Sustained Hypertension due to Pheochromocytoma

Report of Case Cured by Removal of Tumor

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Report of a case of sustained arterial hypertension due to an adrenal medullary tumor, excision of which resulted in return of the blood pressure to normal levels and relief of all symptoms. A brief discussion of the symptoms and signs and several useful diagnostic tests is included.

PHEOCHROMOCYTOMAS are tumors of special interest because they are capable of producing arterial hypertension, both of the paroxysmal and of the sustained type; furthermore, the hypertension they cause is one type that can be completely cured. Recognition of these tumors is of utmost importance since they can be completely relieved by surgical extirpation, and also because it is now known that pheochromocytomas are not as rare as formerly believed. The tumors have been known to pathologists since 1886, when Frankel1 reported the autopsy findings of bilateral adrenal tumors and cardiac hypertrophy in a girl 18 years of age, who for three years had had attacks of palpitation, headaches, and vomiting. The clinical adrenosympathetic syndrome was first described in 1922 by Labbe, Tinel, and Doumer2 and since then, pheochromocytomas have been recognized with increasing frequency. The first successful removal of such a tumor with cure of paroxysmal hypertension was reported in 1927 by Mayo.3 A survey of the available literature now reveals that operations have been performed on at least 77 of these patients (including the present case), with death being reported in 16 cases.4-14 Our case is one of sustained hypertension, with complete relief of symptoms following excision of a left adrenal medullary tumor.

CASE REPORT

The patient, a 23 year old, white man, first entered Emory University Hospital on October 23, 1947, complaining of headaches and weakness of his legs. These symptoms began in May, 1945, shortly after the patient had been rejected by the Army because of hypertension. He had passed the preinduction physical examination in January, 1945.

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Following their onset the headaches increased in severity. They usually occurred when the patient awakened in the mornings and improved during the day. They would recur for two or three days and then the patient would have none for several more days. Hot weather and physical exertion seemed to initiate them. The patient also noted episodes of weakness in his legs, with the attacks lasting one to three days. There was no numbness or dragging of his feet. He had mild palpitation occasionally. He also complained of nocturia three to ten times nightly without dysuria or daytime frequency. Pitting edema of his ankles which would clear up overnight was noted in January, 1947. At this time he was seen by a civilian physician, who noted a blood pressure of 260/130, a gland the size of a pecan in his left axilla, and a palpable spleen and liver. A diagnosis of malignant hypertension was made.

The symptoms became progressively worse until the patient was admitted to Emory University Hospital.

On admission, the blood pressure in the patient’s right arm was 240/124; in his left arm, it was 260 plus/120; and in his right leg, 260 plus/150. Physical examination revealed no abnormality except for extreme constriction of the retinal arterioles without hemorrhages or exudates, a slightly enlarged heart with a Grade 1 systolic murmur at the apex, and frequent extrasystoles. The liver and spleen were not palpable. The left testicle was undescended.

The blood count revealed 4,750,000 red blood cells per cu. mm. with 15.9 grams (103 per cent) of hemoglobin, and 17,800 white blood cells with 4 per cent band forms, 68 per cent segmented polymorphonuclear neutrophiles, 8 per cent eosinophiles, and 20 per cent lymphocytes. On fourteen urine examinations the specific gravity varied between 1.002 and 1.012. There were three to twenty pus cells per high-powered field. On October 25, a trace of sugar was noted. The urinary output averaged 3,000 to 4,000 cc. daily.

An electrocardiogram showed left ventricular hypertrophy of the concordant type with frequent extrasystoles arising from multiple foci (fig. 1, A). Amytal sedation lowered the blood pressure from 190/110 to 154/94. The cold pressor test showed practically no rise (fig. 2, A). Tetraethylammonium chloride caused no significant change in blood pressure. When 0.037 mg. of histamine base was given...
Fig. 1. A.—Electrocardiogram (before operation) showing left ventricular hypertrophy of the concordant type. The frequent ventricular extrasystoles are not illustrated.

Fig. 1. B.—Electrocardiogram (after operation) showing disappearance of left ventricular hypertrophy pattern with return to sinus rhythm.

Fig. 2.—Left: The cold pressor test (before operation). Right hand immersed in ice water for sixty seconds at each of the arrows. Right: The histamine test (before operation). Time of intravenous injection shown by arrow.
intravenously, there was an immediate fall in blood pressure from 205/130 to 136/70, followed by a precipitous rise to 260/146, associated with a severe reaction with flushing, hyperventilation, numbness of the tongue, lips, and extremities, carpopedal spasm, and nausea (fig. 2, B). Massage over the adrenal areas failed to produce any attacks. Hyperventilation would easily produce headaches, carpopedal spasm, and a rise in blood pressure from 184/122 to 244/150. Intravenous urograms failed to reveal any deformity or evidence of a tumor.

