterior cerebral artery.

Case 12. A male, aged 45, was admitted on the first occasion on 14th June, 1950, with a complaint of headache and vomiting of two hours' duration. Two years previous to this time he had attacks of vomiting, which lasted about one hour and were followed by bitemporal headache of a throbbing character. The attacks had become more and more frequent and in the past six months occurred once weekly, at irregular intervals, sometimes in the morning and sometimes at night. He experienced abdominal pain only after vomiting and felt weak during and after the attacks. He was well between attacks. On admission the blood pressure was 125/85 and the fundi normal. The temperature varied between 98 and 100°F., a trace of albumin was present in the urine, but no sugar was found. Blood urea was 30 mg.%. A barium meal revealed no abnormalities in stomach and duodenum and an E.C.G. showed left axis deviation. He was discharged three weeks after admission. About three days after his discharge he started to vomit. This persisted and occurred about twice weekly. On various occasions blood was present in the vomitus. He was sick and vomited about a cupful of blood on the day prior to his second admission on 9th April, 1951, and six hours later brought up a slightly larger amount of blood, when he felt pain in the legs from the knee to the sole of the foot. He had had dyspnoea for the past 9 months, especially on exertion, and he could not walk more than 30 yards without having to rest. Examination showed a fairly well-built man who lay easily in bed, except when on his left side. The right leg was cold and bluish in colour. No palpable masses were detected in the abdomen. Blood pressure on admission varied from 130/90 to 170/110. Next day it was 125/80.

His temperature was 104.8°F. Urine contained albumin but no sugar. The condition of the fundi was not noted. His condition rapidly deteriorated and he died next day, 10th April, 1951.

At post-mortem (24 hours after death) a tumour, measuring 10 × 6 × 4 cm. and weighing 140 g., was present in the left adrenal gland (Fig. 17). It was encapsulated and on section the surface showed a great deal of post-mortem autolysis. It was dark red in colour and areas of central softening and paler areas of infarction were noted. Large thrombosed vessels were seen in the centre of the growth. The right adrenal was normal in size and shape and the cortex and medulla well-defined. There was no evidence of haemorrhage.

Microscopically, the tumour was surrounded by a thick fibrous capsule which enclosed a few remnants of adrenal cortical cells. Areas of haemorrhage were noticed outside the capsule. Three distinct cellular patterns were observed. In some parts the cells were composed of mature phaeochromocytes arranged in solid trabeculae broken up by large sinusoidal spaces to form large alveoli similar to those described previously. The pattern changed abruptly in other parts, where the cell borders were indistinct and the cells had a trabecular arrangement with an ill-defined alveolar formation (Fig. 18). The granular basophilic character of the cells was not obvious, the cytoplasm was eosinophilic and nuclear pleomorphism, although present, was not outstanding. The nuclei were either round or oval in shape and, while some were vesicular in character, others were dense and hyperchromatic (Fig. 19). Unfortunately, it was not possible to determine the chromaffin nature of these cells, since the post-mortem was not carried out until 24 hours after death when, as was expected, the chrome reaction was negative. Between those two areas the alveoli were small and the cells more basophilic and granular as seen in Cases 9, 10 and 11. Large areas of the tumour were either haemorrhagic or composed of amorphous necrotic cells. Vessels : In addition to the vascular sinusoids mentioned above, thick-walled veins and capillaries were present in the growth. There were no tumour cells in any of the vessels and no evidence of capsular invasion was found. There were no metastases from this tumour.

The heart (500 g.) showed marked left ventricular hypertrophy and an old infarct was present in the wall of the left ventricle. The affected area was thin and fibrosed and there was aneurysmal dilatation with endocardial thrombus formation. The remainder of the myocardium showed patchy fibrosis. In spite of the myocardial changes, only a minimal degree of atheroma was present in both coronary vessels. There was no evidence of thrombus formation in the coronary vessels which were quite patent along their whole length. The kidneys were normal in size and shape and on section no abnormalities were noted. Microscopically, there was slight hyalinization of the arterioles to a few glomeruli only, and arteriosclerotic changes were seen in the arcuate arteries. Pancreas : The islet tissue appeared normal and in haematoxylin and eosin sections no lesions were noted in the interlobular vessels. A well-formed thrombus (apparently an embolus from the left ventricle) was present and completely blocked the lumen of the lower end of the right tibial artery. A frothy blood-stained exudate was noted in the trachea and bronchi, and a marked degree of congestion and oedema in both lungs. There was evidence of recent haemorrhage into the abdominal cavity in the region of the left kidney. A small prominent vessel was seen at the lower end of the oesophagus but no rupture could be detected. Erosions were present in the mucosa of the body of the stomach and no other cause for the haematemesis was found.

DISCUSSION.

Nomenclature.

