ADRENAL-SYMPATHETIC SYNDROME

CHROMAFFIN TISSUE TUMOUR WITH PAROXYSMAL HYPERTENSION

BY

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The chromaffin cells of the adrenal medulla are a part of the scattered "chromaffin tissue system." The tumours of these cells, the pheochromocytoma or adrenal paraganglioma, are nearly always benign, but usually produce paroxysmal hypertension ending fatally if the tumour is not removed.

There are reports of 152 cases of pheochromocytoma. The only extra-adrenal paraganglioma that have produced the hypertensive picture are those arising in the retroperitoneal tissues between the kidneys: of 13 such cases, 9 had the cardiovascular syndrome typical of the adrenal cases, and they form part of one clinical problem and are considered with the adrenal cases here. Of these 165 cases, 90 have been described since 1929, and 36 operations have been reported.

Paragangliomata arising from the intrathoracic sympathetic chain, from below the bifurcation of the aorta, from the coccygeal body, from the carotid body, and in the wall of the intestine are described, but very few of these are true tumours of the chromaffin tissue system (Da Costa, 1939-40; Christie, 1933) and none has given the cardiovascular picture.

In 1886 Frankel reported an autopsy finding of bilateral adrenal tumours and cardiac hypertrophy in a girl of 18 who for three years had had attacks of palpitation, headaches, and vomiting. The first full clinical description was by Labbé, Tinel, and Doumer (1922) who observed the paroxysmal hypertension in the attacks. The first case in which the correct diagnosis was made and followed by operation and cure was that of Pincoffs and Shipley (1929).

The final important step was by Beer, King, and Prinzmetal (1937) who showed that during the crises the blood contained large amounts of adrenaline.

Incidence and pathological anatomy. The incidence of pheochromocytoma in men and women is equal. Cases with the cardiovascular syndrome occur at all ages; mostly between 20 and 50 years. The association with generalized neurofibromatosis is recorded in nine cases.

The common lesion is a benign adenoma of one adrenal body. Sixteen bilateral tumours are recorded: of these, 8 showed a cardiovascular syndrome and 6 were malignant. Malignant pheochromocytomas are rare (15 cases), but may show a hypertensive picture. In about one case in ten the tumour is extra-adrenal, lying between the adrenal and the midline.

In size the tumour is usually like an orange, but tumours weighing from 13 to 2000 grams are described. The surface is often bossy and a line of remnants of cortical tissue is common. On section there are usually hemorrhagic cysts set in fibrous tissue.

Histology. (See Geschickter (1935) for good illustrations and Edwards (1937) and van Goidsenhoven and Appelman (1934) for methods of staining.) The commonest picture is of polyhedral cells of notably varied size and shape arranged in alveolar masses separated by fibrous septa, resembling cirrhotic liver with hyperplasia. The abundant cytoplasm is finely granular and the nucleus round or oval with a single nucleolus. Multinucleated giant cells and syncytiot sheets of cells are sometimes seen. Occasionally there are groups of cells resembling lymphocytes. The cells may be arranged round vascular spaces giving pseudo-rosettes (Peyron, 1930).

In tissues fixed with chrome salts the characteristic chromaffin reaction is seen. The brown granules may be seen in the cytoplasm or nucleus, or in the stroma.

Adrenaline in tumours. That these tumours give strongly positive reactions to chemical tests for adrenaline (Edwards, 1937) was shown thirty years ago. These results have now been confirmed by demonstrations of a pressor principle behaving like adrenaline. The quantitative estimations vary from 0.12 up to 20 mg. (Belt and Powell, 1934) per gram of tumour tissue (normal adrenal medulla about 0.4 mg.).

Association of other adrenal body tumours with hypertension. Paroxysmal hypertension has been reported with adrenal ganglieneuroma (Rogers, 1933), with neuroblastoma (Ernould and Picard, 1934) and with cortical tumours (Rimbault and Delmas, 1939; Plazy and Germain, 1932). Persistent hypertension has been found with retroperitoneal ganglieneuroma (Jergensen, 1933), with an adrenal
"sympatheticoblastoma" (Binger and Craig, 1938) and is, of course, not uncommon with adrenal cortical tumours.

Two cases are here reported, one fully and one more shortly, and this is followed by a general discussion of the clinical picture, diagnosis, and treatment.

**Reports of Two Cases**

An aircraftman, aged 29, awoke one morning with profuse sweating, pain across the epigastrium, and vomiting. These continued and on the third day he felt very ill and was sent to hospital. There was no palpitation. He had never had any illness like this before.

