CLINICAL PROGRESS

Pheochromocytoma

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PHEOCHROMOCYTOMA, a tumor of the chromaffin tissue that secretes pressor amines is not common, but is being diagnosed more readily today than formerly, and the safe surgical removal of these tumors often makes a correct preoperative diagnosis a lifesaving measure.

Although successful surgical removal of a pheochromocytoma was accomplished in 1927 by Charles H. Mayo, the first correct preoperative diagnosis was not made until 1929, when it was made by Pineoffs. At that time it was thought that pheochromocytoma would produce only paroxysms of hypertension, but by 1942 it was evident that pheochromocytoma could produce sustained hypertens
tion.

Clinical progress in the diagnosis of this uncommon and exceedingly important tumor has been great in the 11 years since the first pharmacologic test with histamine was introduced. The tests with histamine and phenolamine (Regitine) can be used easily and safely, and with other pharmacologic tests have played a major role in diagnosis. The introduction in 1952 of the quantitative estimations of the urinary catechol amines and in 1950, 1953, and 1954 of the pressor amines in the blood has added further accuracy to the diagnosis of pheochromocytoma.

In this paper we plan to review briefly the clinical features of pheochromocytoma, to appraise and evaluate the tests used as an aid in diagnosis, and to discuss some of the difficulties encountered in arriving at a diagnosis, the surgical aspects of the condition, and postoperative care.

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ANATOMY AND PATHOLOGY

Pheochromocytomas usually arise from the adrenal medulla but they may occur along the entire length of the sympathetic nervous system, that is, wherever chromaffin tissue is found in the ganglia of the cervical, thoracic, and abdominal sympathetic chains. Four intrathoracic pheochromocytomas, 1 tumor in the celiac ganglion, and several in the organ of Zuckerkandl, located on either side of the aorta at the origin of the inferior mesenteric artery, have been reported. Pheochromocytoma usually occurs as a unilateral, well-encapsulated, benign tumor; however, it may be bilateral or multiple on one side. The exact incidence of each of these unusual findings is difficult to state with certainty, although it is estimated that 10 per cent of the pheochromocytomas are malignant and metastasize.

CLINICAL FEATURES

Paroxysmal Hypertension. Pheochromocytomas secrete epinephrine and norepinephrine in varying amounts. If a tumor secretes these pressor amines intermittently, episodes or attacks will develop. These attacks consist of a sudden rapid rise of the blood pressure with tachycardia, great anxiety, severe headache, pallor, particularly of the face, numbness, tingling and coldness of the hands and feet, sometimes nausea and vomiting, pain in the epigastrium extending into the precordial region, and lastly excessive sweating. In any case, 1 or more of these symptoms and signs may be lacking.

The frequency of attacks varies greatly. They may occur as often as 10 to 20 times a day to only 1 a day or only 1 every 2 to 3 months. Commonly, these attacks last 10 to 15 min.,

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but they may last only a few seconds or may persist for several hours. Patients frequently complain of weakness and exhaustion following the attack. If the attacks have been occurring for more than 2 to 3 years, the usual story is that the attacks are increasing in frequency but usually not in severity. Between attacks the patients may be in good health. Severe attacks may lead to death from cerebral hemorrhage, shock from a number of different causes, or pulmonary edema.

In the past, the diagnosis of pheochromocytoma was made by observation of the patient in a spontaneous attack that might be produced by physical exertion, bending or stooping, turning on the side, massage of the abdomen on the side of the tumor, and roentgenologic examination. For such palpation to produce symptoms, however, the tumor must be large. In the past, too, evidence of an adrenal tumor would sometimes be seen in a roentgenogram of the kidney or excretory urogram. However, displacement of the kidney may not be demonstrated in the roentgenogram or excretory urogram, even in the presence of a tumor.

The usual laboratory studies in the absence of an attack reveal essentially normal findings in the patient who has paroxysmal hypertension caused by pheochromocytoma. The basal metabolic rate is elevated to more than +10 per cent in a small number of cases. Occasionally, values for blood sugar may be elevated.

In patients suffering from attacks of various kinds, including paroxysmal attacks of hypertension, the most common conditions to be excluded are migraine, histaminic cephalgia, hyperthyroidism, coronary occlusion, coronary insufficiency with a rise in the blood pressure, and anxiety states with various types of somatic reactions. Many patients give a history of having had an elevated blood pressure with or without associated symptoms. These must be considered by the clinician and, if the story seems at all typical of pheochromocytoma, pharmacologic tests should be carried out.