The term phaeochromocytoma is restricted to adrenal medullary tumours which assume a yellow-brown colour when treated with a solution of potassium dichromate. In view of this reaction they are often referred to as *chromaffinomas* or *chromaffin tumours*. When the growth occurs in extra-adrenal sites, *e.g.*, aortic bodies, mediastinum or organ of Zuckerkandl, the term ' paraganglioma ' is used. However, there does not appear to be any justification for differentiating between adrenal and extra-adrenal chromaffin tumours. Since the term phaeochromocytoma refers simply to the yellow-brown colour of these tumours following

chrome treatment, it is suggested here that all adrenaline or noradrenaline secreting tumours, irrespective of their origin, should be called ' phaeochromocytoma.' This seems advisable since it is well established that tumours may occur in the glomus jugularis, carotid body, aortic bodies and organs of Zuckerkandl which do not give a true chrome reaction and secrete neither adrenaline nor noradrenaline. Although they resemble to some extent the small alveolar type of phaeochromocytoma, such tumours are believed to arise from chemo-receptor cells in those paraganglia and so the term chemodectoma is used to describe them. Thus it becomes apparent that the term paraganglioma may refer either to a chromaffin tumour or chemodectoma. Some paraganglia, notably the organ of Zuckerkandl and aortic bodies, give rise to both phaeochromocytoma and chemodectoma, while the growth in the glomus jugularis and carotid body appear to be predominantly chemodectoma.

TABLE 1.

Phaeochromocytoma.

Site, age and sex incidence in 283 reported cases of phaeochromocytoma.

	Site				Age and sex					
	Cases in literature		Present series of 12 cases		Age	Males		Females		
	No.	%	No.	%		Rept'd cases	Present series	Rept'd cases	Present series	Not stated
Right adrenal	118	48	6	50	0-10	5	—	3	—	—
Left adrenal ..	81	33	5	42	11-20	8	—	16	—	—
Bilateral ..	21	9	1	8	21-30	32	4	32	—	—
Multiple ..	9	4	—	—	31-40	25	1	35	—	—
Mediastinum ..	3	1	—	—	41-50	26	1	33	2	—
Extra-adrenal	12	5	—	—	51-60	8	—	18	3	—
Not stated ..	27	—	—	—	60+	10	—	9	1	11
	271	100	12	100		114	6	146	6	11

Site, age and sex incidence in 283 *reported cases of phaeochromocytoma.*

Table 1 shows the site, age and sex incidence observed in a review of 283 reported cases including the 12 in this series. Unfortunately few of the reports contain sufficient information to allow the tumour to be classified histologically but general statements can be made with regard to site and sex incidence. Thus 48 per cent of the series occurred in the right adrenal, 33 per cent in the left and 9 per cent were bilateral; 114 cases were male and 146 female. All age groups are represented but clearly the tumour occurs more frequently between the ages of 20 and 50.

Histological structure of phaeochromocytoma.

It is evident from examination of the 12 tumours in this series that they represent four histological types :—

1. Large alveolar type.
2. Small alveolar type.
3. Intermediate type.
4. Malignant type.

1. *Large alveolar type* (Cases 1, 2, 7 & 8). Three of the four tumours were large in size, one was small (Case 8). All four were surrounded by a thick fibrous capsule in which the remains of adrenal cortical cells were seen. The histological structure characteristically consists of large cellular trabeculae composed of mature phaeochromocytes with marked cellular and nuclear pleomorphism and, in some cases, bizarre nuclear forms. Large thin-walled sinusoidal spaces lined only by tumour cells break up the solid cellular trabeculae and produce the large alveolar appearance characteristic of this group (Fig. 20). When stained by haematoxylin the cell cytoplasm is finely granular and basophilic, a feature which may be of considerable value in diagnosis. After fixation in dichromate solutions the granules are coloured olive green by Schmorl or Sevki's Giemsa method. The close relationship of the vascular spaces to the tumour cells appears to provide a route by which pressor substances could gain access to the blood and may account for the adreno-sympathetic attacks which are commonly encountered in this group. The sinusoidal spaces often contain tumour cells (mature phaeochromocytes) but this may be a result of handling and fixation. Nevertheless, the presence of clumps of mature cells in many thick-walled veins (Case 1, Fig. 21), shows that tumour cells may pass into the veins but it should be appreciated that such a finding cannot be considered as absolute evidence of malignancy.

2. *Small alveolar type* (Cases 3, 4, 5, 9, 10 & 11). All six tumours were small in size and varied from 1 to 3 cm. in diameter or 8 to 25 g. in weight. All were incidental post-mortem findings and consisted of small flesh-coloured nodules, surrounded by a yellow covering of adrenal cortical tissue. They were easily recognised at post-mortem in most cases, although in one (Case 11) the diagnosis was made only after histological examination.

The tumours are separated from the overlying adrenal cortex by a thin fibrous capsule which passes through the zona reticularis. The cells are arranged in small alveoli, separated by strands of loose fibrous tissue or in some instances by well-formed blood capillaries. Isolated alveoli are seen lying in a clear pseudo-myxomatous matrix in certain cases (Cases 10 & 11, Fig. 13). There is considerable individual variation in the cellular appearance of the tumours in this group. They may consist of mature phaeochromocytes similar to those seen in group 1 (Fig, 14, Case 11), but in most cases the individual cell membranes are not

prominent and the alveoli are more compact (Fig. 12). The typical basophilic reaction of the cytoplasm is obvious and the nuclei are small and less vesicular. Nuclear pleomorphism is present but is not a marked feature. The vascularity of the tumour differs from that of group 1 by the absence of sinusoidal spaces, but thick-walled veins with prominent longitudinal muscle bundles are present. Many of the large veins are dilated and filled with thrombi. Numerous capillaries lined by reticulin pass into the tumour. The association of phaeochromocytoma and cortical adenoma was seen in three cases (9, 10 & 11).

In spite of the small size of the tumour many features of the adreno-sympathetic syndrome were obvious in retrospect in three cases.

