Pheochromocytoma - A Survey Of Current Concepts

Henry L. Green
A considerable amount of information is now available about the physiology, clinical behavior, and management of pheochromocytoma. Unfortunately, much of this data is so widely scattered through the literature that it is accessible only by time-consuming search. The author has attempted to bring it together. A few of the less common features are included for their interest. No pretense of exhaustiveness is made, although many of the articles referred to are themselves reviews.

HISTORY

The first pathological description of what was probably a pheochromocytoma was published by Fränkel in 1886.13 Labbé22 is credited with recognition of the syndrome of paroxysmal hypertension associated with these tumors. Ante-mortem diagnosis was first accomplished by Vaquez in 1926.44 Charles Mayo first excised such a neoplasm, apparently without realizing what it was.22 In 1929, Pincoffs was able to predict the presence of a pheochromocytoma, the diagnosis being later confirmed at surgery.39

TERMINOLOGY

The terms pheochromocytoma and chromaffinoma refer to the functioning tumor of the adrenal medulla. They may also be used to designate ectopic chromaffin tumors. Paraganglioma is used synonymously by some authors, while others apply it only to the extra-adrenal chromaffinomas. Formerly it was thought that the carotid body tumor and related neoplasms were also paragangliomas. These have since been shown to be neither chromaffin positive nor of ectodermal origin. Carcinoid tumors have also been considered paragangliomas in the past.39

INCIDENCE

Approximately 400 cases of pheochromocytoma have been reported. This figure belies their true incidence. For example, Graham15 found 8 pheochromocytomas in the course of 1700 sympathectomies performed on hypertensive patients (0.47%).

The sex incidence is about equal, except in childhood when boys predominate.3,14 It is found at any time of life, from infancy to old age, but most often between 20 and 40 years.2,20,29 A familial occurrence has sometimes been noted, especially for tumors involving the organs of Zuckerkandl, and for those associated with neurofibromatosis.5,17 About one tenth of the reported cases have been in pregnant women.39

PATHOLOGY

Pheochromocytomas may develop wherever chromaffin tissue occurs, either embryologically or in the adult.15 The commonest location is in or about the adrenal (82%), particularly the right one.21,39 They also found along the cervical, thoracic, or abdominal sympathetic chain.26 In the chest they may be seen roentgenographically as paravertebral masses even before the onset of symptoms.29 They are also located along the major vessels of the abdomen (presumably arising from the organs of Zuckerkandl and other bodies) and the mesentery of the small intestine.21,39 Very rarely they occur in the urinary bladder,23,38 or intracranially.48

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About 10% are bilateral. In children both multiple and extra-adrenal tumors are considerably more common. Their size varies from the microscopic (detectable only by the effect of surgical manipulation of the affected adrenal) to huge masses weighing up to 8 pounds. The majority weigh less than 100 grams. At operation a peculiar brown pigmentation of the perirenal fat may be seen. Benign chromaffinomas are well encapsulated, compressing but not invading the neighboring organs. Cystic and necrotic areas in the tumor reflect its great metabolic demand. Calcification is sometimes seen, even on x-ray.

Microscopically the architecture is variable even within the same tumor. Nests, trabeculae, cords or other arrangements of cells lie in the highly vascular stroma. The cells are large but tend to resemble those of the adrenal medulla. Lipochrome and brown pigment are seen in the cytoplasm in chromate fixed specimens. Multiple infarcts are common.

The affinity for chrome salts has been directly attributed to the catecholamine content of the tissue. Chemical analysis of chromaffin tumors has repeatedly confirmed this correlation. However, a patient was recently cured of hypertension by surgical removal of a non-chromaffin paraganglioma from the aortic bifurcation. Analysis of both the patient's urine and the tumor revealed large amounts of catecholamines.

About 10% of pheochromocytomas are malignant. The incidence is higher for bilateral tumors and for those associated with persistent hypertension. Metastases occur to liver, lungs, bones, regional lymph nodes, and other organs. As with other endocrine tumors, malignancy is very difficult to assess histologically, and those originally considered benign may later be found to have metastasized.