Perirenal aerograms also failed to outline an adrenal mass.

On November 20, 1947, exploration of both adrenal glands through bilateral lumbar incisions revealed a normal right adrenal gland and a well-encapsulated tumor the size of a large egg in the left adrenal area. The tumor was completely excised. It measured 6.0 by 4.0 by 3.2 cm. and weighed 49 grams. No fluctuation in blood pressure occurred on the operating table. On November 22, a pericardial friction rub was noted. Serial electrocardiograms at this time showed no evidence of myocardial infarction or pericarditis. The patient's wound continued to drain but his fever subsided and he was sent home on December 2, 1947 (fig. 3).

The pathologist's report (concurred in by several examiners) was that the tumor was a malignant pheochromocytoma.

The patient returned to the hospital December 13, 1947, complaining of fever and pain in the left lower chest and left upper abdominal quadrant aggravated by deep inspiration. The left lumbar wound was still draining. A pleural friction rub was audible in the left axilla. A pericardial friction rub was again noted. The patient's temperature was 101.4 F. His pulse was 108, respirations 22, and blood pressure 160/95. X-ray examination revealed elevation of the left diaphragm, a tenting adhesion from the left diaphragm to the pericardium, and pneumonitis or atelectasis at the left lung base. An electrocardiogram showed changes compatible with acute pericarditis. A culture of the urine produced diphtheroids.

The fever slowly subsided under penicillin, streptomycin, and sulfadiazine therapy, but the pain and pericardial rub persisted and the signs of atelectasis and fluid remained at the left base.
On December 21, the blood pressure was 120/80. The same day, 450 cc. of turbid, yellow fluid with a specific gravity of 1.020 was withdrawn from the left pleural space. Cultures of this fluid failed to produce any bacteria. The wound continued to drain. The pericardial rub was present intermittently. A blood culture failed to grow any bacteria. On January 22, 1948, the left adrenal area was explored and about 1 oz. of unabsorbed oxycel gauze was found and removed. The patient responded well after this operation. His wound of metastasis. The electrocardiogram showed disappearance of the left ventricular hypertrophy pattern (fig. 1, B).

**Discussion**

The incidence of pheochromocytoma is about equal in both sexes. Most cases occur in persons between the ages of 20 and 50 years of age, but may occur in those of any age. Neff and his associates reported the successful removal of a pheochromocytoma from a 16 month old girl with hypertension and the adrenogenital syndrome.

The clinical attacks are the most impressive feature of the syndrome. They may vary in severity, frequency, and duration. They usually last for a few minutes to a few hours, but may occasionally last two or three days. There may be a history of attacks for several weeks or as long as sixteen years prior to diagnosis. They usually increase in frequency, up to two or more...
times a day; although there may be occasional remissions, lasting as long as ten years. The attacks may occur at any time, but seem to have a predilection for the early morning. Between attacks, the patient is usually healthy. At the onset of an attack, palpitation is common, with headaches and pain in the precordial or epigastrum. Nausea and vomiting are frequent. Anginoid pains, epigastric pain, roaring in the head, occipital headache, heat in the face, and sneezing are some of the other symptoms described. Tachypnea is common. Pulmonary edema occurred at one time or another in 9 patients reported by Howard and Barker; of these died in their first attack. Palpitation, with a sense of vigorous heart action, either slow or fast, occurred in 93 per cent of their 18 cases and sweating in 78 per cent. Vasomotor phenomena with pallor at first, usually followed by flushing and sweating, are common. There may be tremors. The pupils dilate. The neck veins may distend. Bauer and Belt reported a case in a patient whose thyroid gland swelled with each attack. After the attacks there is intense prostration lasting from a few minutes to a day.

The blood pressure may be normal or elevated between attacks. In 51 cases reviewed by Green in 1946, only 14 patients showed intermittent hypertension, while 37 had chronic hypertension. During an attack, the blood pressure usually rises to extreme heights, usually over 260/120. In some cases, it has shown wave-like fluctuations at five- to fifteen-minute intervals.

Hyperglycemia and glycosuria appear in about one-fourth of the cases. Albuminuria may be seen during an attack.

There is wide variation in the effect of pheochromocytomas on carbohydrate metabolism. Possibly in persons with the least stable carbohydrate homeostatic mechanism, overactivity of epinephrine from the tumor causes increased liver glycogenolysis. A prolonged hyperglycemia of nonpancreatic origin may lead to irreversible pancreatic islet-cell damage and diabetes. Two cases have been reported of typical diabetes mellitus cured by removal of an associated pheochromocytoma. In these cases, permanent damage was shown by the retention of abnormal glucose tolerance curves, even though there was no longer hyperglycemia and no need for insulin after removal of the pheochromocytomas.