3. *Intermediate type* (Case 12). The single example of this type forms an interesting link between the benign and malignant phaeochromocytoma. Histological features characteristic of the large alveolar type, as well as the small alveolar type of benign phaeochromocytoma, are seen in many parts of this growth, but the cellular pattern of the remainder does not conform to either. The cells in this area are arranged in large trabeculae with only an indefinite attempt at alveolar formation (Figs. 18 & 19). Their cytoplasm is eosinophilic and the granular character of the cells not obvious. The nuclei are either round or oval in shape, some vesicular and others hyperchromatic.

In accordance with the accepted embryological development of the chromaffin cells—

Sympathogonia⟶Phaeochromoblast⟶Phaeochromocyte—

the cells in this portion of the tumour would appear to resemble the phaeochromoblast, in which the cytoplasm is eosinophilic and non-granular. However, it should be appreciated that although many of the cells in the tumour appear to be immature, they may be in the process of conversion to the phaeochromocyte (Blacklock, 1952) hence the rather mixed appearance of the tumour.

The histological data presented by the 11 benign tumours in these three groups clearly show the very varied appearance of the phaeochromocyte cell as seen in the small alveolar group (Type 2) with the large mature cell most commonly encountered in the large alveolar group (Type 1). The cases further demonstrate the fine dividing line which exists between the immature cell or phaeochromoblast and the phaeochromocyte.

4. *Malignant type.* The possibility of the supervention of malignancy in these tumours has acquired importance in recent years with more frequent recognition of phaeochromocytoma. Thirty-one malignant cases have been recorded, but when reviewed critically there is insufficient evidence of malignancy in 19; 5 can be explained on the basis of multicentric origin, and thus there are 7 cases only in which the growth appears to be malignant (Tables 2, 3 & 4). Numerous criteria of

malignancy have been used in the 31 cases. Marked pleomorphism, bizarre nuclear forms (Barlow, 1947), invasion of capsule (Broster & McKeith, 1944 ; Chamovitz & Fanger, 1949 ; Ortega, 1952), invasion of the adrenal vein (Kaulbach, 1937 ; Espersen & Dahl-Iversen, 1946, Case 2) and inferior vena cava (Washington *et al.*, 1946) have been interpreted, singly or collectively, as evidence of malignancy. Although such features may be seen in malignant tumours in general, the cases recorded in this paper have shown that pleomorphism and bizarre nuclear forms are characteristic features also of simple chromaffin tumours. Venous invasion by mature phaeochromocytes cannot be considered irrefutable evidence of malignancy (see Case 2). This point is also stressed by Roth *et al.* (1952). The significance of venous invasion by immature cells (phaeochromoblasts) cannot be assessed and further observations are required on this aspect of the problem. Likewise, capsular invasion is difficult to interpret. Cells of the adrenal medulla as well as those of the compressed adrenal cortex are seen within and occasionally outside the capsule and the difficulty arises of determining whether the cells are the result of invasion or are in fact merely displaced medullary cells. The significance of capsular invasion by immature cells also is a matter for further observation. Broster and McKeith report capsular invasion by immature cells in a patient alive and well nine years after surgical removal followed by deep X-ray therapy. Thorn *et al.* (1944) on the other hand found extensive capsular invasion by ' tumour masses ' and death one year later from local extension of the tumour (Chamovitz & Fanger, 1949).

The cytology of the tumour is important but again not diagnostic of malignancy. The presence of immature cells in the primary growth may lead to considerable difficulties in interpretation, especially if the tumour is a biopsy specimen. Although Wahl and Robinson (1943) believe that paraganglioma do not metastasize unless mixed with undifferentiated elements, in our opinion the presence of these immature cells in a tumour need not be interpreted as evidence of malignancy (see Type 3). We agree with McGavack *et al.* (1942) that the histological features usually indicative of malignancy are equally characteristic of benign phaeochromocytomas. It would appear that in the present state of our knowledge, all phaeochromocytomas without metastases should be classified as benign.

Metastases themselves demand special consideration in this type of growth. For example, a phaeochromocytoma may be associated with another malignant tumour which has metastasized, and it is important to exclude metastases arising from an associated tumour. Mandeville and Sahyoun (1949) report association with bronchial carcinoma, while Eisenberg and Wallerstein (1932), Muntz *et al.* (1947) and Rothermich (1952) noted a carcinoma of thyroid in their cases. Conley and Junkerman (1951) found a carcinoma of kidney with a phaeochromocytoma.

TABLE 2.

Malignant phaeochromocytoma.

? Malignant but rejected because of insufficient evidence.