On admission he was in a state of collapse. The extremities were blue and cold. His mouth temperature was normal. The pulse was 80, tiny, but hard; the blood pressure, 197/167. No signs of disease were detected in the heart or lungs. There was herpes febrilis of the lip and vague tenderness of the right side of the abdomen. The urine showed a trace of albumen.

He was treated with warmth, rest, morphone, and fluids by mouth. There was no further vomiting and he improved steadily. Next day he felt and looked much better; the following day the blood pressure was 125/100, and a provisional diagnosis of paroxysmal hypertension from adrenal medullary tumour was made.

*Previous history.* The family history was of no significance. Up to 25 years of age he was healthy save for insomnia at times and, at 22, a right-sided orchitis, which left the testicle atrophic.

From the summer of 1937, that is, for four years, nearly every morning shortly after getting up, he had a few minutes' nausea, usually accompanied by palpitation, but without vomiting. After this nausea passed off he felt weak for 10 to 15 minutes.

In July, 1938, he had an attack of thumping of the heart—the rate-and rhythm being unaffected. Later that summer for half one day he felt ill and for a week after had severe headache and felt weak.

From November, 1938, to April, 1939, he had severe headaches. Three weeks after they started he began to have attacks of thumping of the heart during which the headache was worse. He was in St. Thomas's Hospital in December, 1938, and while in bed there the palpitation recurred frequently, the forcible beat of the heart being visible from several feet away. No signs of organic disease were found, except that the blood pressure was 144/100. The palpitations continued for a time sometimes accompanied by choking feelings and vomiting. After they ceased the headaches gradually cleared up.

At the end of 1939 and occasionally since he noticed that sometimes when leaning to the left he would suddenly feel nervous and dizzy.

In July, 1940, he joined the R.A.F. Sometimes, during the next winter, he had a momentary feeling of intense weakness in the legs while walking. In February, 1941, at a medical examination for aircrew he says that his blood pressure seemed to arouse interest; at a re-examination it was 120/70 and he was passed.

During the summer of 1941 on several occasions at drill he was told he was pale. Only sometimes was this pallor accompanied by subjective feelings of trembling, anxiety, and faintness, lasting up to half a minute. Later these sensations occurred about twice a day and he also noticed that choking would bring them on.

In July, 1941, the severe paroxysm described led to his admission to hospital. While there he had some further minor crises which may be conveniently described here.

One afternoon he was observed to be pale. He said he felt well but had just been passing water which since cystoscopy, for which a meatotomy had been needed, had been painful. His blood pressure was found to be 210/135; ten minutes later it was 150/105 (at rest at this time it varied from 120/95 to 130/110). This was evidently a symptomless paroxysm of hypertension induced by painful micturition. Similar attacks were observed on succeeding days.

During the perirenal pneumography a second insufflation gave severe pain. He became very distressed, complaining of suffocation; his face was congested and his blood pressure was 240/170. This attack lasted about ten minutes and was followed by prostration for half an hour.

*Progress in hospital and investigations.* Two days after admission he looked and felt well. For the next two weeks, however, he had a symptomless pyrexia, often from 99 to 100.6° F., for which no cause could be found.

Psychologically the patient was a placid, well-balanced person without conscious anxiety feelings and of normal sexuality.

X-ray of the chest showed no disease of heart or lungs, but a dextrocardia with transposition of viscera was revealed. The teeth were healthy. The blood two days after admission showed R.B.C., 5·0 million; Hb. 98 per cent (Haldane); W.B.C., 21,200 (neutrophils 82 per cent, lymphocytes 11 per cent, monocytes 7 per cent), and eleven days later Hb. 85 per cent, W.B.C. 8000 (neutrophils 75 per cent). Blood chemistry (20/9/41) gave serum chloride as sodium chloride 560 (normal 560-
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620), sodium 326 (normal 325–350), potassium 46 (normal 16–20) mg. per 100 c.c.—a very significant rise in potassium level.

A rounded tender mass was palpable high up in the left loin. As the pyrexia abated this mass seemed to become less easily felt and less tender. Repeated examinations of the urine revealed only an occasional trace of albumen; its specific gravity ranged from 1024 to 1001 in tests, and the urea clearance was 113 per cent normal. X-ray showed no renal stone, and cystoscopy a normal bladder. Intravenous pyelography showed the left kidney slightly depressed with a little deformity of the upper calyx.

Attempts to induce attacks by the various manoeuvres described below were made but none of these affected the blood pressure level. As noted above, for a few days after cystoscopy he had symptomless paroxysms of hypertension induced by the dysuria. These were an important confirmation of the diagnosis. Adrenaline was given intramuscularly. The pressure which was about 160/120 before the injection was little affected by 0·25 c.c. of 1/1000 solution, but after 1·0 c.c. it rose to 205/140 for a few minutes. As the rise began the patient said it was like the beginning of an attack. On another day 1·25 c.c. gave pallor and palpitation but only a slight rise of pressure. A cold pressor test (Hines and Brown, 1933) gave a "positive" result, the pressure rising from 135/100 for 3½ minutes to reach 160/120 with a slower fall.