PATHOLOGIC PHYSIOLOGY

The clinical features associated with these tumors are due to their secretion of biologically active chemicals and to their mechanical effects. In most cases the hormones produced are mainly epinephrine and norepinephrine. The latter usually accounts for the greater fraction. However, neoplasms containing large amounts of 3-hydroxytryptamine and DOPA have been described.

There is only a crude relationship between the chemical nature of the secretions and the clinical picture produced. Pharmacologically, epinephrine is known to raise the systolic blood pressure and pulse rate. Elevation of the blood sugar, hypermetabolism, apprehension, mydriasis, and other phenomena are also produced. Norepinephrine increases both systolic and diastolic blood pressure, slows the pulse, and has far less effect on the other body processes. Thus a small chromaffinoma producing mainly norepinephrine gives rise to the clinical picture of essential hypertension, while epinephrine secreting tumors are apt to be associated with nervousness, pallor, diabetes, etc. However, large doses of epinephrine will elevate the diastolic pressure, and large doses of norepinephrine produce metabolic symptoms. The ratio of the concentrations of the two hormones also seems to play a part. Following
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the removal of a malignant pheochromocytoma its metastases may continue to elaborate pressor substances. 45

In the metabolism of epinephrine and norepinephrine, they are apparently converted into their 3-methoxy derivatives. Unlike their parent compounds, these substances are effective substrates for monoamine oxidase. This enzyme converts them into 3-methoxy-4-hydroxy mandelic acid (vanillylmandelic acid, V.M.A.). This is excreted in the urine along with the glucuronides of 3-methoxyepinephrine and 3-methoxynorepinephrine. Only a small percentage of the epinephrine and norepinephrine is excreted unchanged. 50

CLINICAL FEATURES

An impressive variety of syndromes may be produced in different patients. In 70% of cases there is sustained hypertension. Upon this there may or may not be superimposed paroxysms of increased blood pressure and metabolic activity. Less often the "classical picture" is seen, with normal blood pressure between crises. 35,39,45,48,49 Almost any of the symptoms may so dominate the illness as to make the diagnosis obscure. Recurrent vomiting, 14 abdominal symptoms, 14 or night sweats 47 may be the presenting difficulty. The patient may develop a myocardial infarction, a stroke, or pulmonary edema without ever having had previous evidence of the tumor. 18,21 On the other hand, asymptomatic pheochromocytomas have been discovered during surgery for some unrelated condition. 48 Usually the patient has had difficulty for a period of 6 weeks to 10 years. 21 Moore 34 has emphasized the great difficulty of eliciting the symptoms even when they are present.

In childhood the picture is about the same as in the adult, except that hypertension is almost invariably sustained. 34

Table 1 presents a list of the commoner symptoms in approximate order of frequency. 15 Obviously the variations which may occur from patient to patient are innumerable.

Table 1

<table>
<thead>
<tr>
<th>Common symptoms of pheochromocytoma</th>
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<tbody>
<tr>
<td>Headache (usually pulsating, severe)</td>
</tr>
<tr>
<td>Palpitation</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Sweating</td>
</tr>
<tr>
<td>Dyspnea</td>
</tr>
<tr>
<td>Weakness</td>
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</tbody>
</table>

Other symptoms include pain and numbness of the legs, 21 tingling and coldness of the hands and feet, 21 and blurred vision or even blindness. 35 Subjective and objective coldness associated with vasoconstriction is a typical feature. 31 Raynaud's phenomenon has been described. 27

Crises may be precipitated by a wide variety of circumstances, commonly involving some change of posture or other mechanical stimulus to the tumor, (Table 2). Wingo 49 has called attention to the fact that many of these stimuli involve a small initial reduction in blood pressure. He postulates that the attack may represent an inappropriately dramatic response of the tumor to this hypotension.
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Table 2
Factors Precipitating Paroxysms