Other endocrine disorders have been reported in conjunction with pheochromocytomas. In the family reported by Calkins and Howard as having multiple familial pheochromocytomas, there were 4 members with thyroid disease. These observers theorized that there might be some direct action on the thyroid by the secretion of the pheochromocytoma which induces nonsecretory thyroid enlargement, perhaps through its vascular effects. Certainly, thyroid enlargement and an elevation of the basal metabolic rate are not uncommon in persons with pheochromocytomas and may lead to a mistaken diagnosis of hyperthyroidism. In another case of pheochromocytoma studied at Emory University Hospital and previously reported by Strickler, the basal metabolic rate was +41 and +74 on two separate determinations.

There seems to be an unusually high incidence of associated generalized neurofibromatosis, this condition having been reported in nine cases of pheochromocytoma.

Pheochromocytomas originate from the chromaffin tissue system. Chromaffin tissue is widely scattered in the body. Tumors have been reported arising from the intrathoracic sympathetic chain, from below the bifurcation of the aorta (organ of Zuckerkrandl), from the coccygeal body, from the carotid body, and in the wall of the intestine, but none of these has produced the cardiovascular picture. Only those in the adrenal glands or in the retroperitoneal tissue between the kidneys have shown associated hypertension.

Pheochromocytomas of all sizes have been reported, varying from a few centimeters to very large, melon-sized, cystic masses. In 15 cases the tumors have been bilateral in or near both adrenal glands, and in two other cases there have been simultaneous tumors in Zuckerkrandl's body and in the retroperitoneal ganglia. One-third of these cases were malignant, and, according to Calkins and Howard, in none of these was there constant or paroxysmal hypertension. In the recent literature, how-
ever, there have been a few reports of patients with hypertension and malignant pheochromocytomas.\textsuperscript{6,7} The question of malignancy in pheochromocytomas is a difficult one to evaluate at present, because the histologic features usually denoting malignancy are a rather characteristic and diagnostic feature of the most benign pheochromocytomas.\textsuperscript{25}

In 1942, there were 8 undoubtedly malignant cases with metastases reported among the 100 cases gathered by McGavack, Benjamin, Speer, and Klotz.\textsuperscript{25} These metastasized widely to the regional lymph nodes, liver, bones, lungs, pleura, skin, intestines, and kidney, in that order of decreasing frequency.

The secretion from pheochromocytomas has usually been felt to be epinephrine. In 1937, Beer, King, and Prinzmetal\textsuperscript{26} demonstrated a pressor substance in the blood during a hypertensive crisis, which they thought was epinephrine. However, actual proof of this fact is difficult. Demonstration of a pressor substance in the blood is not conclusive alone, for other substances may confuse the reactions, as in chronic lead poisoning and tuberculous destruction of only one adrenal gland.\textsuperscript{8} Many persons have demonstrated that the excised pheochromocytoma contains a greatly increased amount of epinephrine over that encountered in the normal adrenal gland. In a recent case there were 2,300 mg. of epinephrine in a 350-gram tumor of the right adrenal gland.\textsuperscript{13} The patient died on the operating table, and autopsy revealed two small pheochromocytomas of the left adrenal gland, as well as carcinoma of the thyroid gland with metastases from the thyroid tumor to lymph nodes in the cervical and paratracheal regions, again illustrating the somewhat tenuous connection between pheochromocytomas and thyroid abnormalities.

**Differential Diagnosis.** Paroxysmal hypertension has been reported with adrenal ganglioneuromas, with neuroblastomas, and with adrenal cortical tumors. Persistent hypertension has been found with retroperitoneal ganglioneuromas, with an adrenal sympathetico-blastoma, and is not uncommon with adrenal cortical tumors.\textsuperscript{15}

Paroxysmal hypertension can occur in: (1) pheochromocytomas, (2) essential hypertension, and (3) symptomatic hypertension. In essential hypertension, the blood pressure is always raised between attacks, the onset and end of attacks are gradual, convulsions and loss of consciousness are common, widespread symptoms are rare, and posture and pressure over the adrenal glands do not precipitate attacks. Symptomatic paroxysmal hypertension may be seen as recurrent attacks in lead poisoning, eclampsia, tabes dorsalis, aortic regurgitation, angina pectoris, thalamic tumors, nephritis, epilepsy, traumatic or vascular damage to the brain, meningitis, diseases of the gasserian ganglion, sciatic neuritis, infectious diseases, or allergy.\textsuperscript{8,15}