*Sustained Hypertension.* The patient who has sustained hypertension caused by pheochromocytoma may have a more or less continuous secretion of the pressor substance from the tumor. However, some patients with sustained hypertension may have attacks similar to those experienced by patients who have only paroxysmal hypertension. During these attacks the blood pressure rises to an even higher level. At times, the clinical picture may be identical with that of essential hypertension. This fact, of course, adds difficulty to the differential diagnosis of these 2 conditions. The usual picture, however, is increasingly severe headaches, excessive perspiration, and rather marked nervousness and tremulousness. The patient is almost always thin, and over a period of months or years has gradually lost weight. If the condition is unrecognized, symptoms may progress and reflect secondary cardiovascular changes, such as loss of vision and symptoms compatible with congestive heart failure. Coronary occlusion and even thrombosis of the basilar artery have been known to occur in individuals whose tumors have not been removed.

The usual laboratory studies on this group of patients are more significant than on patients who have only paroxysmal hypertension. The basal metabolic rate of the patient with sustained hypertension due to pheochromocytoma is invariably increased and is usually more than +10 per cent; the highest figure that we have encountered was +101 per cent. Diabetes mellitus or elevation of the fasting blood sugar is not uncommon. Excretory urography reveals the presence of a suprarenal mass with downward displacement of the kidney in only a few of these cases.

As these laboratory findings indicate, hyperthyroidism, essential hypertension, coronary heart disease, diseases of the central nervous system, and renal lesions must all be considered in the differential diagnosis.

**When Should a Pheochromocytoma Be Suspected Clinically?**

With our present knowledge the clinical diagnosis of pheochromocytoma is still a challenge. When should a pheochromocytoma be suspected is an important question. The ages of the patients with pheochromocytoma have ranged from that of infants to 70 years.
However, more tumors occur in the early adult years. Many of the patients with pheochromocytoma have lost weight and all of the patients we have encountered have been thin. Hypertension, either paroxysmal or sustained without renal disease or coarctation of the aorta, should be suspected of being due to pheochromocytoma. It must be remembered that the patients with sustained hypertension due to pheochromocytoma may have symptoms identical to those with essential hypertension, although in most patients with pheochromocytoma the hypertension is of shorter duration. Patients who have no family history of hypertension, whose hypertension is of recent onset, who are nervous or have hypermetabolism or headaches should bring pheochromocytoma to mind. Many such patients should be subjected to further laboratory tests in order to rule out the possibility.

**Pharmacologic Tests**

It is important that certain drugs are useful in the diagnosis of pheochromocytoma. These are extremely helpful, not only for the purpose of screening relatively large numbers of patients who might have pheochromocytoma but also for the purpose of establishing a definite diagnosis.

The histamine test, the first pharmacologic test, was introduced in 1945. From 1945 to 1947 it was the only available pharmacologic aid in the diagnosis of pheochromocytoma. During the next 4 years piperoxan, tetraethylammonium bromide, methacholine chloride, and phentolamine hydrochloride (Regitine) were added.

The pharmacologic tests are of 2 types. Histamine, tetraethylammonium bromide, and methacholine chloride (Mecholyl) stimulate the discharge of the pressor substances from the tumor. Thus, tests with these drugs are useful in cases of paroxysmal hypertension to produce attacks similar to those that occur spontaneously. Phentolamine (Regitine) and piperoxan (Benzodioxane), on the other hand, lower blood pressure by blocking the pressor effect of epinephrine and norepinephrine in the blood if a pheochromocytoma is present. They are used in cases of sustained hypertension; after their administration a precipitous fall in blood pressure demonstrates the presence of circulating pressor substances.

Although we have used all these drugs as they were introduced, we have more frequently used histamine for patients with paroxysmal hypertension and Regitine for the patients with sustained hypertension. If the resting blood pressure is less than 170 mm. Hg systolic and 110 mm. diastolic, histamine is used for the pharmacologic test, but if the blood pressure is greater than these figures, Regitine or piperoxan is employed. The use of any one of these drugs requires certain precautions.

Basal blood pressures are always obtained for at least half an hour before any test is started. This is most important.

