CLINICAL PROGRESS

Pharmacologic and Chemical Tests as an Aid in the Diagnosis of Pheochromocytoma

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One of the known causes of hypertension is a pheochromocytoma, a tumor of the medullary portion of the adrenal gland that secretes epinephrine or norepinephrine in varied but increased amounts. It produces either sustained hypertension or paroxysmal hypertension frequently associated with bizarre symptoms during the attack, together with hypermetabolism and high blood sugar in some instances. Although pheochromocytoma is rare, it is being diagnosed oftener and will become increasingly important with safe surgical removal. Thus the correct preoperative diagnosis becomes imperative and can sometimes be lifesaving.

An estimated 90 per cent of pheochromocytomas arise from the adrenal medulla, but they may occur wherever chromaffin tissue is found along the sympathetic nervous system. Of pheochromocytomas found outside the adrenal glands, 6 have been found in the thorax, 4 in the urinary bladder, and 18 in the organ of Zuckerkandl. Multiple tumors may occur in both adrenal glands or along the aorta in the sympathetic chain; some of the latter tumors may be metastatic, as approximately 10 per cent of pheochromocytomas are malignant. Familial pheochromocytoma has been reported.

When the patient has paroxysmal hypertension, the 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 one case, one or more of these symptoms may be lacking. Occasionally a physician may be fortunate enough to observe a patient in one of these attacks, but often only the history of the attacks is available and it may be inconclusive.

For the patient with sustained hypertension the physician may not have even a history of attacks to point the way to a correct diagnosis. Today, however, pharmacologic and chemical tests are helpful in screening a relatively large number of patients for pheochromocytoma and are a definite aid to a correct diagnosis.

Pharmacologic Tests

Fifteen years have elapsed since we first introduced the histamine test for pheochromocytoma. Although we have used all the drugs suggested for testing as they appeared, we now use histamine for the patients with paroxysmal hypertension, because it stimulates discharge of pressor substances from the tumor and produces attacks similar to those occurring spontaneously, and we now use phentolamine hydrochloride (Regitine) for the patient with sustained hypertension,

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because it decreases blood pressure by blocking the pressor effect of epinephrine or nor-epinephrine in the blood if a pheochromocytoma is present.

To carry out these tests correctly, certain prerequisites are necessary: The first is a reliable basal blood pressure. With the patient lying comfortably, the blood pressure is observed for at least half an hour to obtain the correct basal value. This is highly important in the interpretation of the results after use of histamine or Regitine.

Cold Pressor Test, a Prerequisite

Before either the histamine or the Regitine test, the cold pressor test is performed, except when the diastolic blood pressure is more than 150 mm. Hg. The cold pressor test is done by immersing one of the patient's hands well above the wrist in a pail 8 inches high in water of 4 C. for 1 minute and measuring the blood pressure on the opposite arm at 15, 30, and 60 seconds during the immersion. The highest blood pressure during this painful stimulus indicates the lability of the blood pressure. If a patient has a history of blood pressure of 230/160 at one time and of 130/90 at another, the carefully determined basal blood pressure may be 130/90 and it may rise to 230/160 during the cold pressor test. Such a patient has very labile blood pressure and probably no pheochromocytoma, but if the rise in blood pressure during the cold pressor test is much less than to 230/160, pheochromocytoma may be suspected. The average increase in the blood pressure during the cold pressor test in our cases of proved pheochromocytoma was 40/29, with a range from 12 to 68 mm. systolic and from 10 to 78 mm. diastolic.

The cold pressor test is an integral part of the histamine test, since the response of the blood pressure to cold is used as the measuring stick for the response of the blood pressure 2 minutes after the intravenous injection of histamine. In our experience a cold pressor test has never produced an attack in a patient with pheochromocytoma because there is a sudden rapid rise in the blood pressure during the cold pressor test, whereas it is the sudden rapid fall in blood pressure that stimulates the secretion of the tumor. Furthermore, knowledge of the lability of the blood pressure is important on the third and fourth days after operation if a pheochromocytoma is removed, when pain may produce an elevation in blood pressure.