The electrocardiographic findings are given later (see p. 7).

Operations and progress. Mr. L. R. Broster kindly agreed to operate and it was decided to do an exploratory laparotomy and to remove the tumour by the lumbar route at a second operation.

The evidence obtained from a perirenal pneumography by Mr. G. C. Sawyer was too indefinite to help in deciding the site of the tumour. Also, the insufflation on the right side was painful and led to an unpleasant attack.

At an exploratory laparotomy a tumour the size of a tangerine orange was found above the left kidney. The right adrenal body was normal. The blood pressure which before the operation had been rising from 130/108 to 150/112 was after induction 180/120 and remained there throughout, being unaffected by squeezing the tumour. The pulse, 110 and regular at first, soon became irregular in force and after manipulation of the tumour there was an irregular tachycardia (rate 200) for ten minutes. This may have been due to the use of cyclopropane in the presence of excess adrenaline (Burstein et al., 1940). There was no disturbance after the operation and no significant change in the white blood count two days later.

The tumour was removed two weeks later on 24/9/41, under gas-oxygen-ether preceded by omnoxon-scopolamine.

For combating the expected fall in blood pressure after removal of the tumour, a 1/100,000 solution of adrenaline HCl in normal saline was prepared. When the patient was anesthetized a slowly running continuous intravenous drip of normal saline was inserted with provision for switching over to the adrenaline solution if necessary. This drip was kept going during and for some hours after the operation. The tumour was removed through a lumbar incision. The blood pressure, 175/110 at the beginning, rose during the operation to 225/145, and fell to 90/70 in ten minutes after the removal of the tumour. About 10 c.c. of the adrenaline solution restored it to 120/80 for ten minutes, but for some hours after the operation it was about 80/60 and the patient was slightly cyanosed and sweating profusely. The day after it was 140/105, settling on the third day to 130/95. He was given sodium desoxytocosterone for three days.

He made an uninterrupted recovery and was discharged three weeks later, having had no recurrence of the minor symptoms that were previously of daily occurrence.

When he was discharged, though he was free of infection his white count was still raised, 17,500, neutrophils 78 per cent (the day after the operation it had been 23,000 and 77 per cent). He went to an R.A.F. hospital, and while there he had four minor attacks, and then no further attacks in a year. As the tumour was histologically malignant he was given deep X-ray therapy six months after the operation. He returned to civil life and is working very hard. His weight is well maintained and he writes that he is fit and entirely free of any of the symptoms he had before the operation. This was confirmed by an examination at which his blood pressure was normal.

Description of tumour. The tumour was a flattened ovoid 5·5 × 4·5 × 2·5 cm., weighing 63·5 grams. The surface showed bluish bosses and a line of cortical remnants (Fig. 1). Section showed a fibrous capsule surrounding a matrix which was hard and pearly white in the centre and in which were set round areas of purplish fleshy tissue corresponding to the bosses on the surface (Fig. 2). There were two irregular areas of yellow tissue.

Histology (Dr. H. W. C. Vines). The tumour has a well defined fibrous capsule, into which the tumour cells appear to be infiltrating to some extent. Some lymphatic spaces contain tumour cells. The tumour is composed of large polyhedral cells, many compressed into spindle cells. There are a few multinucleate cells and some with deeply staining pyknotic nuclei. Mitoses are rare. There are small areas of necrosis with replacement by very loose areolar fibrous tissue; and areas of
Fig. 1.—Case 1. Drawing of tumour, slightly under actual size. The line of cortical remnants and the bosses are visible.

Fig. 2.—Case 1. Section across tumour, slightly under actual size. The fibrous capsule, the fleshy cysts, pearly fibrous matrix, and two areas of yellow fatty tissue are seen.

Fig. 3.—Case 1. Microphotograph; $\times 175$; Hx and E. Showing cells of varied shapes and sizes; giant cells visible by the cleft; and at bottom perivascular arrangement of cells.
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hemorrhage. The vessels are numerous and many are thin-walled but not sinusoidal. There is some patchy deposit of hemosiderin. In some areas perivascular survival of the tumour cells presents the appearance of pseudo-rosettes, or of a papilliferous arrangement. The tumour cells give a chrom reaction (Fig. 4). The growth does not appear entirely benign. It may be called a pheochromoblastoma.

