Pheochromocytoma, Factors in the Accurate Pharmacologic Diagnosis*

GRACE M. ROTH, Ph.D.** and WALTER F. KVALE, M.D.***
Rochester, Minnesota

Pheochromocytoma or the tumor of the medullary portion of the adrenal gland is a challenge to the clinician, investigator, biochemist, surgeon and pathologist. Although intrathoracic pheochromocytomas are rare, it is important that the chest physician and chest surgeon should be aware of the hazards of such tumors. The correct preoperative diagnosis of pheochromocytoma can be a lifesaving measure.

An estimated 90 per cent of pheochromocytomas 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. In addition pheochromocytomas have been found in the organ of Zuckerkandl located on either side of the aorta at the origin of the inferior mesenteric artery.

Only four intrathoracic tumors have been reported in the literature and two were successfully removed. The first two were noted at necropsy; the first was found by Miller1 in 1924 in the right costovertebral region at the level of the sixth rib. The second, reported by Philips2 in 1940, was found at the apex of the left pleural cavity and probably arose from the first left thoracic ganglion. In the third case the diagnosis was made preoperatively for the first time and the tumor was successfully removed. This case was reported in 1949 by Maier.3 Pheochromocytoma was suspected because the patient had an unexplained hypertension and an intrathoracic tumor near the sympathetic chain in the costovertebral region. Because of this, blood pressure readings were made at intervals of five minutes during the operation and epinephrine (adrenalin) was ready for immediate use. Care was taken to minimize manipulation of the tumor during the freeing of the mass in order to avoid hypertensive crisis. Within five minutes after the blood vessels leading to the tumor were clamped, the systolic blood pressure dropped from 210 to 110 mm. of mercury and a few minutes later was barely obtainable. Adrenalin was given intravenously and the blood pressure rose gradually and remained normal throughout the first postoperative day. The patient is still in good health.

In the fourth case, reported in 1950 by Overholt,4 the diagnosis of pheochromocytoma was not suspected until operation. A lesion in the chest was noted on routine examination. The blood pressure was normal and

*Presented at the 21st Annual Meeting, American College of Chest Physicians, Atlantic City, New Jersey, June 2 to 5, 1955.
**Section of Physiology, Mayo Clinic and Mayo Foundation.
***Section of Medicine, Mayo Clinic and Mayo Foundation.
The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.
the only significant symptom was a definite history of mild intolerance to heat. A diagnosis of posterior mediastinal neurofibroma was made, and the patient was prepared for operation. When the patient was placed on the operating table, the blood pressure was found to be 240/160 mm. of mercury, and the pulse rate, 160 beats per minute. The systolic blood pressure shortly rose to 270 and a pheochromocytoma was suspected. The tumor was lying half on the fourth, fifth, sixth and seventh vertebral bodies and half on the heads of the adjacent ribs. It was in line with the sympathetic chain which could be seen to disappear into it from above and emerge from it below. The vascular supply of the tumor was divided, and when the interruption of the supply was completed, a precipitous fall in blood pressure occurred to 90/70 mm. of mercury. At this time, blood was pumped rapidly into the vein and five minims of phenylephrine hydrochloride (neosynephrine) was given intravenously. An additional three minims of neosynephrine was given with an elevation of the systolic blood pressure to 100 mm. for the duration of the closure; however, when the patient was returned to bed, the blood pressure fell to 40 mm. of mercury systolic and neosynephrine was again given with effect. Today this patient is well.

Pertinent information, in addition to that on primary lesions in the chest, may be obtained from routine x-ray examination of the chest and physical examination about the neck. In one of our patients who had a pheochromocytoma primary in the left adrenal, a lesion was noted in the right seventh rib in the routine roentgenogram of the thorax. This was later found to be a metastatic lesion from the tumor in the adrenal. A second patient had an enlarged node in the left supraclavicular region five months after removal of a tumor from the hilus of the liver behind the common bile duct and foramen of Winslow. A histamine test gave a negative result 10 days after removal of the hilar tumor, but was positive five months later. After removal of the node from low in the deep cervical chain, the histamine test again gave negative results. Because the histamine test was positive for pheochromocytoma before both operations, the usual preparations were made for the operations. Both of these patients have returned with further metastasis.

Bartels and Cattell have reported a similar case. Their patient remained well for a year after the removal of a tumor from the left adrenal, and then swelling developed in the right side of the neck. Biopsy revealed this to be a metastatic pheochromocytoma.