Histamine Test Followed by Regitine Test for Paroxysmal Hypertension

After the cold pressor test, when the blood pressure has returned to basal levels in the patient who has paroxysmal hypertension and a basal blood pressure of less than 170/110, 0.05 mg. of histamine base in 0.5 ml. of normal saline solution is injected intravenously with a tuberculin syringe. The needle is left in the vein, the empty syringe is removed immediately, and a syringe containing 5 mg. of Regitine is attached for immediate administration if the blood pressure becomes alarmingly high.

Blood pressure is determined every 30 seconds for the next 2 minutes (fig. 1). It always decreases 30 seconds after the injection of histamine, or the histamine has not entered the vein. Immediately thereafter the blood pressure increases rapidly and usually is max-
Phenohromocytoma

If a pheochromocytoma is present, the characteristic clinical signs and symptoms of a severe attack appear concomitantly with the increase in blood pressure to well above the cold pressor level. Regitine hydrochloride, 5 mg., is injected 2 minutes after the histamine or before, if the rise in blood pressure makes it necessary.

Within 1 minute after the injection of Regitine the clinical signs and symptoms of a severe attack will disappear and the blood pressure will decrease if a pheochromocytoma is present. Thus, histamine can be given safely, and 2 positive reactions will be noted. Occasionally, when a large or active tumor is present, after the first fall and cessation of symptoms on administration of Regitine, the blood pressure and symptoms may reappear and more Regitine may be needed. Recently, in a patient with a 700-Gm. tumor 50 mg. of Regitine were necessary to reduce the blood pressure to basal levels in 10 minutes (fig. 1). This knowledge was important in the care of the patient during operation, as 50 mg. of Regitine were necessary to keep the blood pressure at a safe level during operation.

If the patient has only mild essential hypertension, the blood pressure will not rise as high after the injection of histamine (that is, will rise little if any above the height during the cold pressor test), and the headache will not disappear nor will the blood pressure fall rapidly after the injection of Regitine. If Regitine is given alone to a patient with labile hypertension between paroxysms, the blood pressure may not change even in the presence of a tumor because the concentration of pressor amines is not elevated in the blood between attacks. Therefore, false-negative results will be obtained.

Regitine Test for Sustained Hypertension

For the patient with sustained hypertension (a basal blood pressure of more than 170/110), 5 mg. of Regitine hydrochloride are administered intravenously, not intramuscularly. If a pheochromocytoma is present, the blood pressure should decrease at least 35/25 in the first 3 or 4 minutes after injection and then should return to the previous basal level in 10 to 15 minutes (fig. 1). Regitine will cause a decrease in the blood pressure of some particularly apprehensive patients during the first 1 or 2 minutes after injection in the absence of a pheochromocytoma, but in the next minute the blood pressure returns toward the basal level and the test is considered as being negative for such tumors.

Why Are So Many False Results Reported from the Pharmacologic Tests?

The first difficulty comes from not obtaining a reliable basal blood pressure. The second may be failure to observe the blood pressure quickly enough as the timing is very precise.

The third may be a difference in the blood pressure of the 2 arms. To eliminate this third source of error, the blood pressure is measured routinely in both arms in our laboratory; if any disparity is found, determinations are made simultaneously in both arms during pharmacologic tests. In 5 of our 66 patients with proved pheochromocytoma the simultaneous determination of blood pressures in both arms was necessary during the Regitine tests.

A fourth difficulty concerns previous medication. Before any of these tests, administration of any sedative or narcotic should be prohibited for at least 48 hours and possible self-medications should be checked, or the pharmacologic tests may yield false-positive results. In patients with paroxysmal hypertension, sedatives inhibit the rise of blood pressure during the cold pressor test. As a result, the increase of blood pressure during the histamine test may be greater than that during the cold pressor test, and thus may suggest the presence of a tumor that does not exist.