Author.	Site and size of tumour.	Microscopical nature of tumour or secondaries.	Blood pressure.	Photographs given.
Gravier & Bernheim (1924)	Bilateral. Size of manderine.	Two sets of cells—(*a*) like sarcoma, (*b*) atypical epithelioma. They believe they arise from sympathetic tissue. No mention of chrome reaction. Post-mortem—multiple gummata in lung. Metastases in mediastinum.	Not stated.	No.
Bonnamour *et al.* (1927)	Site not stated.	Usual characteristics of paraganglioma with siderophil granules in some cells. Intense keratinization with formation of cell nests. Chrome reaction not stated. Metastases—pleura ; tumour cells in vessel of lung. Morphology different from primary, large spherical nucleus.	Not stated.	5 photographs, one showing keratinization in the adrenal tumour.
Lewis & Geschickter (1934)	Large tumour in region of kidney ; could not be removed.	Histology revealed a malignant tumour. Epithelial cells predominated. Occasional ganglion cell and many malignant giant cells. Chrome reaction not mentioned. Patient died 6 days after operation. No post-mortem permission.	Not stated.	No microscopic photographs.
Evans & Stewart (1942)	5.5 × 4.5 × 4 cm. 63 g. Right adrenal.	Phaeochromocytoma of low-grade malignancy diagnosed. No details.	250/150 to 150/118.	No.
Broster & McKeith (1944)	5.5 × 4.5 × 2.5 cm.	Large polyhedral cells. A few multinucleate, some with deeply staining pyknotic nuclei. Mitoses rare. Vessels—many thin-walled but not sinusoidal. Growth not entirely benign, may be called phaeochromoblastoma. Tumour cells appear to be infiltrating capsule to some extent. Some lymphatic spaces contain tumour cells (Dr. Vines' report). Positive chrome reaction.	Hypertension present. Patient well 1952. (Personal communication—Broster).	Yes.
Cahill (1944). Case 1.	—	Post-mortem report on male, 59 years. Malignant phaeochromocytoma with metastases to liver and lymph glands. No photographs or microscopic description.	—	—
Espersen & Dahl-Iversen (1946). Case 2.	Left adrenal. 4.5 × 3 × 2 cm.	Tumour is malignant since it had shown invasion of tumour cells into a vein. Patient died 2½ hours after operation.	210-265.	No.
Soffer *et al.* (1946). Case 1.	Phaeochromocytoma.	No details ; considered simple by author. Later, metastases in liver (Chamovitz & Fanger).	Not stated.	Yes.
Washington *et al.* (1946)	Right adrenal. 413 g.	No extension through capsule but invasion of right adrenal vein and extension into I.V.C. They consider this sufficient evidence on which to make a diagnosis of malignancy. Careful examination of regional lymph glands showed no gross involvement by tumour.	200/150.	Invasion of I.V.C Six photographs.
Barlow (1947)	533 g. 1 × 17 × 9 cm. Left adrenal.	Pleomorphism. Large grotesquely shaped nuclei. Have all characters of malignancy. Positive chrome reaction. Superior part of tumour adherent due to invasion of diaphragm.	180/120 to 140/110.	Yes.

TABLE 2 (cont'd).

Author.	Site and size of tumour.	Microscopical nature of tumour or secondaries.	Blood pressure.	Photographs given.
Mayock & Rose (1947)	42.8 g.	Gigantic tumour cells. Bizarre nuclei. Tumour cells in blood vessels. Considered possibly malignant, but unlikely.	130/80 to 320/160.	No.
Spatt & Grayzel (1948). Case 1.	Right and left adrenals. Normal in size. Nodules in both medullae —composed of phaeochromocyte cells.	Metastases—multiple secondaries in brain—no size. Histology—islands and cords of cells of varying size and shape and staining characters. Chrome reaction not stated.	160/100.	Adrenal and brain. Adrenal cells consistent with phaeochromocytes. Brain—islands of cells as described.
Mandeville & Sahyoun (1949). Case 2.	Right and left adrenals. Large whitish nodules with somewhat yellowish haemorrhagic centres.	Polymorphonuclear cell type—small round cells, spindle cells, polyhedral cells and giant cells. Secondaries in liver, pancreas, diaphragm, chest wall. Microscopic appearance as before. No chrome reaction. Bronchogenic carcinoma present.	Not stated.	Liver—cells of different shapes and sizes. No alveolar arrangement.
Bartels & Cattell (1950)	8 cm. 260 g. Left adrenal.	No detailed description. Pathological diagnosis—phaeochromocytoma. Metastases—right cervical (metastatic phaeochromocytoma). No details.	200/100 to 112/80. Normal post-operative.	No.
Console *et al.* (1950). Case 5.	Right and left adrenals.	No detailed description. No chrome reaction. Metastases in lung and cervical glands—no details.	260/180 to 130/80.	No.
Smith *et al.* (1950).	6 × 4 × 3.2 cm. 49 g. Left adrenal.	No description, merely statement. Pathological report (concurred in by several examiners) was that tumour was malignant. No metastases.	240/124 to 160/95 post-operative. 132/74 in few months.	No.
Allen *et al.* (1951).	355 g. Right adrenal.	No description of cells. No chrome reaction. Metastases in neck of femur—no description.	184/126	No.
Fernando *et al.* (1951).	7.5 cm. in diameter. Right adrenal.	Large and small lymphocyte-like cells. Rosettes, some multinucleate cells. No metastases.	190/150 to 200/165.	Yes.
Stokes (1952).	Bilateral. Photograph, but no size given.	Both tumours—evidence of vascular malignant new growth. Cells large and polyhedral. Tumour invaded adrenal cortex and, in one situation, tumour cells in structure resembling a lymphatic vessel and, in another, present in the wall of a vein. Appearance consistent with bilateral malignant phaeochromocytoma. Chrome reaction not mentioned. No metastases.	250/170 to 190/110.	Microscopic. 2 photomicrographs.

TABLE 3.

? Malignant phaeochromocytoma, possibly of multicentric origin.