The cold pressor test is an important part of the histamine test as the rise of the blood pressure during the cold pressor test measures the lability of the blood pressure and is the measuring stick for the response of the blood pressure 2 min. after the intravenous injection of histamine. Reports in the literature indicate that the cold pressor test might precipitate an attack in a patient with pheochromocytoma. No attack has been precipitated by a cold pressor test in any of the patients whom we have tested. After the cold pressor test is completed, basal blood pressures are obtained again before any injections are given.

For the histamine test as we carry it out, 0.05 mg. of histamine base in 0.5 ml. of normal saline solution is placed in a tuberculin syringe and is injected intravenously. The blood pressure always falls 30 sec. after the injection or the histamine did not enter the vein. Immediately thereafter, the blood pressure rises rapidly if the patient has a pheochromocytoma, and the clinical signs and symptoms of a severe episode appear. The test is considered positive for pheochromocytoma if, after the initial decrease, the blood pressure rises at the end of 2 min. far above that reached in the cold pressor test. The average rise in blood pressure in patients with a pheochromocytoma is more than 60 mm. Hg systolic and 40 mm. diastolic.

For the Regitine test on patients with sustained hypertension, Regitine is admin-
istered rapidly intravenously in a dose of 5 mg. The test is considered positive for pheochromocytoma if the systolic blood pressure decreases more than 35 mm. and the diastolic more than 25 mm. Regitine is not given intramuscularly, for a negative result may be obtained in the presence of a tumor. Regitine rather than piperoxan is used for the first test on patients with sustained hypertension, as administration of Regitine is followed by fewer side reactions and no hazardous pressor responses when the patient has essential hypertension. It is true that Regitine has a greater tendency than piperoxan to cause a fall in the blood pressure during the first minute when no pheochromocytoma is present, but if the blood pressure returns to the basal level in the next minute, this reaction is considered negative for pheochromocytoma.

Factors which May Affect Results. For 48 hours before any of these tests are carried out, the use of any sedative or narcotic should be prohibited. In the patient with paroxysmal hypertension false positive results may be obtained if sedatives or narcotics have been administered within that time, as sedatives inhibit the rise of the blood pressure during the cold pressor test that is the measuring stick.

In patients with sustained hypertension, potassium thiocyanate, barbiturates, Demerol, morphine, chloral hydrate, and probably many other sedatives may cause a fall in blood pressure similar to that produced by pheochromocytoma following intravenous administration of Regitine or piperoxan. Shock seems greater in the patient who has had sedation and no tumor than in the patient with pheochromocytoma and no sedation, although the fall in blood pressure may be the same. In one of our patients with severe sustained hypertension as many as 3 tests with Regitine gave false positive reactions, but after sedation was stopped for 5 days, a negative result with Regitine was noted. This patient subsequently died as the result of complications of hypertension, and at postmortem examination no pheochromocytoma was found. The false positive reactions were attributed to codeine and chloral hydrate.

We have had similar experience with other patients in that false positive reactions were obtained with the Regitine test when the patients were under the influence of sedation, and negative results after cessation of the sedation; again these patients were explored and no tumor could be found.

It is logical to sedate many patients with severe hypertension. Nevertheless, if there is a high index of suspicion for pheochromocytoma, if the patient is young, that is, less than 50 years of age, and if the hypertension is of relatively short duration, then sedation should be withheld until a Regitine test can be performed. Even the patient with hypertensive encephalopathy with markedly elevated blood pressure can be given Regitine intravenously without ill effects. If the test gives a negative result, then appropriate measures can be instituted to lower the blood pressure.

Antihypertensive drugs similarly affect the Regitine test, as false negative results occur in patients who are taking drugs to lower their blood pressure. In 1 patient who had been receiving hydralazine hydrochloride (Apresoline), Regitine tests were negative for pheochromocytoma on 2 occasions. After treatment with Apresoline had been discontinued, the Regitine test was repeated and the result was positive. The tumor was found at operation. In another patient who had been receiving Apresoline, an equivocal result was obtained from the Regitine test. After treatment with Apresoline had been discontinued for 8 days, the Regitine test was positive for tumor and at operation a tumor was found.

It is probable that the rauwolfia drugs influence the Regitine test also, although we have no surgical proof as yet.