A sudden hypertensive reaction during any operative procedure should cause the surgeon to suspect pheochromocytoma. Today the antiadrenergic drugs are available to combat the hypertension resulting from these tumors during operation, and phenylephrine hydrochloride (neosynephrine) and norepinephrine (arterenol) are available to restore the blood pressure to normal levels after the removal of the tumors.

Pheochromocytoma may be associated with sustained hypertension or with paroxysmal hypertension associated with attacks similar to those following the administration of large amounts of epinephrine or norepinephr-
rine. Thus any patient who has a paravertebral tumor in the thorax and gives a history of paroxysmal hypertension associated with tachycardia, headache, intolerance to heat, excessive sweating and sometimes nausea and vomiting should be suspected of having a pheochromocytoma. Likewise a patient with a tumor in the thorax and sustained hypertension with or without these same symptoms may also be suspected of having pheochromocytoma, particularly if the history of hypertension has been short.

In order to establish a correct diagnosis before operation, there are simple pharmacologic tests which can be carried out by a physician in a short period.

The Pharmacologic Tests

In cases of paroxysmal hypertension due to pheochromocytoma, administration of histamine, tetraethylammonium chloride (TEAC) and metha-

![Figure 1: Changes in blood pressure during the cold pressor test, histamine test and regitine test. Left. The rise in blood pressure during the immersion of one hand in cold water at 4°C for 1 minute and after the intravenous administration of 0.05 mg. of histamine base in 0.5 cc. of physiologic solution of sodium chloride should be noted. Thirty seconds after the injection of histamine the blood pressure fell and 2 minutes later rose precipitously. These observations indicate a pheochromocytoma. Center. The rise in blood pressure during the cold pressor test and the more precipitous rise following the injection of histamine should be noted. At the height of the response to histamine which was due to the release of the pressor amines, regitine, given intravenously, produced a precipitous fall in blood pressure together with a cessation of all clinical signs and symptoms; thus two tests were positive for pheochromocytoma. Right. The sudden rapid fall of the blood pressure after the intravenous injection of 5 mg. of regitine is interpreted as a positive result indicative of pheochromocytoma. Practically no fall but instead a rise in the blood pressure followed intramuscular administration of 5 mg. of regitine. This indicates that a pheochromocytoma is not present. This was a false negative result in this case.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21276/ on 06/26/2017)
choline chloride (mecholyl) stimulates the discharge of the pressor substances from the tumor and produces characteristic attacks similar to those that occur spontaneously. In cases of sustained hypertension, phentolamine (regitine) and piperoxan lower the blood pressure by blocking the pressor effect of epinephrine and norepinephrine in the blood if a pheochromocytoma is present. In the pharmacologic test with these drugs, one is dependent on a precipitous fall in blood pressure for the demonstration of the 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. At this time, we should like to discuss all the precautions concerned with these tests.

The cold pressor test is an integral 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 two minutes after the intravenous injection of histamine (Fig. 1). For the histamine test as we carry it out, histamine is never given as an infusion; 0.05 mg. of histamine base in 0.5 cc. of normal saline solution is placed in a tuberculin syringe and is injected intravenously. The blood pressure always falls 30 seconds after the injection or the histamine did not enter the vein. Immediately thereafter the blood pressure rises rapidly, and the characteristic clinical signs and symptoms of a severe episode appear. In any one patient, one or more of the characteristic symptoms of the episode may be lacking.

For the result of a test with histamine in the patient with normal levels of blood pressure between attacks to be interpreted as positive for pheochromocytoma, the rise in blood pressure two minutes after the injection should be at least 60 mm. systolic and 40 mm. diastolic. The average rise for 19 patients with pheochromocytoma was 106 mm. systolic and 56 mm. diastolic. This was an average of 70 mm. systolic and 19 mm. diastolic above the average response of the blood pressure during the cold pressor test.