Author.	Site and size of tumour.	Nature of tumour and metastases				
		Primary		Metastases		
		Description of cells.	Chrome reaction.	Description of cells.	Chrome reaction.	Blood pressure.
Lewis & Geschickter (1934). Case 1.	Enormous mass in lumbar region.	Tumour composed of epithelial masses, surrounded by a loose delicate stroma. Nuclei large and have appearance of those in a malignant tumour. At the margin the tumour resembles a typical carotid body tumour. In other parts of section many small cells with dense nuclei as in neuroblastoma.	No mention.	1. Elongated mass 1″ long in region of 2nd lumbar vertebra. 2. Anterior to cervical vertebrae.	No mention.	No mention.
Cahill (1944). Case 5.	Phaeochromocytoma, Right adrenal.	No description.	No mention.	Tumour removed from meninges, diagnosed microscopically as phaeochromocytoma. No description of cells. Size of growth not given.	No mention.	No mention.
Soffer *et al.* (1946). Case 2.	Left adrenal. 530 g. 13 cm.	No description. Phaeochromocytoma of adrenal.	No mention.	4 cm. medial to 1st tumour, weight 25 g. 'This tumour should be interpreted as a metastasis.'	No mention.	140/80 to 300/160.
Cross & Pace, also reported by Richards & Hatch (1951). Case 5.	Right adrenal. Firm red-yellow encapsulated mass.	Many cells with large irregular nuclei containing two or more eccentric nucleoli. Cytoplasm acidophil and with occasional bluish granules. Variation in cell size. 10-50 μ.	No mention.	? Metastasis between lamina of C.6 and 7. Histological appearance similar to primary.	No mention.	120/70 to 225/133.
Ortega (1952).	Retroperitoneal tumour at level of inf. mesenteric artery.	Cells are typical phaeochromocytes. Well differentiated cells completely penetrated capsule and have invaded perivascular and perineurial lymphatics.	No mention.	Two masses (2 cm.) in retropleural space at level of 4th and 8th ribs. Similar histology to primary. Similar invasion of local structures.	No mention.	210/105.

Author considers possibility of retropleural growth being multicentric but dismisses this in view of extensive permeation of lymphatics.

Phaeochromocytoma may occur simultaneously in several sites normally occupied by chromaffin cells and in this way multiple simple tumours have been encountered (Snyder & Vick, 1947 ; Cahill, 1948, Cases 1 & 2 ; Hubble, 1951). Whether or not multiple tumour growths can be considered as metastases from a phaeochromocytoma will depend on the site and nature of the cells. If the deposits are present in any site where chromaffin tissue is found normally and especially if the tumour cells are mature phaeochromocytes, then the question of a multicentric origin must be considered. The growths described by Ortega (1952) ; Cahill (1944, Case 5) ; Cross and Pace (1950), reported also by Richards and Hatch (1951) ; Soffer, quoted Chamovitz and Fanger ; and Lewis and Geschickter (1934) could be malignant but they can be explained equally well on the basis of multicentric origin. If complete removal of all such foci is not undertaken or is impossible, then symptoms will persist and the prognosis for the patient will be the same as with a truly malignant phaeochromocytoma. Thus it is important for the surgeon to appreciate the possibility of multicentric foci in the sites mentioned and the importance of their removal.

When metastases occur in sites where chromaffin tissue does not exist normally they must be considered as true secondary deposits. On this basis 7 of the 31 tumours appear to be malignant (Table 4). The liver was involved in 5 cases, bones in 4, pleura and lung in 5, small intestine in 2 and lymph glands in 5. The lymph glands involved were cervical (Kaulbach, 1937), mediastinal (Chamovitz & Fanger, 1949 ; Pyle, 1951), para-aortic (King, 1931) and mesenteric (Eisenberg & Wallerstein, 1932).

The tumour cells in the metastases appear to be either mature phaeochromocytes similar to those seen in the primary (Eisenberg & Wallerstein, 1932 ; McGavack *et al.*, 1942 ; Chamovitz & Fanger, 1949), or immature cells (phaeochromoblasts, Pyle, 1951), or a mixture of both (King, 1931). In some instances the cells are difficult to identify (Buchner, 1934 ; Kaulbach, 1937). Absolute proof of the chromaffin nature of the cells is given in one case only (Eisenberg & Wallerstein, 1932), although Willis (1948) refuses to accept this since no details of the chrome reaction are supplied by the authors. In all others the chrome reaction is not mentioned, is dubious, or Zenker-acetic acid has been used as the fixative and the reaction vitiated. A bio-assay of the metastases for adrenaline and noradrenaline has not been performed in any of the reported cases, and although the mature phaeochromocyte cell has a characteristic basophilic appearance as described, it may be difficult to identify in a metastasis consisting predominantly of immature cells. Under these circumstances, bio-assay for catechols would be of limited value.

TABLE 4.

Malignant phaeochromocytoma.

