Some Aspects of Pheochromocytoma

The diagnosis and management of pheochromocytoma still impose problems, although ordinarily the diagnosis is not too difficult. Many of the 66 patients in our series who were later proved to have pheochromocytomas at operation or at necropsy were referred to our associates or us with the diagnosis already made or strongly suspected. On the other hand, we could not verify the previous diagnosis of pheochromocytoma in many cases. Because of the type of operation and the operative risk, the correct preoperative diagnosis is most important.

Pheochromocytomas, tumors of the medullary portion of the adrenal gland, cause paroxysmal or persistent hypertension. In general, patients whose tumors are secreting epinephrine and norepinephrine intermittently have paroxysmal hypertension, and those whose tumors are secreting pressor substances continuously have persistent hypertension.

All patients with paroxysmal hypertension complain of spells or attacks. Excruciating headaches, usually of only 1 to 15 minutes’ duration, are the commonest symptom, but frequently they are accompanied by drenching sweats and palpitation. Occasionally paroxysmal sweating and palpitation may occur in a patient without headache but with an unusually high basal metabolic rate. Also present can be tachycardia, nervousness, tremor, dyspnea, great anxiety, pallor or flushing of the face, nausea and vomiting, varying types of distress or pain in the abdomen and chest, pain and numbness in the legs, and tingling and coldness of the hands and feet.

Many of these symptoms are common to a variety of diseases, such as migraine, brain tumor, coronary insufficiency and anxiety tension states with their associated symptoms; therefore, no matter how excellent the story may be for pheochromocytoma and no matter how high the blood pressure is when the attack occurs or how well documented this observation is, the diagnosis must be confirmed by pharmacologic or chemical means before operation is carried out. We had one patient, a physician, who gave an excellent story for paroxysmal hypertension due to pheochromocytoma. He had had repeated spells of severe headache and perspiration associated with marked increase in the blood pressure. Histamine tests, however, repeatedly gave negative results, and the level of pressor amines in the blood before and after stimulation with histamine was always within normal limits. It was subsequently concluded that the patient was having spells of cerebrovascular insufficiency. At this time, almost 2 years later, he is comparatively well, although he has had a coronary occlusion from which he has recovered. Certainly an exploration at the time that he was having his spells would have been extremely hazardous.

Patients with persistent hypertension may have symptoms indistinguishable from those of essential hypertension, but many of them have attacks similar to those experienced by patients with only paroxysmal hypertension.

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The usual picture, however, is that of increasingly severe headaches, excessive perspiration, nervousness, tremor, palpitation, and loss of weight. Most patients are thin, but an occasional patient is obese. The most striking symptom is excessive perspiration, then come nervousness, tremor, and headache.

Laboratory findings from the usual tests are not of much help in the diagnosis of pheochromocytoma causing paroxysmal hypertension. The basal metabolic rate may be high and, if no other cause for hypermetabolism is found, pheochromocytoma should be suspected. The blood sugar may be increased, but values for blood sugar are generally of no help. The excretory urogram may show a mass above one kidney or downward displacement of one kidney, but this only localizes the tumor; it is not diagnostic.

Laboratory findings from the usual tests are of more help in the diagnosis of pheochromocytoma causing persistent hypertension. The basal metabolic rate is frequently very high, often +40 to +60 per cent and in 1 case +140 per cent; hyperthyroidism and other causes of hypermetabolism must be excluded in these cases. The blood sugar is frequently high, but is not diagnostic. The excretory urogram has the same value as it does in pheochromocytoma causing paroxysmal hypertension.

Two drugs are now used almost exclusively by us in testing for pheochromocytoma. Histamine is used when pheochromocytoma causing paroxysmal hypertension is suspected. The results are not always accurate, but in our experience histamine gives a more accurate test than tetraethylammonium chloride. A dose of 0.05 mg. of histamine base in 0.5 ml. of isotonic solution of sodium chloride is injected rapidly intravenously. The result is considered positive when, after an initial decrease 30 seconds after the injection, the blood pressure rises significantly, with a maximum, at the end of 2 minutes, considerably above the maximum reached during the cold pressor test. We have emphasized on previous occasions and we emphasize again the extreme importance of determinations of basal blood pressure and the cold pressor test in interpreting the results of the histamine test. The cold pressor test is as much a part of the histamine test as is the injection of the histamine itself. If the rise in blood pressure 1 to 2 minutes after the injection of histamine is significantly greater than the maximal rise in blood pressure after the cold pressor test, then the pharmacologic test may be considered as positive for pheochromocytoma. Failure to compare the increase after histamine with the increase during the cold pressor test is the cause of many incorrect interpretations of the histamine test. The rise in blood pressure after the cold pressor test must be evaluated as well.

Phentolamine hydrochloride (Regitine) is used for tests on the patient with sustained hypertension suspected of having pheochromocytoma. Piperoxan is no longer used, mainly because it causes more unpleasant side reactions than phentolamine. Results are considered positive if the blood pressure decreases more than 35 mm. of mercury systolic and 25 diastolic from the basal level and remains decreased for 3 to 4 minutes. A slight decrease in the blood pressure in the first 2 minutes after intravenous injection with a return to basal level is not a positive result. Five milligrams of phentolamine (Regitine) are injected rapidly for this test.

Basal blood pressures should always be determined before a pharmacologic test is made on a patient suspected of having pheochromocytoma. Drugs such as narcotics, sedatives, and cyanates should be withheld for at least 48 hours before tests, as they may produce false-positive results. Antihypertensive drugs will produce false-negative results and hydralazine (Apresoline), at least, should be withheld for 8 to 10 days before these tests.