In patients with sustained hypertension, sedatives and tranquilizers may cause a fall in blood pressure typical of that produced by pheochromocytomas following the intravenous administration of Regitine (fig. 2) and this would be a false-positive result.

On the other hand, various antihypertensive drugs may produce false-negative results. Since most of these drugs act longer than sedatives, the difficulties are even greater (fig. 2).
Figure 2


Regitine tests on 3 of our patients were negative while they were receiving antihypertensive drugs, but were positive after use of these drugs was stopped for 8 to 10 days. Tumors were subsequently found at operation.

The difficulties due to use of vasoconstricting drugs will be described with the pressor amines.

One patient had a good history of attacks for pheochromocytoma when lying on his left side, but our first pharmacologic tests on him gave negative results because he was taking various antihypertensive drugs. When he returned 6 months later, he had not been taking any drugs. During this examination basilar artery thrombosis and myocardial infarction occurred (fig. 3). Later in the hospital turning on his left side raised the blood pressure and produced severe headache. While he was lying on his back, his blood pressure was 130/90; when he turned onto his left side, it rose to 280/190. Blood drawn at the height of the blood pressure (fig. 3) contained 30.7 μg. of pressor amines per liter of plasma. When 5 mg. of Regitine were given, the blood pressure fell rapidly but rose again. This reaction was positive for pheochromocytoma. A tumor weighing 80 Gm. was successfully removed.

The ideal time to do the pharmacologic tests is before any antihypertensive drugs are given. If this is impossible, administration of antihypertensive drugs should be discontinued for 8 to 10 days.

Observations on Blood Pressure

In our series of patients with pheochromocytoma, the average basal blood pressure of those with normal blood pressure between episodes was 117/78, that of the patients with labile blood pressure was 151/105, and that of the patients with sustained hypertension was 215/146. The increases in blood pressure on the cold pressor test were the same for pa-
PHEOCHROMOCYTOMA

patients with normal blood pressure between attacks and for patients with labile blood pressure. Although the rise with histamine was slightly greater in the patients with normal blood pressure (108/59) than in those with labile blood pressure (75/46), the basal level was considerably higher for patients with labile blood pressure. Although we suggest that a fall in blood pressure of 35/25 may be considered as being a positive result of the Regitine test, the average fall on testing in our 19 patients who were later proved to have pheochromocytoma was 78/53.

Tests for Pressor Amines

Turning to the chemical tests on the blood, it seems obvious that if increased amounts of epinephrine and norepinephrine could be found in the blood at the height of the paroxysmal attack or in the blood of the patient with sustained hypertension, the accurate diagnosis of pheochromocytoma would be relatively simple. In 1953 fluorometric methods were developed for the determination of pressor amines in the plasma by Lund, Natelson and associates, and by Weil-Malherbe and Bone. The last method was modified by Manger and associates for the separation of epinephrine and norepinephrine. For a time we used the Manger modification, but recently we have been determining only the total epinephrine-like substances by the method of Weil-Malherbe and Bone as an aid to diagnosis.

In our series of 490 patients without pheochromocytoma on whom 572 determinations of pressor amines (epinephrine-like substances in the plasma) were made, the mean values were 2.5 µg. per liter of plasma, with a range of 0.75 to 5.5 µg. The concentration of pressor amines in 36 patients with pheochromocytoma ranged from 6.9 to 360 µg. per liter of plasma.

Pitfalls

It has become evident on use, however, that the chemical tests for pheochromocytoma present pitfalls, just as do the pharmacologic tests. Blood collected when the tumor is not secreting will contain small or normal amounts of epinephrine and norepinephrine. However, if the blood is obtained before and at the maximal increase of blood pressure during a histamine test (fig. 4), the pressor amines are greatly increased in a patient with pheochromocytoma. Therefore, normal blood pressure and normal plasmapressor amines before histamine test. Center. Catecholamines negative elsewhere. With positive results of the Regitine test, pressor amines in blood were increased at the height of the blood pressure. An 80-Gm. tumor was removed later. Right. Negative results of histamine and Regitine tests with increased level of pressor amines. Exploration showed a lymphoblastoma, but no pheochromocytoma.