The problem of when to do a Regitine test on a patient with sustained hypertension who has been taking antihypertensive drugs is exceedingly difficult to solve. If the antihypertensive drug employed is long acting, as Apresoline and rauwolfia are, then treatment with the drug should probably be discontinued for several weeks before the pharmacologic test is carried out. If the antihypertensive drug is short acting, such as the veratrum preparations and ganglionic-blocking agents, then
use of the drug needs to be discontinued for only 1 or 2 days before the tests.

A difference in the blood pressure in the 2 arms may occasionally produce a false positive result in patients with either paroxysmal or sustained hypertension. The following case serves as an example. The basal blood pressure in a patient varied greatly in the 2 arms. When the blood pressure was measured on the arm with the highest pressure, it fell 80 mm. systolic and 40 mm. diastolic after the intravenous injection of Regitine. This could easily have been interpreted as a positive reaction to a pheochromocytoma. However this decrease only equalized the pressures in the 2 arms. When the blood pressures were determined simultaneously in the 2 arms, there was little or no fall in the blood pressure in either arm following the intravenous injection of 5 mg. of Regitine. If a tumor were present, a pronounced fall would have occurred on both sides. Therefore, the blood pressure is measured routinely on both arms of all patients and if there is any disparity, blood pressure is determined simultaneously in both arms during the pharmacologic tests.

The pharmacologic tests have been of great aid in making a diagnosis of pheochromocytoma, but because of reasons given previously they are not always successful or accurate. If the results of the tests with histamine or Regitine are doubtful or negative when the clinical evidence is strongly indicative of a pheochromocytoma, then the results of the tests should be questioned and the tests should be repeated, or a test with one of the other drugs should be used. No one single test is always completely reliable.

If doubt remains as to the accuracy of the diagnosis, measurement of the quantity of epinephrine and norepinephrine, both in the urine and the blood, may be helpful.

Studies of Pressor Amine

The introduction of fluorometric methods for quantitating epinephrine and norepinephrine in blood\textsuperscript{10, 11, 2} and urine\textsuperscript{2, 3} has greatly aided in evaluating patients suspected of having pheochromocytoma. Chemical quantitation of pressor amines in the blood or urine is, except for surgical exploration, the most direct and accurate method of establishing the presence of a functioning pheochromocytoma. However, it is important that a pheochromocytoma either be secreting epinephrine or norepinephrine spontaneously or be induced to secrete the pressor amines during the period that blood or urine is being collected. Otherwise the finding of a normal concentration of pressor amines in a sample does not exclude the diagnosis of pheochromocytoma.

Using a modification of the method of Weil-Malherbe and Bone\textsuperscript{11, 22} we have measured the pressor amines in the plasma of 25 of our patients with pheochromocytomas. Fifteen of these patients had sustained hypertension and 10 had paroxysmal hypertension. In all but 1 of the 15 patients with sustained hypertension the concentration of pressor amines was elevated significantly, that is, to more than 3.5 $\mu$g. of epinephrine-like substance per liter of plasma. One patient, however, had a normal concentration of epinephrine-like substance (2.2 $\mu$g./L. of plasma) when the blood pressure was 182 mm. Hg systolic and 110 mm. diastolic. When 0.05 mg. of histamine base was administered intravenously, the blood pressure increased to 264 mm. systolic and 164 mm. diastolic and the concentration of epinephrine-like substance rose to 15.8 $\mu$g./L. of plasma. Of the 10 patients with paroxysmal hypertension 2 had normal concentrations of pressor amines when the blood pressure was normal. However, after a provocative test (that is, after the histamine test) the pressor amines and blood pressure were significantly elevated in all these patients. Before drawing blood for quantitation of pressor amines, the intravenous administration of histamine to all patients with paroxysmal or mild sustained hypertension seems indicated when pheochromocytoma is suspected.

The concentration of pressor amines is usually less than 3.5 $\mu$g./L. of plasma in cases of essential hypertension. The pressor amines in plasma are not significantly increased after histamine stimulation in patients without pheochromocytoma.

It is interesting that during anesthesia and manipulation of pheochromocytomas at opera-
tion, marked liberation of pressor amines into the blood usually occurs. It is well known that various drugs, for example, some sedatives, analgesics, and antihypertensive medications, may cause falsely positive or negative results when pharmacologic tests, such as Regitine and histamine, are used. Thus far, however, the concentration of pressor amines in the plasma and the chemical method of analysis have not been found to be influenced by the administration of antihypertensive drugs or sedatives.