<table>
<thead>
<tr>
<th>Change of posture (bending, stooping, lateral flexion)</th>
<th>Alcohol</th>
<th>Sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>exertion</td>
<td>histamine (as in gastric analysis)</td>
<td>laughing</td>
</tr>
<tr>
<td>trauma to side or abdomen</td>
<td>amobarbital sodium sedation</td>
<td>sexual intercourse</td>
</tr>
<tr>
<td>local heat</td>
<td>TEA chloride</td>
<td>shaving</td>
</tr>
<tr>
<td>perirenal air insufflation</td>
<td>pain</td>
<td>gargling</td>
</tr>
<tr>
<td>general anesthesia</td>
<td>hyperventilation</td>
<td>straining at stool</td>
</tr>
<tr>
<td>parturition</td>
<td>emotional stress</td>
<td>sneezing</td>
</tr>
<tr>
<td>meals</td>
<td>postural hypotension</td>
<td>having BP taken</td>
</tr>
<tr>
<td></td>
<td>carotid sinus pressure</td>
<td>urination (pheochromocytoma of bladder)</td>
</tr>
<tr>
<td></td>
<td>change of temperature</td>
<td></td>
</tr>
</tbody>
</table>

The frequency of attacks ranges from several dozen a day to one every few months. They last from seconds to hours, commonly 10 or 15 minutes. They tend to increase in frequency but not severity. While the patient is often exhausted following paroxysms, he may be well between them. Some experience isolated symptoms, varying in severity, beginning and ending gradually, and lasting hours or days. There may be continuous hypermetabolism and/or hyperglycemia with paroxysmal hypertension. Severe attacks may end fatally.9,20,21,24

As stated, the blood pressure is usually elevated continuously, but paroxysms may be superimposed. Following an attack, the pressure may return to previous levels or hypotension of various degrees may occur. Dybkær9 feels that adaptation of the body to the high concentration of pressor substances accounts for the various sequelae of an attack. When secretion diminishes slowly, the blood pressure gradually falls to its former level. With more abrupt fall in concentration, it drops below that level, but returns spontaneously. A sudden cessation of secretion may result in shock or even death.

Either systolic or diastolic blood pressure or both may be raised. The pulse rate may be fast or slow. Postural tachycardia and less reliably postural hypotension have been considered of diagnostic importance.15,41

Some degree of fever is common, probably because of hypermetabolism coupled with impaired heat dissipation due to vasoconstriction. Even hyperpyrexia may occur, especially in the terminal stages.11,35,41

Characteristically the patient is thin.21 Shivering is not uncommon.9 When combined with sweating, a striking picture is produced. There may be pallor, flushing, or mottling of the face.9,15,18,21,35 The peripheral arteries may be constricted, even to the point of disappearance of the pulses.35 The pupils may be dilated.9 The fundi often reflect the degree of hypertension.35 In addition the retinal vessels may show constriction.35

An abdominal mass, either the tumor itself or a displaced liver or kidney, is palpable in 15% of cases. Even when it is not, palpation or massage of the flank may trigger an attack, if the tumor is sufficiently large. This sign should be deliberately sought. A syringe of phentolamine is kept ready for emergency use. If a
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paroxysm is produced, termination of it by injection of the drug will also be of confirmatory value.5,20,25 Certain diseases seem to show a peculiar association with pheochromocytoma. Five percent of the patients have neurofibromatosis.5 Von Hippel-Lindau's disease (angiomatosis retinae and cerebelli) may occur along with the neoplasm.49 There appears to be an increased incidence of gallstones.21 Rarely, Cushing's syndrome is a concomitant.15,18

DIAGNOSIS

There are many circumstances that should call to mind the possibility of pheochromocytoma. Each author emphasizes a somewhat different set of indications for applying the screening tests. They may be summarized as follows;2,3,18,20 21,24,25,49.

1. In the hypertensive
   a. paroxysmal hypertension or wide fluctuation within the hypertensive range
   b. hypertension in young individuals, pregnant or puerperal women, or in the absence of positive family history
   c. hypotension of recent onset
   d. severe hypertension
   e. hypertension with a normal pressor response
   f. hypertension associated with a postural fall in blood pressure and/or rise in pulse rate
   g. paradoxical response to ganglionic blocking agents
   h. hypertension associated with diabetes, hypermetabolism, fever, sweating or neurofibromatosis

2. A rise in blood pressure associated with general anesthesia, when no other cause is evident. If this occurs, the procedure should be discontinued until pheochromocytoma has been ruled out, as surgery for unrelated conditions carries a 50% mortality in the presence of such a neoplasm

3. "Seizures" characterized by any combination of the symptoms previously mentioned, especially if precipitated by factors such as those listed in Table 2

4. Nervous or hypermetabolic symptoms

5. Headache

6. Shock following the administration of a phenothiazine drug

Kvale states that it is probably rarely necessary to consider the diagnosis in an obese patient.