Adrenaline content (Dr. Derek Richter and Dr. F. C. MacIntosh). This was done on an extract made of a slice across the tumour. By colour reaction with iodine, the adrenaline content was 5-25; and by biological test on atropinized eviscerated cat, 8 mg. per gram of wet tumour tissue (normal adrenal content 0-4 mg. adrenaline per gram.).

Case 2. Short notes of a case which came to my notice during the preparation of this paper, are included. A clerk, aged 25, was invalided out of the Army in 1940 for "heart trouble." He had been breathless on exertion, with a few attacks of nocturnal dyspnea. There was no history of nephritis.

One night he developed severe breathlessness. His doctor gave him morphia and sent him to hospital. On arrival he was very cyanosed with audible bubbling respiration and was bringing up a blood-stained froth. There was no overfilling of the veins and no edema of the ankles. In the chest many crepitations and bubbling noises were heard. His blood pressure was 160/120. The blood urea was 40. He was given oxygen, atropine, and later morphia, but he failed to improve and died nine hours after admission.

At autopsy, both lungs were grossly congested. The heart was of average size, the right auricle dilated, the left of normal size; the mitral valve admitted three fingers. The vessels were normal. The liver showed acute congestion only; the kidneys and the other organs were normal excepting the right adrenal body. This was rounded and enlarged, about 2 inches in diameter. On section there was towards the periphery a large cyst filled with blood and tumour tissue. Histological examination showed normal left adrenal and kidney. The right adrenal showed alveolar masses of polygonal and polymorphic cells in a fibrous stroma (Fig. 5). Chrome staining was not done.

CLINICAL PICTURE

Chromaffin cell tumours of the adrenal medulla may give—(i) Recurrent paroxysms of generalized vasoconstriction accompanied by a remarkable but transient hypertension; the adrenal sympathetic syndrome; (ii) Chronic hypertension with renal and cardiac failure, resembling malignant hyper-
tension, (iii) Addison’s disease from local pressure on the cortex, an uncommon picture, or (iv) No symptoms. The descriptions given here deal chiefly with the first type which is the commonest, most easily recognized, and most treatable one.

The history of attacks usually extends over several years, even as long as 16 years (Allen, 1940). But they may end fatally after a few months or even days (Edwards, 1937). Sometimes there is a steady progress from mild occasional attacks to frequent and severe ones, but attacks may cease for a time, even for ten years (Hamilton, 1940). At first the blood pressure level is normal between paroxysms, but later these are often superimposed on a persistent hypertension. This may already be present at the earliest examination and occurs in about half the cases of long duration.

The first attack may be severe, but more often the early ones are mild. Or there may have been transient malaise, headaches, nausea, digestive troubles, diverse pains, dizzy spells, palpitations, the significance of which is not realized until a more severe paroxysm occurs. If the condition is not treated these major crises recur. The paroxysms vary in severity and clinical picture but in individual subjects they are often of one type. They may recur irregularly at long intervals, or several times a day, or daily at a set time.

Precipitating factors. Where attacks occur before breakfast, fasting may be a factor, but it is as common for them to occur after meals. Constipation may induce the vascular crises (Foucar, 1939). More easily understood as precipitating causes are exercise and emotion. Pain led to attacks in the present case. Drinking 1500 c.c. of water caused one fatal paroxysm (Howard and Barker, 1937). Attacks occur at operation, even before manipulation of the tumour. By far the commonest precipitating factors are postural, e.g. bending the trunk, combing the hair, etc. Where flexion of the trunk leads to attacks there is usually a palpable tumour, but it is not always flexion to the side of the tumour that provokes them. A steady pressure for two minutes to the adrenal region or to a palpable tumour may induce a paroxysm at once or after a few minutes (MacKenzie and McEachern, 1938). A sharp blow on the abdomen, warming the renal region, pressure on the carotid sinus, and the cold pressor test are other reported methods that may be tried in a suspected case.

But it is to be noted that in half the cases no special precipitating factors have been recorded.

The paroxysms. The recurrent vascular crises are the most important feature of the clinical picture. There is a sudden generalized vasoconstriction producing symptoms and signs from many parts of the body and so causing a characteristic picture. Less commonly patients may complain of symptoms limited to one system, e.g. of recurrent epigastric pain and vomiting or recurrent headache. The accompanying rise of blood pressure shows that it is the symptoms and not the vasoconstriction that is limited in distribution. A more detailed history or examination may yield other evidence of the widespread vasoconstriction. Symptomless paroxysmal rises of blood pressure have been noted by four authors.