When the basal blood pressure is less than 170 mm. of mercury systolic and 110 mm. diastolic, histamine is the drug of choice for testing, but when the blood pressure is more than 170/110, phentolamine is the drug of choice. When the blood pressure rises greatly after the injection of histamine, phentolamine is employed to lower it. Thus both histamine

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and phentolamine may be used for the same patient having a pheochromocytoma, and positive results from the 2 tests for the tumor may be obtained.

The diagnosis must be made with the aid of pharmacologic and chemical tests. In evaluating the results of these tests, it is well to remember that all the tests can give falsely positive and falsely negative results, and that only by careful appraisal of all the symptoms, findings, and laboratory data available can a decision be reached that exploration is necessary.

The pharmacologic tests with histamine and phentolamine can be performed by any physician, providing the necessary precautions are exercised. If the results of the tests are doubtful or negative, the test should be repeated. No single test is always completely reliable. If doubt still exists, measurement of the catecholamines in the urine and the pressor amines in the blood should be made. These tests may necessitate reference of the patient to a medical center where facilities for such studies are available.

Chemical quantitation of the pressor amines (epinephrine and norepinephrine) in the blood is the most direct method of establishing the presence of a functioning pheochromocytoma. However, a pheochromocytoma must be secreting epinephrine or norepinephrine spontaneously, or the sample of blood for analysis should be collected at the height of the blood pressure response to histamine. Otherwise the finding of a normal concentration of pressor amines in a sample does not exclude pheochromocytoma.

The concentration of pressor amines in the blood is nearly always less than 3.5 μg. per liter of plasma in cases of essential hypertension and does not increase significantly after stimulation with histamine in such patients. We have found increased concentrations in the blood in some patients taking tetracycline (Achromycin) and also in patients with renal insufficiency, jaundice, increased intracranial pressure, or lymphoma. Thus it is important to realize that other conditions may cause elevated concentrations of pressor amines in the plasma that may lead to a false diagnosis of pheochromocytoma. Hemolysis or hyperbilirubinemia or both can interfere with the chemical analysis and cause erroneously elevated concentrations in the blood. Only under conditions in which the tumor is actively secreting will the results be positive. Finally, it is important to remember that elevated concentrations of pressor amines in the blood may result from the use of some epinephrine-like substances. We have observed this in 8 patients who were using epinephrine by nebulizer. Even the use of vasoconstrictor agents for nasal stuffiness is under suspicion as a cause of elevated levels of pressor amines in the blood.

The qualitative test for urinary catecholamines in 24-hour specimens of urine provides another useful procedure for the detection of a pheochromocytoma that is releasing catecholamines. When the result is positive, quantitative determination of the catecholamines in hydrolyzed urine provides additional information in establishing the diagnosis. Values of more than 250 μg. per 24-hour specimen of urine are considered positive for pheochromocytoma. The results of the test are positive only under conditions in which the tumor is actively secreting the pressor substances. Salicylates will produce falsely positive results.

In patients suspected of having a pheochromocytoma that is causing paroxysmal hypertension, it is our practice to perform a histamine test and in some cases to determine the amount of pressor amines in the blood before and after the injection of histamine. If the patient has the tumor, the result of the histamine test is usually positive.

In patients suspected of having a pheochromocytoma that is causing persistent hypertension, it is our practice to do a phentolamine test or to test a 24-hour specimen of urine for catecholamines. If the result is positive, the diagnosis may be established by finding elevated values for pressor amines in the blood.
Once the diagnosis of pheochromocytoma has been made, localization of the tumor is not necessary. Perirenal insufflations of air are unnecessary and hazardous. We recently had a patient, a girl aged 16 years, who went into shock after perirenal insufflation of air elsewhere. Exploration subsequently revealed a pheochromocytoma of the right adrenal gland.

Exploration usually is carried out through a transverse upper abdominal incision. This type of exposure allows the surgeon to explore both adrenal regions and the abdomen. Tumors have been found beneath the hilus of the liver, around the kidneys, and along the great vessels of the abdomen.

These tumors are usually single and benign and usually occur in one adrenal gland. However, they may be multiple on one side, on both sides, or may be located wherever chromaffin tissue is found. They may be benign but subsequently become malignant and metastasize.

Careful study of 66 patients with pheochromocytoma has suggested that tests should be undertaken on the following types of patients: (1) any patient who complains of spells associated with severe headache and perspiration, with or without other symptoms; (2) any patient with hypertension who is young, or has a short history of hypertension or severe hypertension of groups 2 to 4, or is thin and has a history of fluctuating hypertension; (3) any patient with hypermetabolism without hyperthyroidism; (4) any patient who responds in a paradoxical manner to the ganglionic blocking agents; and (5) any patient who responds unsatisfactorily to an anesthetic and whose blood pressure rises. For the last-mentioned patient, administration of anesthetic should be stopped immediately.

If these criteria are followed, it is unlikely that a pheochromocytoma will be missed. The greatest obstacle to correct diagnosis is previous medication before all tests. It is true that many patients will undergo tests and that many tests will be performed without yield, but to suspect a pheochromocytoma, confirm its presence, and then have it removed successfully may be lifesaving. Unfortunately, not all patients are cured when the tumor is removed. A few of the tumors are malignant and some that were first considered benign have become malignant and metastasized.

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References

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