Author.	Site and size of tumour.	Nature of tumour and metastases				
		Primary		Metastases		
		Description of cells.	Chrome reaction.	Description of cells.	Chrome reaction.	Blood pressure.
King (1931)	Left adrenal 2 × ¾" (nodule in it 1 × ½"). Right slightly smaller and contained a nodule.	Cells large 20-30 μ. In one part character of cells changed. Cells ovoid or spindle. Protoplasm small in amount. Alveoli larger.	Large cells—positive. Others—negative.	Liver, skin, lungs, lymph glands and bowel. Two types of cell— 1. Typical phaeochromocyte. 2. Anaplastic type.	Positive. Negative.	Normal.
Eisenberg & Wallerstein (1932)	Both adrenals twice normal in size.	Typical description of benign phaeochromocytoma.	Positive.	Gum, left lung (upper lobe size of orange), right lung (entire lobe), liver, spleen, intestine, mesenteric glands, left psoas muscle, 5 upper left ribs, 6-10 dorsal vertebrae. Similar to primary.	Positive.	No hypertension.
		Papillary adeno-carcinoma of thyroid : none of the secondaries resemble this.				
Buchner (1934)	Right adrenal. Size of walnut. Left adrenal. Size of hen's egg.	Same picture in right and left. Cellular tumour consisting of densely congregated large polygonal cells with fine vesicular nucleus. Cytoplasm bluish-violet and finely granular. Bizarre cells present.	No mention.	Several nodules in liver, thyroid and cervical lymph glands. Tumour cells arranged in small alveoli. Cells somewhat smaller and eosinophil but, according to shape and nuclei, are similar to cells in tumour of adrenal.	No mention.	—
Kaulbach (1937)	Left adrenal. Size of child's head. Tumour thrombi in left adrenal vein.	In parts structure of cortex is imitated. Cells show typical pleomorphism with granular pink cytoplasm. Giant nucleus, bizarre shaped. Small cells with rich chromatin nucleus—appear to be sympathogonia. Sudan IV stains most of the cells. Fat globules small and never coalesce.	No mention.	Lungs. Tumour thrombi in vein (left adrenal). Alveolar arrangement—smaller cells than primary. Mitosis prominent and atypical nuclei. Fat less Multiple tumour in small lung capillaries.	No mention.	160/90 to 190/140.

TABLE 4 (cont'd).

Author.	Site and size of tumour.	Nature of tumour and metastases				
		Primary		Metastases		
		Description of cells.	Chrome reaction.	Description of cells.	Chrome reaction.	Blood pressure.
McGavack *et al.* (1949)	Right adrenal. 930 g. 15 cm.	Cells and nuclei vary in size and shape. In some cases tumour cells arranged in whorl-like manner about blood vessels.	Giemsa stain shows purplish granules within cytoplasm of cells. Identical with granules of normal medulla.	Ribs, ileum, right femur, skull, lumbar vertebrae, pleura and liver. Similar to primary.	As in primary.	85/70 to 122/82.
Thorn *et al.* (1944). Later Chamovitz & Fanger (1949)	Left adrenal. 9 × 7 × 6 cm.	Tumour cells in nodular masses separated by fine strands of connective tissue. Many endothelial lined spaces among cells. In some areas extensive invasion of capsule by tumour masses and some extra-capsular extension.	Positive. Assay 0.278 mg. adren./cc. extract.	1. Tumour in origina site. 2. Extension between 2 kidneys. . Tumour in mediastinum, 4 × 2 × 1.5 cm. Similar to original but greater pleomorphism. Cells polygonal, size 25-35 μ, occasionally 80 - 100 μ. Tumour cells extensively invaded blood vessels, lymphatics and fibrous capsule. Mediastinal mass showed lymph nodes almost completely replaced by tumour tissue similar to that in primary growth.	Indefinite. Zenker acid used.	Elevated. Patient died one year after original operation.
Pyle (1951).	Right adrenal. 17.5 × 13 × 10 cm. 1070 g.	Cellular tumour with alveolar masses of malignant pleomorphic cells. Some bipolar. Occasional multinucleate giant cell. Cytoplasm granular. Some mitotic figures present.	Zenker fixation gave dubious reaction.	Lung, pleura, bones, liver, pancreas, mediastinal nodes, para-aortic nodes. Similar to primary.	Zenker fixed. Negative reaction due to immaturity of cells.	220/130 to 150/80.

One case (6) in this series illustrates the difficulty of diagnosing malignancy from histological examination of the tumour. The history was not helpful and the specimen was received 24 hours after operation when the chrome reaction and qualitative biological assay were negative. The diagnosis depended purely on histological examination of the tumour and, although the patient died with metastases one year after operation, it was not possible to confirm their nature as post-mortem permission was refused. The cellular picture in some parts of the tumour (Fig. 3) resembled phaeochromocytoma, but the large size of the growth, its atypical cellular appearance in many areas and absence of adreno-sympathetic attacks make differentiation from a non-hormonal adrenal carcinoma difficult. The association of adrenal carcinoma and phaeochromocytoma has not been described in any of the reported cases, but McGavack *et al.* (1942) recorded a malignant phaeochromocytoma simulating adrenal carcinoma, while the child reported by Neff *et al.* (1942) had evidence of adrenal virilism which regressed on removal of the tumour. In neither case, however, did histological examination of the tumour reveal the presence of adrenal cortical cells. Many cells in the tumour and metastases reported by Kaulbach (1937) contained fine lipoid granules in their cytoplasm. As most reported cases of phaeochromocytoma give negative results for fat, unless in cells immediately adjacent to areas of necrosis, it is possible that the lipoid cells reported by Kaulbach are cortical in origin, since such fine lipoid granules are consistently seen in the cells of the zona reticularis. Thus, it would appear that in the examination of the malignant tumours chrome reaction and biological assay for adrenaline and noradrenaline should be carried out, bearing in mind the possibility that growths which are de-differentiated or undifferentiated may be negative to both tests.