Preceding the attack, there may be paraesthesiae or an indefinite malaise which the patient recognizes as the aura of his attack. The commonest first symptom is palpitation, but various feelings in the extremities, epigastric pain, sinking feeling or nausea, subeentral constriction or cardiac pain, lusty sneezing (in three cases), throbbing in the temples, dizziness, headache, or a sensation of shakiness or languor may mark the onset of the paroxysm. As it proceeds some or all of these symptoms may develop. A progress of symptoms upwards from the feet is described in several cases, when warmth or tinglings of the feet may be succeeded by cramps in the calves and thighs, then by abdominal colic and epigastric pain with nausea and vomiting, followed by thoracic angina radiating to the arms, then fullness, choking or pain in the neck, throbbing in the temples, dizziness, and finally an atrocious headache. Nausea is described in nearly all attacks and vomiting in most of them; and epigastric discomfort is often noted. Pain in various sites, severe headache, and vertigo are common. Sweating, a sense of hair-pulling (Nuzum and Dalton, 1938), lachrymation, and salivation are symptoms of pharmacological interest. Where the attacks are severe, spitting of blood (from acute pulmonary oedema) may be described. In other cases a condition resembling shock or collapse occurs.

In these major paroxysms the patient is obviously ill. The face is usually pale and anxious, but may be congested or blotchy or may alternate between pallor and redness. Coldness of the extremities is described in nearly every case; usually blanched, the hands may be purplish. A moderate rise of body temperature is common. The pulse is not infrequently noted as being weak or small; in the present case it was tiny but hard. The pulse rate may be up or down and may react differently in different attacks, or variably during one attack. Rhythm irregularities may occur. The heart beat is very forcible and may shake the bed. The second sound at the aortic area is loud and ringing; a transient aortic diastolic murmur may be heard at the height of the paroxysm (Bernal, 1933).

The systolic pressure may rise in a few minutes from 120 to over 300 mm.; and the diastolic in proportion. The level may vary widely during the attack. An initial apnoea or tachypnoea may be seen. An abdominal tumour, not always in the loins, is palpable in about one third of cases; it
may be, in fact, a kidney pushed down by the adrenal tumour. Other common signs are swelling of the neck veins and dilatation of the pupils. During the attack there may be anuria or oliguria with albumen and casts in the urine, and azotemia, which may exceed 150 mg. urea per 100 c.c. Hyperglycemia and glycosuria are common. The white blood cell count shows a rise due entirely to rise in lymphocytes, the percentage of which rises 25 or 30 per cent (MacKenzie and McEachern, 1938; Hatieganu et al., 1939).

Demonstration of excess of adrenaline in the blood. The first success was by Beer, King, and Prinzmetal (1937) perfusing the eviscerated rabbit’s ear. Strombeck and Hedberg (1939) using a chemical method demonstrated a 30 times normal adrenaline content in the blood between attacks, with a 1000 times normal content in the attack. Earlier workers and also Biskind et al. (1941) were unable to find any pressor substance in the blood.

Duration and termination of paroxysms. The attacks may last minutes, hours, or days. The common length is one to two hours. The end of the attack may be marked by flushing of the face and neck, and abundant sweating, sometimes with salivation, lachrymation, and dilatation of the pupils. The blood pressure falls and after short attacks may reach a normal level in a few minutes. After the paroxysm there is commonly a feeling of extreme prostration lasting from a few minutes up to several hours. Headache usually persists for some time after the attack.

Localized and minor paroxysms with symptoms of limited distribution are common; in these, however, closer investigation will often give evidence of symptoms or signs involving other systems. Labbé, Tinel, and Doumer’s patient attended for daily bouts of vomiting; Shipley’s had diarrhoea and vomiting. Periodic nausea, headache, and abdominal pain immediately or an hour or two after meals, may be attributed to dyspepsia. Angina pectoris is a common symptom and may be the most prominent. Palpitation may be the only complaint. Acute pulmonary edema is not rare and in this disorder it may occur in the absence of cardiac enlargement or coronary artery disease. Shock or collapse may occur, as in the present case. In another case, during a paroxysm lasting three days, and giving a clinical picture of shock, the blood pressure varied between 90/70 and 240/150 without change in the general condition (van Goidsenhoven and Appelman, 1934). The cases resembling malignant hypertension are discussed below.

Severe headache, alone or with vomiting; and transient vertigo may occur by themselves. Transient loss of consciousness has been recorded in five cases, but all of these had persistently raised blood pressure. Periods of fatigue, lassitude, or weakness may be the salient feature (Fein and Carman, 1937; Hegglin and Nabholz, 1937). Sensations of anxiety may be the cause of consulting a physician (Palmer and Castleman, 1938).

Cases with lumbar pain and abnormal urinary findings; with recurrent glycosuria resistant to insulin; with bouts of malaise and pain; or with congestion of the face combined with profuse sweating; and other minor attacks are unlikely to be elucidated unless paroxysmal hypertension is found to accompany the symptoms, or a major crisis occurs.