The histamine test is used for patients with paroxysmal hypertension but not for sustained hypertension. Usually when there is sustained hypertension with a basal blood pressure of more than 170/110, regitine is used. For the patient with mild persistent hypertension and a history of paroxysmal attacks, with a basal blood pressure of less than 170/110, both histamine and regitine are used as follows: The needle is left in the vein following the administration of histamine and another syringe containing regitine is attached. The blood pressure is determined repeatedly for two minutes after the injection of histamine, then regitine is injected. If the rise in blood pressure after the injection of histamine is due to the pressor amines from a pheochromocytoma, all symptoms will disappear and the blood pressure will fall in 30 to 60 seconds after injection of regitine. Therefore, histamine may be given with safety and two positive
Tests will be obtained (Fig. 1). If the patient has mild essential hypertension, the blood pressure will not rise as high when histamine is given as it will if the patient has a pheochromocytoma, and after the administration of regitine the headache will not disappear and the blood pressure will not fall rapidly. If regitine is given alone to such a patient between paroxysms, the blood pressure may rise instead of fall in the presence of a tumor as there will be no pressor amine in the blood to cause the precipitous fall in blood pressure between attacks.

To the patient with sustained hypertension, 5 mg. of regitine is administered intravenously, not intramuscularly for the test. As you will note in Figure 1, a negative result may be obtained when regitine is given intramuscularly in the presence of a tumor. Regitine rather than piperoxan is used for the first test on patients with sustained hypertension as there are fewer side reactions with regitine and no hazardous pressor responses when the patient has essential hypertension. True, regitine has

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21276/)
a greater tendency to cause a fall in the blood pressure during the first
minute when no pheochromocytoma is present, but the blood pressure
returns in the next minute to a level which will be considered negative
for pheochromocytoma.

Before any of these tests are carried out, the use of any sedative or
narcotic should be prohibited for 48 hours and possible self-medication
should be checked as the pharmacologic tests may yield false positive
results under these conditions. First, sedatives inhibit the rise of the
blood pressure during the cold pressor test which is the measuring stick.
The effect of sedation is demonstrated in Figure 2. In a case of paroxysmal
hypertension, histamine produced a rise greater than the cold pressor
test during sedation, thus indicating the presence of a tumor. Both
piperoxan and regitine produced a marked fall during sedation. However,
when the sedation was discontinued for 48 hours, the two minute rise
with histamine was less than that of the cold pressor test and three
times as much regitine as given during sedation did not produce the
previous fall in blood pressure. No tumor was found at operation.

In a patient with sustained hypertension, barbiturates, meperidine
hydrochloride (demerol), morphine, chloral hydrate and probably many
other sedatives produce a fall in blood pressure following intravenous
administration of regitine or piperoxan typical of that produced by a
tumor. 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. The false positive
result during sedation and the negative result after discontinuation of
sedation are indicated in Figure 3. The fact that a false positive result
is obtained during sedation has been proved by operation as no tumors
were found. When a patient has a severely elevated blood pressure, it is
always logical to hospitalize and to sedate him. Subsequently, while he
is in the hospital and under sedation, the pharmacologic tests are carried
out and a false positive result is obtained which would indicate the presence
of a tumor.

It is a good idea when screening patients for pheochromocytoma to
measure the blood pressure on both arms because a difference in blood
pressure of from 10 to 80 mm. of mercury systolic has been found in the
two arms of the same patient. Two cases will be cited briefly to demon-
strate how a false positive diagnosis may be obtained during the pharma-
co logic tests.

In the first patient a histamine test and a cold pressor test were carried
out first on the right arm and subsequently on the left arm. The basal
blood pressure in the two arms varied by 52 mm. systolic and 38 mm.
diastolic. The blood pressure on the cold pressor test rose approximately
the same amount in both arms. In order to have a positive result from
the histamine test on the right side the blood pressure should rise con-
siderably higher than it did during the cold pressor test on that same side.
If the blood pressure is not measured simultaneously in both arms or is
measured in one arm for the cold pressor test and in the other arm when
the histamine is given, a false positive result could be obtained. By measuring the blood pressure simultaneously in both arms the reaction to histamine was found to be negative.

The second patient was sent to us with a diagnosis of pheochromocytoma. The basal blood pressure varied greatly in the two arms. When the blood pressure is measured on the arm with the highest pressure after the intravenous injection of regitine or piperoxan, the blood pressure may fall to the level of the opposite arm, which in this case was a fall of 80 mm. systolic and 40 mm. diastolic. This could easily be interpreted as a positive response. When the blood pressures were determined simultaneously in the two arms, there was little or no fall in the blood pressure on 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 pressures are determined simultaneously in both arms during the pharmacologic tests.