Chrome reaction in phaeochromocytoma.

Full details of the technique of the chrome reaction are given by Schmorl (1928), Sevki (1934), Blacklock *et al.* (1947) and Symington (1950). Numerous chrome fixatives (Orth, Helly and Müller) give good results; a satisfactory one consists of equal quantities of 5 per cent potassium dichromate and 10 per cent neutral formalin. Zenker fluid with acetic acid is definitely contra-indicated, yet this fixative is frequently used in attempts to produce a positive chrome reaction. The quality of the Giemsa stain is of importance and negative results may be obtained with unsatisfactory batches. A section with a known positive chrome reaction should always be stained as a control. If proven chromaffin material is not available, a satisfactory substitute can be prepared with a small piece of flannel cloth one inch in diameter. It is soaked in a solution of 1 : 1000 adrenaline hydrochloride for a few hours, then in formol dichromate solution for 48 hours, with two changes of fixative, and

transferred to 5 per cent formol dichromate solution for 7 to 10 days, with frequent changes of fixative. After thorough washing in running water the material is stained by Giemsa solution according to the method described by Blacklock *et al.* If the stain is satisfactory the cloth dyes a permanent olive-green colour (positive chrome reaction), but if unsatisfactory a pale blue colour results (negative chrome reaction).

A negative chrome reaction was obtained in the present series when the material was more than 12 hours post mortem. In one case (Fig. 1), examined 5 hours after death, the cells of some alveoli were chrome negative while others were positive. No material was available for examination between 5 and 12 hours post mortem and so the outer limit for a positive chrome reaction cannot be definitely established.

The chrome reaction is not specific and in-vitro experiments by Symington (1950) have shown positive results with such reducing agents as ascorbic acid, sodium bisulphide, as well as adrenaline. False positive chrome reactions can occur naturally ; the siderophile granules in the zona reticularis of the adrenal cortex give a false positive reaction after Giemsa staining without previous chrome fixation.

Biological assay of phaeochromocytoma for adrenaline and noradrenaline.

Until a few years ago the pressor substance in phaeochromocytoma was believed to be adrenaline, although many authors referred to it as an adrenaline precursor (proadrenaline). Recently Holton (1949) and others have shown that the pressor substance consists of two catechols, adrenaline and noradrenaline. Table 5 illustrates their content in the few recorded cases and it is obvious from these results that one or other of these substances may predominate, although generally the noradrenaline content is greater. Goldenberg and Aranow (1950a) were unable to correlate the catechol content of tumours in their cases with paroxysmal or persistent hypertension. The importance of adrenaline and noradrenaline assay of those tumours has been mentioned already. The technique suggested to us by West (1952) for the collection of material from chromaffin tumours is simple. Minced portions of the tumour or its metastases are placed in a weighed universal container with N/100 HCl in the proportion of 10 g. tumour (accurately weighed) to 3 ml. of acid. The specimen is then refrigerated and sent as soon as possible to the pharmocologist for assay. In operative cases it is advisable for the pathologist to be in attendance at the operation so that material for the assay can be collected immediately.

Pathological changes in other organs in phaeochromocytoma.

Heart. There was an increase in the weight of the heart in all but one case (Case 4) in our series. The weight varied from 320 to 620 g. and was associated in all cases with marked left ventricular hypertrophy. Cardiac hypertrophy is one of the most consistent findings in the recorded cases except that of Brown *et al.* (1950) and Case 4 of this present series.

Coronary vessels. Atheroma of the coronary vessels was not a significant finding in any case in this series. Nevertheless, in one of them (Case 12) myocardial fibrosis with aneurysm of the ventricle was found without apparent coronary lesions. Moderate coronary atheroma with stenosis has been recorded by Hubble (1951) in a child of 11½, while some degree of atheroma has been noted by Bachman (1949), Cole (1950) and Berkheiser and Rappoport (1951). The latter found the right coronary occluded by a thrombus in one of their cases aged 68. It is difficult to decide whether or not the adrenal tumour plays any part in coronary atheroma.

TABLE 5.
Adrenaline/noradrenaline assay of tumours.

Authors	Adrenaline (mg./g. tumour or % catechols present)	Noradrenaline (mg./g. tumour or % catechols present)
Holton (1949) .. .. .. 3 tumours	0.32-0.37	6.3-11
Goldenberg & Aranow (1950a) .. 14 tumours—10 persistent and 4 paroxysmal	0.03-9.1	0.95-7.2
Cahill & Monteith (1950) (1) ..	86%	14%
(2) ..	46%	54%
Engel & von Euler (1950) (1) ..	<0.05	4.5
(2) ..	0.75	0.75
Koffler *et al.* (1950)	Trace	1.04
Pitcairn & Youmans (1950) (1) .. 2 tumours (2) ..	Mostly noradrenaline. Mostly adrenaline	
Richards & Hatch (1951) (1) ..	0.32	5.3
(2)	0.37	5.5
Graham (1951)	2.7	10.6
Swan (1951)	0.085	0.875
Allen *et al.* (1951)	3.0	3.0
Huggins & Bergenstal (1951) ..	0.03-6.5	0.95-6.96
Iseri *et al.* (1951)	0.15	0.524
Effersoe *et al.* (1952)	0.14	2.4
Roth *et al.* (1952)	3.1 mg./g. pressor substance 77% epinephrine 23% norepinephrine	

Kidney. Naked-eye changes of pathological significance were observed in only two cases in our series. The appearance of diabetic glomerulosclerosis was seen in one of them (Case 9) and of essential hypertension in the other (Case 8). It is difficult to assess the part played by the tumour in the latter case since the patient was 63 years of age. Nevertheless, the absence of essential hypertensive changes in Case 5 (Table 6), a male of 73 years with persistent hypertension, shows that the latter can exist without secondary renal changes. The most consistent change noticed in this series was arterio-sclerosis of the arcuate and interlobular arteries.