Between attacks. Many subjects enjoy good health in the intervals. Loss of weight and anaemia (rarely severe) are common, and a persistently raised blood pressure is found in half the cases. Neutrophil leucocytosis, dyspepsia, or obstinate constipation may be seen. An abdominal tumour is present in one case in three. Fever occurs rarely. Lassitude or insomnia occur but anxiety is surprisingly rare.

The mode of death. The commoner modes of death after paroxysms are acute pulmonary edema, shock or collapse, and cerebral hemorrhage. Collapse may follow parturition or a minor operation under local anesthetic (5 cases), or a major operation. Death with high fever is described. Chronic renal failure, Addison’s disease, and malignant cachexia are rarer causes. Five cases have died suddenly and unexpectedly in hospital while undergoing investigation or awaiting operation.

Persistent hypertension. Some cases of pheochromocytoma from the start closely resemble malignant hypertension. Others have been followed from a stage in which hypertension occurred only in the attacks to a second stage of continuous hypertension with its usual sequelae. The paroxysms may continue. If they do, symptoms are usually less widespread. Albuminuria, cylinduria, and azotemia are common but may vary remarkably independently of the patient’s symptoms. Even after it has been high for a long period, the blood pressure may fall to normal for a time (van Goidsenhoven and Appelman, 1934).

Electrocardiographic changes during attacks. Auricular premature beats (Rogers, 1933), runs of tachycardia of auricular and ventricular origin (Pincoffs, 1928), and sinus bradycardia with beats arising alternately from S-A and A-V nodes (Burgess et al., 1936, Hegglin and Holzman, 1937) are recorded. A rapid arrhythmia during operation was seen by Hatieganu et al. (1939) and in the present case. QRS slurring (Allen, 1940) and left axis deviation (Kremer, 1936; Rogers, 1933) are recorded. The T wave varies; it may be very high (Pincoffs, 1928; Burgess et al., 1936), flattened (Hegglin and Holzman, 1937), or inverted in leads I and II (Kremer, 1936; Allen, 1940; Rogers, 1933).
After attacks a remarkable lengthening of the S-T interval and variable changes in the T waves lasting a few days after severe attacks were noted by Hegglin and Holzman (1937). In the present case there was inversion of T in all leads lasting for some weeks after the attack. Neither inversion of T in all leads nor such slow recovery is described elsewhere.

Between attacks a normal curve was found in 6 of the 18 cases with reports. Very large P waves were noted in 3 cases, but left axis deviation and diminution or inversion of T were the most common findings. In the absence of repeated examinations it is not certain how permanent these changes were (cf. present case).

Where repeated curves have been taken (Rogers, 1933; Hegglin and Holzman, 1937) there have been notable variations in different attacks. The commonest change seen is flattening or inversion of the T wave in leads I and II. In two cases there was increased prominence of T waves. Experimentally adrenaline, usually but not always, gives increased T waves. The changes in rhythm seen in attacks are probably the resultant of A-V node acceleration from adrenaline and S-A node slowing due to the vagal effect from the depressor reflex. The T wave flattening seen in attacks is probably similarly a vagal effect. The S-T and T variations lasting for a few days after severe attacks observed by Hegglin and Holzman (1937) were considered to be due to metabolic upset in the myocardium. Similar temporary T wave depression may occur for a few days after a bout of paroxysmal tachycardia. The acute hypertension of acute nephritis may be associated with temporary changes in the T wave lasting some weeks. (Master, Jaffe, and Dack, 1936; Langendorf and Pick, 1938). These alterations, which are not exactly parallel to the rise in blood pressure, are probably partly due to the hypertension and partly toxic.

In the case reported here, Fig. 6A, taken a week after admission, showed dextrocardia, left axis deviation, and inversion of T in all leads. These changes were still present three weeks later and were all thought to be associated with the dextrocardia (Schnittker, 1940), but eight weeks after admission the T waves were positive in all leads (Fig. 6B).

Depression of the T wave lasting some six weeks has not been previously described. It is unlikely to have been vagal or metabolic in origin; as it lasted too long. It may be analogous to that sometimes seen in acute nephritis, though T wave inversion in all three leads has not been reported in that disease. According to Goldzieher (1929), a large dose of adrenaline may produce myocardial lesions visible to the naked eye. Subepicardial hemorrhages are recorded in autopsy findings after death in paroxysmal hypertension from pheochromocytoma. The long lasting T wave alterations seen in the present case were probably due to a small myocardial hemorrhage, perhaps involving the conducting system.