Since examination of the patient in an attack is so helpful in diagnosis, various methods of initiating attacks have been devised. Sometimes, attacks can be induced by hyperventilation, as in our case, or by massage over the adrenal area, or by changes in posture. The histamine test of Roth and Kvale is often used.\textsuperscript{27} One-tenth of a cubic centimeter of histamine acid phosphate, 1:1,000, which is equivalent to 0.037 mg. of histamine base, may be given rapidly intravenously. In the normal person it usually produces little effect, but in the presence of a pheochromocytoma, it may cause a severe paroxysm of hypertension after the initial fall in blood pressure. In the present case, the reaction to the test was positive before removal of the pheochromocytoma and became negative after the successful excision of the tumor. Others have also confirmed the reliability of this test,\textsuperscript{11} and still others have used the persistence of a positive reaction as evidence for the diagnosis of another tumor after removal of the first one, and have re-operated and removed a second tumor, following which the reaction has reverted to normal.\textsuperscript{25} However, the histamine test is not specific for pheochromocytoma, but may also give a positive reaction in the presence of adrenal cortical tumors. We have recently observed a patient with sustained hypertension and a positive reaction to the histamine test (with coma and a rise in blood pressure from 210/130 to 290/165). At operation, no pheochromocytoma was found, but bilateral adrenal cortical adenom-
mas were found and removed. Following operation, the blood pressure fell to normal for two weeks then returned to 180/120, and the histamine reaction became negative.

Tetraethylammonium chloride has also been suggested as a test substance for pheochromocytoma.28,29 LaDue28 observed a case with a positive reaction to the tetraethylammonium chloride test, but with negative reactions to benzodioxane and histamine tests.28 In our case, tetraethylammonium chloride produced no symptoms or change in blood pressure. The adrenolytic benzodioxane drugs of the Fournier series have been recommended recently as a test for hypertension due to circulating epinephrine.30 These drugs should lower the blood pressure if it is elevated because of excessive circulating epinephrine. The test has been used in the Emory University Hospital with a dosage of 0.25 mg. of 933 F (piperidyl benzodioxane) per kilogram of body weight given intravenously in two minutes. It has been given to ten patients with hypertension without any untoward symptoms, but so far no fall in blood pressure has been produced and no pheochromocytomas have been found. In the case reported here operation was performed prior to the publication of the use of this test.

The subcutaneous injection of Mecholyl, 25 mg., has been suggested as a diagnostic test for pheochromocytoma.14 Intravenous administration of 0.5 mg. of Mecholyl was tried in our above-mentioned patient with adrenal cortical adenomas, prior to publication of the article by Guarneri and Evans.14 Although this caused an abrupt fall in blood pressure, lower than that caused by histamine, there was no succeeding hypertension, suggesting that the histamine-produced hypertension is not a compensatory rebound to a sudden hypotension.

The treatment of pheochromocytoma is surgical excision. Operation is not without danger. There is an increased susceptibility to paroxysmal tachycardias and to auricular or ventricular fibrillation in the presence of excess epinephrine. This may be one cause of death on the operating table. The patients often show a great rise in blood pressure when the tumor is being manipulated and a great fall in pressure after the veins from the tumor are ligated. For this reason, adequate amounts of epinephrine and adrenal cortical extract should be available prior to beginning the operation, and effort should be made to handle the tumor gently while removing it. It is possible that the benzodioxane drugs might be used to prevent excessive rises in blood pressure due to manipulation of the tumor at operation. Some have recommended preoperative cortical extract and extra salt feedings before operation to guard against acute adrenocortical insufficiency.11 Arterial transfusions may help in avoiding the sudden vascular collapse. This collapse may be analogous to that seen during the operation for coarctation of the aorta when the clamps are too rapidly released. It has been suggested that this is due to splanchnic pooling with cardiac failure associated with diminished venous return.21 In the case of pheochromocytoma, the generalized constriction of the vascular bed due to epinephrine is followed by generalized dilatation when the source of epinephrine is suddenly removed.

Summary and Conclusions

A case report of a patient with sustained hypertension due to a pheochromocytoma of the adrenal gland is presented. The symptoms disappeared and the blood pressure gradually returned to normal following removal of the tumor. The use of various tests in the diagnosis of the condition is discussed.

Addendum

Since this paper was submitted for publication, the patient has remained in good health and his blood pressure has remained at normal levels. A local abscess formed in the region of the sinus tract. This was incised and drained in June, 1949. At this time his blood pressure was 132/74 in both arms. An enlarged and tender lymph node was still present in the left axilla.

References


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