DIFFERENTIAL DIAGNOSIS

1. Hypertension due to other causes. While the hypermetabolic, paroxysmal, and other features of pheochromocytoma are of diagnostic value, their absence does not exclude the diagnosis.15,17,49 In sustained hypertension due to chromaffinoma, the duration of illness is usually much shorter than in essential hypertension. This is not invariable, however, and the other features of the two may be identical. Probably almost all hypertensives should be
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screened for pheochromocytoma. As seen, the syndrome must also be dis­tinguished from the toxemias of pregnancy.1,27

2. *Hyperthyroidism.* Paradoxical weight loss, apprehensiveness, weakness, fine hair, restlessness, and fine tremor may all be caused by pheochromocytoma. The BMR is often significantly elevated. At times thyromegaly and ex­ophthalmos compound the difficulty. The blood cholesterol, protein bound iodine, and radioactive iodine uptake usually help distinguish this syndrome from thyrotoxicosis, but reportedly the PBI can be elevated in pheochromocytoma. Antithyroid drugs are usually fairly ineffective, but they may cause a temporary reduction in BMR.7,17,49

3. *Diabetes.* During paroxysms elevated blood sugar with diminished glucose tolerance are common. Insulin resistant diabetes and even acidosis have been noted, with complete clinical disappearance of the diabetes following removal of the pheochromocytoma. Any diabetic with severe hypertension or with retinopathy characteristic of hypertension should be investigated18,20- 24,26,48,50 Kimmelstiehl-Wilsou disease may be mimicked.

4. *Headache* may be the dominant feature. This may resemble a tension headache or one of the vascular types, such as migraine or histamine cephal­algia.18,29,48

5. *Other neurological disorders,* including stroke, brain tumor, epilepsy, tabes dorsalis, and “acute nervous system infection or allergy” must be differ­entiated.15,18 In children the first impression is frequently that of an in­tracranial lesion.24

6. *Psychosis or neurosis* may be the presenting difficulty. This may take the form of anxiety or hysteria, often with hyperventilation. It may also resemble menopausal tension, agitated depression, or cyclothymic psychosis. Hypertension may not be detected.18 Electroshock therapy or other pro­cedures in such patients may, of course, be disastrous.

7. *Coronary artery disease,* ranging from coronary insufficiency to myocardial infarction may be imitated or may actually co-exist.18,19,20

8. *Gastrointestinal symptoms* may not be very characteristic or may be such as to lead to the diagnosis of an acute abdominal emergency. Shock and ileus may accompany severe abdominal pain. Infarction of the tumor is thought to account for acute pain, whereas chronic symptoms may be caused by pressure on the surrounding structures. Again, there may be no evidence of previous or concomitant hypertension.5,16,19

9. *Miscellaneous conditions* to be differentiated include the following:15,18,49

lead poisoning
hyperinsulinism
various renal lesions, including glomerulonephritis

gastrointestinal hemorrhage
urticaria
angioneurotic edema

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LABORATORY FINDINGS

The routine laboratory tests are not very helpful. Albuminuria occurring after attacks or continuously is found in about two-thirds of cases. The blood sugar is often elevated; in fact the patient may be frankly diabetic. Serum potassium is elevated, especially with a paroxysm, owing to the action of epinephrine. The electrocardiogram may show the changes expected with hypertension due to any cause. A basal metabolic rate as high as 90 or 100 may be found. While classically normal, the cold pressor test has been known to be positive, or even to trigger a crisis. Kvale states that he has not observed this however. The test is almost always abnormal in essential hypertension. Intravenous pyelography may demonstrate a mass.

PHARMACOLOGIC TESTS

If carefully selected and applied, these are valuable screening procedures. Their value is limited somewhat by the lack of uniform criteria for the normal limits of many of the tests.

There are two general types. Blocking tests are used if the patient’s blood pressure is found to be elevated (e.g. over 170/110). A substance is administered which blocks the effect of circulating pressor amines. Provocative tests are intended to cause a paroxysm in a patient whose blood pressure is normal or only slightly elevated (Kvale says under 170/110). If the pressure fluctuates widely, both types of tests should perhaps be done at appropriate blood pressure levels.