**Differential Diagnosis**

The diagnosis rests on the history and the observation of an attack with paroxysmal hypertension and other phenomena. If spontaneous attacks are not seen, efforts should be made to induce one. Frequent readings of the blood pressure may detect symptomless paroxysms. The demonstration of excess adrenaline in the blood during or between crises is a specific test but is not always positive.
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Intravenous injection of adrenaline may produce the same subjective feelings as an attack, but is not without danger. Estimation of serum potassium in the attack is suggested by McQuarry (quoted by Wells and Boman, 1937) since intravenous adrenaline may produce an 86 per cent rise in blood potassium figures. A very high value was found between attacks in the case recorded here. In deciding the site of the tumour, pyelography is much the most useful procedure. Perirenal pneumography is not recommended as it is hazardous and not very useful.

Paroxysmal hypertension occurs in a number of conditions. (1) Pheochromocytoma. (2) Essential hypertension. In this the blood pressure is always raised between the attacks, prodromes are common, the onset and end of the paroxysm are gradual, fits and cerebral eclipses are common, widespread symptoms are rare, and attacks are not precipitated by posture or pressure on the adrenals. Abnormal urinary findings and a leucocytosis are seen both in pheochromocytoma and in malignant hypertension. (3) Symptomatic paroxysmal hypertension. Recurrent attacks may occur in lead poisoning, eclampsia, tubes dorsalis, aortic reflex, angina pectoris, angina vasomotoria of Nothnagel, affections of the vagus, and thalamic tumour.

Where an attack has not been witnessed the history may be difficult to elucidate. Hyperthyroidism, diabetes mellitus, peptic ulcer, acute and chronic nephritis, malignant hypertension, surgical shock, polyarteritis nodosa, migraine, cerebral tumour, angina pectoris, cardiac neurosis, neurasthenia, and anxiety state may be simulated.

The vasovagal attacks described by Gowers (1907) and more recently by Ryle (1928) and Kinnier Wilson (1940) in some instances present a very close similarity to the attacks of the adrenal-sympathetic syndrome. Gowers considered that Nothnagel's syndrome was a closely allied phenomenon, and he pointed out that vasomotor spasm may attain a high degree in vasovagal attacks, being evidenced by coldness and pallor of the limbs and diminution of the pulse. Nothnagel's syndrome (see Lewis, 1931) is apparently identical in symptomatology with the adrenal-sympathetic syndrome. It is possible that some of Gowers' cases (e.g. his Case 1) and some of Nothnagel's were due to pheochromocytoma.

TREATMENT

The treatment of pheochromocytoma is to remove it. Laparotomy should be considered without undue delay as the benefits of successful removal of a pheochromocytoma outweigh the dangers of an operation in a case of secondary paroxysmal hypertension. Palliative treatment by sedatives or X-rays gives only transient relief.

Treatment of the paroxysm. Bleeding is most important. Morphine may be very valuable. Lumbar puncture will lower the blood pressure and relieve the headache in other types of paroxysmal hypertension, and should be useful in this one, especially for the headache which is severe and intractable. Vasodilators may give temporary relief, but worse discomfort later. For collapse following a paroxysm, adrenaline is specific (in contrast to its effect in surgical shock).

Pre- and post-operative measures. These are reviewed by Biskind et al. (1941). Chloroform, cyclopropane, and spinal anaesthesia should be avoided. The abdominal approach is recommended by most recent authors. Where the site of the tumour is uncertain, a laparotomy to locate the tumour and to establish the presence of the opposite adrenal body, with a later removal of the tumour by the lumbar route adds the real risk of a second operation but makes the actual excision a less disturbing procedure. This is important as operation may be accompanied by severe paroxysms. Incision of a large cyst may prevent these (Strombeck and Hedberg, 1939).

Operation was followed by severe shock in 17 of the 37 cases recorded. This shock is best combated by giving a dilute solution of adrenaline intravenously as described in the case report above. Where the blood pressure fails to respond to adrenaline, blood transfusion should be given. Salt and adrenal cortical hormone 10 c.c. should be given after operation.

Results of operation. In their excellent analysis of cases submitted to operation, Biskind, Meyer, and Beadner (1941) report 29 cases. The list is not quite complete: 3 cases (Belt and Powell, 1934; Volhard, 1931; Hatiegano et al., 1939) which died after operation are excluded on inadequate grounds; 2 cases are omitted; one successful (Ody and Piotrowsky, 1933) and one fatal from post-operative shock (Keyser and Walters, 1924); and 3 successful operations have been recorded since (Brunschwig and Humphreys, 1940; Hamilton, 1940; and the present case).