Pancreas. The islet tissue appeared to be increased only in some cases. The material was not fixed for α and β cell staining and such investigations are still required on satisfactory material.

TABLE 6.

Phaeochromocytoma. Kidney lesions in present series.

Case No.	Sex and Age.	Type of hypertension.	Kidney Lesions.				
				Blood Vessels.			
			Glomeruli.	Arcuate and interlobular arteries.	Afferent arterioles.	Tubules.	Interstitial tissue.
1	M. 21	Paroxysmal.	Glomerular capillaries thickened. Few glomeruli fibrosed.	Splitting of elastic lamina.	Partly hyalinized and lumen narrowed.	Nil.	Slightly increased.
2	F. 37 Alive.	Paroxysmal.	—	—	—	—	—
3	M. 39	Persistent.	Not available.				
4	F. 57	Normal.	Walls of glomerular capillaries slightly thickened. Few glomeruli completely fibrosed.	Fibrosis of media. Thickening of intima. Splitting of internal elastic lamina.	Slightly thickened.	—	Slightly increased.
5	M. 73	Persistent.	A few fibrosed, or partly so; most of them normal.	Splitting of internal elastic lamina.	Nil.	—	Slight patchy overgrowth of fibrous tissue.
6	F. 34	Normal.	Thickening of basement membrane of glomerular capillaries.	Reduplication of internal elastic lamina.	Nil.	—	Slightly increased.
7	M. 39	Persistent.	—	Not available.		—	—
8	M. 63	Persistent.	Most of them sclerosed. Peri-glomerular fibrosis.	Fibrosis of media. Splitting of internal elastic lamina. Intimal thickening.	Marked hyalinization with narrowing of lumen.	Irregular, dilated. Pink casts in lumen.	Increased.
			Appearances of essential hypertension.				
9	F. 52	Normal.	Appearances of Kimmelstiel-Wilson kidney (exudative type of glomerulo-sclerosis).				
10	F. 52	—	Few sclerosed, most of them normal.	Fibrosis of media. Splitting of internal elastic lamina. Intimal thickening.	Only a few hyalinized.	—	—
11	M. 23	Paroxysmal.	Normal.	Nil.	Nil.	—	—
12	M. 45	Paroxysmal.	Normal.	Some fibrosis of media. Splitting of internal elastic lamina.	Slight hyalinization of arterioles to a few glomeruli.	—	—

The Contra-lateral Adrenal. This was not examined for lipoids in any case of this series, because of the interval between death and post-mortem. Further observations are required on this aspect. The gland should be fixed in 10 per cent formol-calcium solution for 24 hours, washed in water and then gelatine embedded. Sections (11 μ) can then be examined for cortical lipoids.

SUMMARY AND CONCLUSIONS.

It is suggested that the term ' phaeochromocytoma ' should be applied to all adrenaline or noradrenaline secreting tumours whether they occur in the adrenal gland or para-ganglia.

The site, age and sex incidence is noted in 283 reported cases ; 48 per cent occur in the right adrenal, 33 per cent in the left and 9 per cent are bilateral ; 146 cases are in females and 114 in males. All age groups are represented but the tumour occurs more frequently between the ages of 20 and 50.

The pathological aspects of phaeochromocytoma are discussed with particular reference to the 12 tumours (11 benign and one possibly malignant) personally studied. They represent four different histological types, (*a*) large alveolar type, (*b*) small alveolar type, (*c*) intermediate type, and (*d*) malignant type.

The histological data presented by the 11 benign tumours in the first three groups show the very varied appearance of the phaeochromocyte cell and demonstrate the fine dividing line which exists between the immature cell or phaeochromoblast and the phaeochromocyte.

Thirty-one cases have been recorded as malignant but in many instances the evidence for this is insufficient or unsatisfactory. The possibility of a multicentric origin for the tumour must be considered and the evaluation of the chrome reaction and bio-assay for catechols in the tumours and secondaries is discussed. The difficulty of diagnosing malignancy from histological examination of the tumour alone is shown in one case in our series (Case 6).

Reference is made to the chrome reaction in phaeochromocytoma. Fixation is all important and a mixture of equal quantities of 10 per cent neutral formalin and 5 per cent potassium dichromate is recommended. Zenker acetic acid should not be used since it vitiates the reaction. Post-mortem material should be examined within five hours of death to ensure satisfactory chrome reaction.

The technique suggested by West (1952) is simple and satisfactory for collecting material for bio-assay of catechols in the tumour or its metastases. Minced portions of the tumour or metastases are placed in a weighed universal container with N/100 HCl in the proportion of 10 g. tumour to 3 c.c. of acid.

In operation cases it is advisable for the pathologist to be in attendance at the operation so that material for assay can be collected immediately.