Certain precautions will enhance the reliability of these procedures. Obviously one could easily be misled by a difference between the blood pressures in the two arms. Errors due to spontaneous fluctuations in the pressure should be minimized by following the basal blood pressure for at least 30 minutes before the test, or at least by having the patient rest for a similar period. Similarly the blood pressure should be followed for at least 15 minutes after it has returned to the control level. A cold pressor test should be done before giving any provocative agent to avoid misinterpreting the results obtained.

Many medications are capable of causing false positive or false negative results (see below).

*Phentolamine (Regitine) methanesulfonate test:* Following rapid intravenous injection of 5 mgs. of the drug, the blood pressure is taken every 30 seconds for 5 minutes, and then every minute for 15 or 30 minutes, or until it stabilizes at control levels. A positive result consists of a fall of 35 mms. of systolic and 25 mms. in diastolic pressure. This usually begins immediately, reaches a nadir in 2 to 5 minutes, and lasts 10 minutes to an hour or more. Occasionally, a “fall-rebound-fall” response occurs, which also represents a positive test. A fall the first minute, with return to basal levels in the next minute is negative.

False positive phentolamine tests occur in subjects receiving narcotics, sedatives, rauwolfia compounds, or thiocyanates, and in uremic patients. Sedatives and narcotics should be stopped for 48 hours, thiocyanates 4 to 6 days, and rauwolfia several weeks prior to the test. With these precautions, false positive tests are allegedly rare, although some feel they are not unusual.
False negative tests may be seen in patients being treated with hydralazine and other antihypertensive drugs. Hydralazine should be discontinued for several weeks, and other drugs for several days.

An intramuscular phentolamine test has also been used, but is probably less reliable.

Most workers consider Regitine the blocking drug of choice, as it is quite safe. The side effects are minimal in the recommended dose, consisting of tachycardia, weakness, dizziness and flushing. The test can even be performed on an emergency basis in the presence of hypertensive encephalopathy. To this author's knowledge, two fatal reactions have been reported. Lance feels Regitine may be dangerous in patients with normal basal blood pressures.

Piperoxan (Benodaine) hydrochloride test. This blocking test is performed by giving 0.25 mgs. per kg. (the maximum 20 mgs.) of the drug intravenously over a 2 minute period. The blood pressure is followed exactly as in the phentolamine test. Criteria for a positive test are less well established, but a fall of 35 mms. in systolic or diastolic pressure has been suggested. Again, a “fall-rebound-fall” response is positive.

False positive and negative results probably occur under the same circumstances as in the Regitine test. The drug is not as safe as phentolamine, and side effects may be serious. In essential hypertension, tachycardia, headache, flushing, anxiety, chest or abdominal pain, nausea, vomiting, and dizziness may be seen. In these patients the blood pressure may fall initially, but often rises, at times to dangerous levels. Encephalopathy, convulsions, and pulmonary edema can occur. For this reason Orgain does not recommend the test for routine screening.

An intriguing new test, the piperoxan antidiuresis test, makes use of the fact that the drug abolishes the diuretic effect of pressor amines. This action is even more marked than that on the blood pressure. After an overnight fast the patient drinks a liter of 0.25% sodium chloride solution in 10 minutes. He remains recumbent, and smoking is prohibited. After voiding, urine is collected at half hour intervals for 3 or 4 periods. Immediately following the second voiding, 20 mgs. of piperoxan are injected intravenously over a two minute period. Subsequent urine collections show a prompt reduction in volume, generally one-third or less the previous levels, in patients with pheochromocytoma. Control patients actually showed a slight increase in urinary output. The test is said to be positive even during the normotensive phase of the disease.

The dibenamine hydrochloride test is relatively more dangerous and less reliable than the other blocking procedures and is little used.

Histamine test. After stabilization following a cold pressor test, 0.025 to 0.10 mgs. (usually 0.05 mgs.) of histamine base are administered intravenously in about 0.5 c.c. saline with a tuberculin syringe. Regitine is kept ready for emergency use. Blood pressure is determined every 30 seconds for 5 minutes, and then every minute for 15 minutes or until it returns to the control level. If the drug was
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Injected into a vein, the blood pressure falls after 30 seconds. If the test is positive, it then rises rapidly, 60/35 mms. or more higher than the cold pressor response. This rise occurs one to four minutes after injection and lasts 5 to 15 minutes. Symptoms of a severe paroxysm appear.