If these cases are added, we get a total of 37 operations with 10 deaths. Of these 10 deaths after operation, 7 occurred in 19 cases reported to the end of 1936, and 3 in 18 cases reported since then. Of the 27 survivors, 24 are probably quite well. In one case a recurrence of symptoms after operation responded to X-ray treatment (Borras and Meyer Mota, 1938).
DISCUSSION

The cause of the paroxysm or vascular crisis is a sudden hyperadrenalinæmia of obscure origin which causes a widespread vasoconstriction and also increases the output of the heart. The sharp rise of blood pressure acting through the "depressor" reflex leads to a vagal discharge, which explains why the symptom picture includes not only adrenalinergic mechanisms but also cholinergic ones such as salivation.

A rise of blood pressure without symptoms is probably common. Attacks with symptoms but no rise of blood pressure are mentioned by Labbé, Tinel, and Doumer (1922) and by Bernal (1933). These may occur but it is certain that in most of the paroxysms with only localized symptoms, it is the symptoms and not the vasoconstriction that are localized. This is shown by the rise in systemic blood pressure. The local symptoms are secondary to the rise of blood pressure; abdominal pain probably being due to distension of vessels, angina pectoris to oxygen deficiency in the overworking heart muscle, and so on.

Specific localization of symptoms is seen in other types of paroxysmal hypertension; abdominal in plumbism, cerebral in eclampsia, anginal in aortitis, but each of these is not invariable, e.g. eclamptics may complain of abdominal pain with their paroxysms.

A very striking symptom is the feeling of prostration, which may last for half an hour after an attack consisting of a few seconds' palpitation or dizziness. Freeman et al. (1941) and others have shown that on stopping adrenaline infusion in dogs, shock with oligemia develops. Large doses of adrenaline may be followed by prolonged vagal effect (MacDowell, 1931). According to Goldzieher (1929, p. 81) pheochromocytoma overfunction may lead to complete exhaustion with morphological findings as in muscular overexhaustion.

Adrenaline in large doses diminishes muscle and somatic reflexes by a direct depressant action on the spinal cord (Schweitzer and Wright, quoted by Wright, 1942). This seems a likely explanation of the prostration, which is probably directly analogous to the "nervous exhaustion" felt after intense excitement.

The cause of the persistent hypertension sometimes seen with pheochromocytoma remains obscure. In continuous infusion of adrenaline, the blood pressure after an initial rise returns to normal (Freeman et al., 1941). Strombeck and Hedberg (1939) in their case found the blood adrenaline between attacks was 30 times normal without persistent hypertension. But it is possible that in other cases there is a breakdown of the normal adrenaline destruction mechanism (see Richter, 1940) or there may be a dislocation of the normal mechanisms for regulating blood pressure. The common finding of albumen and casts in the urine after attacks suggests that renal damage sustained during paroxysms may be the cause, but this is doubtful. In some cases of pheochromocytoma with persistent high blood pressure, the kidneys at autopsy have been intact; in others after removal of the tumour the blood pressure has returned to normal, and in others it has returned to normal or below without operation.

On the other hand, it is possible that the vascular crises seen in essential hypertension, aortic valvular disease, tabes, eclampsia, and lead-poisoning, which may so closely resemble those of the adrenal-sympathetic syndrome, are themselves due to sudden discharge of adrenaline. Brandt and Katz (1933) reported that during hypertensive crises the blood has adrenalinergic characters on biological testing, which are absent between the crises. Bernal (1933) obtained a rise of blood pressure by perfusing blood taken from a patient with essential hypertension during a crisis, and also with blood taken from a patient during a bout of lead colic. These are experiments that should be repeated; especially as bleeding is the treatment for any hypertensive paroxysm.

SUMMARY

Two cases of adrenal-sympathetic syndrome due to pheochromocytoma (chromaffin tissue tumour of the adrenal medulla), are described.

The first is unusual in that though he had minor attacks almost daily for four years, there was only one major attack, which led to a diagnosis and operation, with cessation of the attacks.

The syndrome of chromaffin tissue tumours is reviewed. It is noted that while many cases show widespread symptoms, others show only local symptoms, though the vasoconstriction is generalized. Paroxysmal hypertension is the one sign common to all attacks. The treatment is removal of the tumour.
ADRENAL-SYMPATHETIC SYNDROME

The close similarity between the hypertensive paroxysms of pheochromocytoma and those seen in other conditions, notably in essential hypertension, suggests that some of these other paroxysmal hypertensions are due to sudden discharge of adrenaline.

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REFERENCES

Of 220 papers consulted, only those referred to in this paper are listed here. A fuller list and a table of published cases will be deposited in the library of the Royal Society of Medicine. A few more important references are starred.

*Frankel, F. (1886). Virchows Arch., 103, 244.