We have found elevated concentrations of pressor amines in the blood of some patients with renal insufficiency, increased intracranial pressure, and lymphoma. Whether what we are measuring in these patients is epinephrine and norepinephrine or perhaps some other catechol is not certain at this time. It is important to realize, however, that these conditions may cause apparently elevated concentrations of pressor amines that may lead to a false diagnosis of pheochromocytoma if the results of this quantitative test were relied on solely. Hemolysis or bile pigments also can interfere with the fluorescent method and produce falsely high estimations of pressor amines in the blood.

Goldenberg and associates have reported excellent results in detecting the presence of pheochromocytoma by fluorimetric analysis of epinephrine and norepinephrine in the urine. We have had no experience with their method.

It must be remembered that only under conditions in which the tumor is actively secreting the pressor amines will a positive pressor amine test be obtained.

Localization of Tumors

Many diagnostic studies have been employed to localize an adrenal tumor when a diagnosis of pheochromocytoma has been made. These consist of plain roentgenograms of the abdomen, intravenous urograms, aortograms, perirenal injection of air, and presacral injection of oxygen. It is our practice to utilize routinely only the plain roentgenogram and intravenous urogram, as it is not necessary to know prior to operation which gland is involved. The other procedures may not be without some undesirable side effects or hazards and the results are not entirely reliable. They may be employed when considered important in selected cases.

Surgical Aspects

It is our practice always to insert a needle into a vein before induction of anesthesia and to keep it there throughout the operation for pheochromocytoma. Throughout the operation the blood pressure is recorded at intervals of 1 min. by an observer other than the anesthetist. Characteristically, blood pressure will rise moderately or sometimes sharply as anesthesia is induced and the incision is made. If the blood pressure is especially high before anesthesia or during induction of anesthesia, 5 mg. of Regitine may be given intravenously through the previously inserted needle.

It might be well to mention that in an occasional reported case death has occurred during an operation in which the patient had a pheochromocytoma, the presence of which was unknown. Therefore, if the blood pressure of any patient rises sharply with induction of anesthesia without adequate explanation, it is advisable to discontinue the proposed operation and investigate the patient for the possible presence of such a tumor before any surgical procedure is performed.

As the tumor is palpated and manipulated, the blood pressure may rise if unchecked to 300 mm. Hg. Regitine is used to control these hypertensive effects; if 5 mg. does not effectively lower the blood pressure, more is given.

Fortunately all patients with pheochromocytoma whom we have encountered have been relatively thin. This facilitates surgical exposure of the adrenal glands through an anterior approach. We routinely employ a transverse incision placed high in the abdomen and curved somewhat upward. The right adrenal gland may be exposed by retracting the abdominal viscera to the left and downward. The right kidney is pulled downward also and the right lobe of the liver is retracted upward. The peritoneum in the region of the upper pole of the kidney is incised and the adrenal gland comes into view with little dissection in this region. The left adrenal
gland may be exposed in 1 of 2 ways, either by opening the gastrocolic omentum or by incising the peritoneum in the region of the upper pole of the left kidney. If the former approach is employed, the gastrocolic omentum is opened relatively widely to the left of the midline. The stomach and tail of the pancreas are then retracted forward and upward. These maneuvers bring the left adrenal gland into view. This is the method of exposure which we prefer. If the other approach is used, the splenic flexure of the colon is retracted medially and downward, and the peritoneum is incised lateral to the bowel. The retroperitoneal space is then opened, the kidney is pulled downward, and the structures overlying the upper pole of the kidney are retracted forward and upward.

It is important for the surgeon who operates for pheochromocytoma to be cognizant of certain pathologic characteristics of these tumors. Since a pheochromocytoma may be situated wherever chromaffin tissue is present, predominantly along the great vessels in the abdomen or even in the thorax, it is imperative if a tumor is not found in the adrenal gland to make a careful search for other possible sites of origin. An abdominal approach obviously facilitates such exploration.