The mechanism of action is not known. It may be direct stimulation of the tumor, or the paroxysm may be a response to the initial hypotension produced.

This is generally regarded as the most reliable provocative test. False positives are seldom seen,

but may occur with larger doses. It may be falsely negative in patients receiving sedation or anesthesia, or if the control pressure is too high, or if the drug is injected slowly.

There is some danger in the procedure. The blood pressure may fall perilously in the absence of a chromaffinoma, or climb to alarming levels in the presence of one.

A number of deaths have been reported.

Nevertheless, the test is probably indicated in all pheochromocytoma suspects who have a normal or fluctuating blood pressure.

The *methacholine (Mecholyl) chloride, tetraethylammonium chloride, and DMPP provocative tests have little to recommend them.*

Epinephrine tolerance test. This is rarely used. It is based on the decreased response to epinephrine shown by patients with pheochromocytoma, probably due to an adaptation phenomenon.

**CATECHOLAMINE ASSAY**

Improved and simpler techniques of catecholamine assay are continually being perfected. The directness of this approach is a clear advantage. Some even believe that where this method is available the pharmacologic tests are seldom indicated.

Urine assay is most commonly done. A normal resting individual excretes 15-30 mcg. per 24 hours, 80% of which is norepinephrine. It never exceeds 185 mcg.

In the presence of pheochromocytoma, the range is from 180 to 9000 mcg. The increase is usually in the norepinephrine fraction, but can also be epinephrine. Bananas contain large amounts of norepinephrine and should be withheld for the test.

Rauwolfia drugs should be stopped for a month prior to urine collection. Many other substances may interfere with the determination depending on the technique used.

The output is generally high even during normotensive intervals, but may be normal at these times.

If normal, it may reach diagnostic levels under the influence of histamine or general anesthesia.

Although the test is believed to be highly specific, catecholamine output is also somewhat increased in the following conditions:

- asphyxia
- cold exposure
- myocardial infarction
- emotional stress
- electroshock therapy
- increased intracranial pressure

Numerous quantitative and semi-quantitative techniques are used, including bioassay, paper chromatography, photofluorimetry, and chemical analysis.

*At the Henry Ford Hospital the normal range is up to 300 mcg. total catecholamines per 24 hours.*
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A new method determines the urinary output of VMA (see Pathologic Physiology, above). It may be a better test, for this metabolite is excreted far more abundantly than are the pressor amines themselves.40,50

Blood catecholamine assay is also useful. It is apparently unnecessary to withhold drugs for the test. The level is considered significant when over 3.5 mcg. of epinephrine-like substance per liter of plasma is found. It can be normal in the presence of a pheochromocytoma,28 but will be found elevated if the blood is obtained during a histamine-induced paroxysm.20,21 In essential hypertension, the level is usually less than 3.5 mcg. per liter and does not rise significantly after histamine. The plasma catecholamine content also rises in some patients with renal insufficiency, increased intracranial pressure and lymphoma. It is uncertain whether the substances measured in these conditions are the same as those produced by chromaffinomas. With the fluorescent column technique, hemolysis or icterus will produce falsely high results. Users of epinephrine nebulizers may also have elevated blood catecholamine levels.20,21

LOCALIZATION OF THE TUMOR

Because pheochromocytomas occur in so many locations and may be multiple, many authors do not consider exact preoperative localization essential. Rather than subjecting the patient to potentially dangerous procedures, the surgical approach is such as to permit rather wide exploration. If the plain abdominal x-ray and intravenous pyelogram are non-contributory, operation is not delayed.20,24,35

Others feel that exact localization is highly desirable. Aortography, presacral or perirenal oxygen insufflation, retrograde pyelography, selective aortography, and tomography have been employed. The gas insufflation techniques, at least, are not without hazard. Another very ingenious method has been devised, whereby blood is sampled from various parts of the venous system using a catheter under fluoroscopic control. The relative catecholamine content of the specimens helps localize the tumor.45