FIGURE 3: Left. Observations made during sedation. The precipitous fall in blood pressure of a patient with hypertension seems to indicate the presence of a pheochromocytoma. Right. Observations 5 days after sedation had been discontinued. The slight fall in blood pressure should be noted. No tumor was found at operation.
With the introduction of the antihypertensive drugs, another difficulty has arisen, namely false negative results (Fig. 4). In two cases in which a tumor was found at operation, the first had two negative tests followed by a positive test when use of hydralazine (apresoline) was discontinued; in the second case we obtained an equivocal result from the test until use of the drug was discontinued for 8 days. This situation is difficult to deal with because we do not know how long administration of these drugs must be discontinued but apparently for some time. Sometimes, because the sweating disappears when hydralazine (apresoline) is given, the return of sweating may be an indication of the time when a clear-cut test can be obtained. At present we are not able to state definitely the effect of the Rauwolfia compounds on the pharmacologic tests.

By close observation of these various difficulties during the past 10 years, we have carried out 7,500 pharmacologic tests on 6,061 patients, and we have found 55 pheochromocytomas in 45 patients. The diagnosis has been proved correct at operation.

No deaths or untoward effects have occurred in any of these patients during the tests before operation, during operation or immediately after operation. This has been largely due to extremely close and careful observation of the patient during and after operation. In all patients now a transverse abdominal incision is made in order that all tumor-

![FIGURE 4: The blood pressure after the intravenous injection of regitine while the patient was receiving antihypertensive drug, apresoline, should be noted. After administration of apresoline was discontinued for 16 days, a precipitous fall of blood pressure occurred after the injection of regitine. This indicates a pheochromocytoma and the tumor was found at operation. Note the equivocal fall of the blood pressure after the injection of regitine after administration of apresoline had been stopped for 4 days. After administration of apresoline had been discontinued for 8 days, a more precipitous fall in blood pressure occurred after the injection of regitine. This indicates a pheochromocytoma, and, as said before, one was found at operation.](image-url)
bearing regions may be explored. We have determined the blood pressure at intervals of one minute during the operation. Thus, when pronounced hypertensive effects occur, regitine is given immediately to lower the blood pressure and when removal of the tumor is accompanied by a sharp fall in the blood pressure, norepinephrine is administered. After a tumor is removed, a sudden rapid rise in the blood pressure which is maintained indicates the presence of another tumor.

SUMMARY

The precautions which are necessary to procure a successful pharmacologic test for pheochromocytoma have been discussed. These tests with the proper precautions can be carried out quickly and without hazard. A preoperative diagnosis of pheochromocytoma in any patient with hypertension and a tumor located paravertebrally in the chest can be made by these pharmacologic tests. Thus, fatalities or untoward reactions may be avoided during operation because of an unexpected pheochromocytoma.

RESUMEN

Se discuten las precauciones necesarias para llevar a cabo una prueba farmacológica con éxito en el feocromocitoma. Estas pruebas con las precauciones adecuadas pueden realizarse pronto y sin peligro. Se puede hacer un diagnóstico preoperatorio de feocromocitoma en cualquier enfermo con hipertensión y tumor localizado paravertebralmente en el tórax. Puede evitarse la mortalidad durante las operaciones a causa de un feocromocitoma inesperado.

RESUME

L'auteur discute les précautions nécessaires pour l'obtention d'un test pharmacologique satisfaisant pour le diagnostic de phéochromocytome. Ces examens avec les précautions nécessaires peuvent être poursuivis rapidement et sans danger. Un diagnostic préopératoire de phéochromocytome chez chaque malade atteint d'hypertension et de tumeur paravertébrale localisée dans le thorax, peut être fait par les tests pharmacologiques. C'est pourquoi les erreurs et les réactions douteuses dues à un phéochromocytome inattendu peuvent être évitées pendant l'opération.

ZUSAMMENFASSUNG

Die zur erfolgreichen Durchführung eines pharmacologischen Testes auf Phaeochromozytom notwendigen Kautelen wurden besprochen. Diese Tests können unter Berücksichtigung der richtigen Vorsichtsmaßnahmen schnell und ohne Risiko ausgeführt werden. Durch diese pharmakologischen Tests kann bei jedem Patienten mit Hypertonie und paravertebralem intrapulmonalem Tumor die Diagnose eines Phaeochromozytoms
gestellt werden. Hierdurch können Todesfälle und unerwünschte Reaktionen während der Operation durch das unerwartete Vorhandensein eines Phaeochromozytoms vermieden werden.

REFERENCES