During the surgical removal of one of these tumors, the surgeon should palpate and “squeeze” the tumor as little as possible, as such maneuvers may result in the blood pressure reaching alarming heights. Likewise the blood vessels of the tumor should be secured as soon as possible in order to obviate too great pressor effect during mobilization and extirpation. If the blood pressure does not fall and remain down after a tumor is removed, another lesion should be suspected and searched for.

Fortunately, a pheochromocytoma causes no significant alteration in the important functions of the adrenal cortex. If bilateral tumors are present, it is almost always possible to preserve some adrenal tissue on one or both sides. If this is not possible, immediate and vigorous steps must be taken to combat adrenocortical insufficiency by the intravenous administration of hydrocortisone.

Supportive Measures and Operative and Postoperative Care

Extremely close and careful observation of the patient during and after operation for pheochromocytoma is essential. Wide variations in blood pressure may occur during operation, as pressor substances are liberated from the tumor in excessive amounts. Immediately after removal of the tumor, the arterial tension may fall to alarming levels because of the abrupt disappearance of major amounts of pressor substances from the blood stream. If pronounced hypotension does not develop and persist shortly after the removal of the pheochromocytoma, as said before, the surgeon should suspect the existence of another tumor. If hypotension does exist, intravenous administration of 4 to 8 mg. of levarterenol bitartrate U.S.P. (Levophed bitartrate) in each liter of dextrose is begun in the operating room and continued until it is no longer necessary. Arterial pressure is controlled in a satisfactory manner by altering the rate of flow of the intravenously administered levarterenol. It is not necessary to maintain the blood pressure at preoperative levels, maintaining it from 100/70 to 110/80 is adequate. In some instances substitution therapy has been necessary for only a few hours. In 1 instance it has been necessary for 6 days in order to maintain the blood pressure at 90/60.

Our Series

During the past 11 years, we have carried out a total of 8,873 pharmacologic tests for pheochromocytoma on 7,993 patients. No serious side reactions have occurred. A correct preoperative diagnosis of pheochromocytoma has been made on 51 patients at the Mayo Clinic by the use of pharmacologic tests and the determination of the pressor amines in the blood. Sixty-one tumors have been found at operation on these 51 patients. No deaths or untoward effects have occurred in any of these patients during the tests before operation, during operation, or immediately after operation.

Malignant tumors with metastasis were
more common in our patients with sustained hypertension than in our patients with paroxysmal hypertension. The tumors ranged in weight from 10 to 713 Gm.; the largest and smallest tumors in our series were found in patients who had only paroxysmal hypertension. We have removed as many as 3 distinct tumors from the vicinity of 1 adrenal gland.

**Discussion**

Perhaps too much attention has been directed toward a relatively rare clinical entity. We doubt that this is true, for the current literature indicates an apparent increase in the diagnosis of this tumor. We believe that this increase is due to the fact that the syndrome produced by the tumor is being thought of more commonly and that this increasing interest has been due to tests that have become available to determine whether or not this tumor is present. Pheochromocytomas cause the most curable type of surgically treated hypertension, and they are most curable if the tumor can be detected early enough before it produces secondary cardiovascular damage and even death.

The histamine test, if performed properly and always in conjunction with the cold pressor test, will yield evidence on which to base a diagnosis of pheochromocytoma causing paroxysmal hypertension in most cases. It is more reliable than the tests of tetraethylammonium chloride and methacholine chloride. It has been safe in our hands.

Regitine is a valuable drug for screening patients with sustained hypertension suspected of having pheochromocytoma. Obviously, it cannot be used on all patients complaining of hypertension. It probably is not necessary to use it on obese patients, for we have yet to see an obese patient with pheochromocytoma. But it should be used on all young patients with hypertension, those with a short history of hypertension, and those with hypertension, group 3 or 4 or severe group 2. Certain precautions must be considered before the test is performed. Piperoxan can be used in a fashion similar to that of Regitine.

If tests with these drugs fail to settle the question of whether a patient has pheochromocytoma, estimation of the pressor amines in the blood at the level of the highest blood pressure will clinch or disprove the diagnosis. Technical difficulties at this time make it impossible to test all patients with hypertension for pressor amines as a routine. Perhaps that time will come. Until then, stressing the importance of pheochromocytoma and diagnosing it when it exists deserve the attention of all physicians. Results of surgical treatment are gratifying in virtually all cases, and sometimes are lifesaving if the tumor is not malignant and has not metastasized.

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