Interestingly, tumors producing both norepinephrine and epinephrine tend to lie in connection with one of the adrenal glands. Those elaborating norepinephrine alone are usually ectopic.45

TREATMENT

The only successful form of treatment is surgical removal of the tumor. X-ray therapy has been disappointing.13

Preoperatively it may be necessary to control dangerous swings in blood pressure.43 Phentolamine methanesulfonate is apparently of great value here. In one case42 a continuous infusion of the drug not only prevented the hypertensive crises, but eliminated the intervening periods of shock. Surgery was then carefully planned and carried out two and a half days later. These workers used a concentration of 30 mgs. per liter, given intravenously at 20-80 drops per minute, depending on the intramuscular frequent blood readings. Intermittent Regitine had been unsuccessful in their patient. On the other hand, Emanuel et al19 warn that the drug does not seem to protect humans from arrhythmias induced by pressor amines.
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The operating team should be well prepared for the emergencies that are apt to arise. Continuous monitoring of the blood pressure by an intraarterial cannula is probably worth while. The anesthetic agent and body position must be chosen carefully. When anesthesia is induced and the incision is made, blood pressure rises to various degrees. Five mgs. of Regitine IV may be advisable at this time. Various surgical approaches are used. A high transverse abdominal incision permits wide exploration.

The tumor should be treated gently and its vessels ligated early. As it is palpated, 5 mgs. or more of Regitine may be used to control paroxysms. With tying of the vessels, shock often occurs. This is controlled by the administration of pressor agents sufficient to maintain the blood pressure at about 100/70 to 110/80. It is probably even advisable to make the fall a gradual one by giving these drugs relatively early. If no drop occurs, the surgeon should search for additional tumor tissue. Preservation of some adrenal cortex is important. If this cannot be done, intravenous hydrocortisone should be at hand.

After surgery Thorne recommends leaving the patient undisturbed on the operating table for several hours. Extremely close observation is still necessary, for the blood pressure may drop unexpectedly. Urinary catecholamine determination will help assess the completeness of the operation.

PROGNOSIS

Untreated pheochromocytomas are generally fatal in a few years, their course resembling that of malignant hypertension. Death is usually caused by pulmonary edema, coma, cerebral hemorrhage, or shock during surgery or other circumstances. The author is aware of one report of fatal hemorrhage into a previously asymptomatic tumor.

When found in relation to pregnancy, the disease may be fatal before or after parturition, often within a day of delivery. The overall maternal mortality has been about 50%, while that for the infant is approximately 40%.

The fatality rate in childhood is about 54%.

Surgical removal of the tumor often results in cure. Partial or complete reversal of the changes in the circulatory system may result. If hypertension persists, the possible causes include the presence of additional tumors or metastases, irreversible vascular damage due to previous hypertension, and the presence of essential hypertension. Operative mortality has been 20 or 30%, but will probably decline with improved understanding of the disease. Many of the deaths are due to shock, which is seen during 10 to 50% of operations when the veins draining the tumor are ligated. This is believed due to the sudden deprivation of the large amount of pressor amines to which the organism has adapted. Disuse atrophy of the other adrenal medulla and surgical injury of the adrenal cortex may be contributing factors.

Spontaneous shock has also been described. Whether this is due to sudden cessation

*Benzodioxane and dibenamine have also been employed to control the blood pressure during surgery.
of secretion or is related to the shock-like state seen in epinephrine-infused animals is uncertain. Several reports describing such crises are in the literature. In some patients, deep shock alternates with bouts of severe hypertension. Rarely shock appears as the presenting difficulty. One report describes the appearance of shock following intramuscular administration of 10 mgs. of prochlorperazine. The tumor may be infarcted and become functionless during the hypotensive episode.

Other complications include loss of vision, congestive failure, myocardial infarction, basilar thrombosis, severe diabetes, and, of course, the usual sequelae of hypertension. Rarely, Addison's disease may result from compression of the adrenal cortex. As already implied, when significant levels of pressor amines have been present long enough, hypertension may no longer depend on them, and may persist after otherwise successful surgery.

**SUMMARY**

The diagnostic and therapeutic problems associated with pheochromocytoma are presented in detail. It is hoped that this will encourage increased recognition and more successful management of these tumors.

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Pheochromocytoma