In contrast, in certain conditions such as azotemia, jaundice, and lymphoblastoma, fluorescent substances other than pressor amines are present in the blood and appear with the technic used as increased amounts of pressor amines. In 1 patient with lymphoblastoma, results of the pharmacologic tests were negative for pheochromocytoma but the clinical findings and an elevation of pressor amines indicated a pheochromocytoma. An adrenal tumor was not found on exploration or later at necropsy (fig. 4).

Chlorpromazine (Thorazine) may increase fluorescent substances other than pressor amines in the blood; 1 patient with a high
level of substances presumed to be pressor amines died and an adrenal tumor was not found. Tetracycline also causes the appearance of fluorescent substances other than pressor amines. A normal volunteer took 3 doses of tetracycline of 250 mg. each by mouth 6 hours apart. After the third dose, presumably the level of pressor amines had increased from 1.9 to 6.9 µg. per liter of plasma. Extremely high levels (7.4 to 40 µg. per 100 ml. of plasma) of fluorescent substances were found in 4 patients receiving this antibiotic. After administration of the drug was stopped for 4 to 6 days, these values decreased. One of these patients was explored and no adrenal tumor was found. It was significant that results of the Regitine tests were negative in these patients. Other drugs also may have such fluorescent properties.

Two further difficulties have arisen. First, there is evidence that the concentration of pressor amines may be depressed in a patient with pheochromocytoma during the early administration of antihypertensive drugs. However, the growth of the tumor is not inhibited and, as it grows, the increase in levels of pressor amines may be re-established and blood pressure may increase even though use of the antihypertensive drug is continued.

An annoying side reaction to Rauwolfia is nasal stuffiness. Many vasoconstrictors are used locally for this difficulty and also for vasomotor rhinitis and asthma. These substances produce high levels of pressor amines in the blood and increased amounts of catecholamines in the urine. Such increases have been interpreted as due to pheochromocytoma. These vasoconstrictive drugs also produce a profound fall in blood pressure for as long as 40 minutes after the intravenous injection of Regitine (fig. 5). In contrast, in the presence of a pheochromocytoma the fall in blood pressure may be as great, but the pressure begins to increase in 3 to 4 minutes and returns to the basal level in 10 to 15 minutes. The prolonged lowering of blood pressure from the vasoconstrictor drugs after injection of Regitine alerts the physician to the possibility that something other than a pheochromocytoma is producing the response. We have never administered any vasoconstrictor drug during this prolongation of lowered blood pressure. Six other patients who came with a history of positive pharmacologic tests and elevated pressor amines were using nasal vasoconstrictor drugs. After use of the drugs was stopped the tests were negative.

Forty-five additional determinations for pressor amines on patients who had been receiving vasoconstrictor substances for nasal stuffiness or asthma, or tetracycline, gave an average of 8.2 µg. per liter of plasma, with a range of 4 to 40 µg.

An Unusual Circumstance Giving False-Positive Reactions

An interesting diagnostic problem was presented by a 21-year-old paraplegic patient with normal levels of blood pressure who periodically had severe headaches, excessive sweating, and a signi-
fluent elevation in blood pressure. A pheochromocytoma in the urinary bladder was suspected. The cold pressor test showed a slight hyperreaction. The initial blood pressure was low, but during the next 40 minutes it rose to 210/132, with sweating, some shaking, and a severe headache (fig. 6). Blood drawn at this time showed an elevated level of pressor amines. Administration of 5 mg. of Regitine produced a positive reaction for pheochromocytoma. At the end of 10 minutes when the blood pressure was lower, the sweating ceased. Because of previous experience with paraplegic patients, the bladder was emptied. Blood pressure returned to normal, and a histamine test carried out 30 minutes later gave negative results but the level of pressor amines in the plasma was still elevated at that time.

The next day, after the bladder was emptied, another histamine test gave negative results, and concentrations of pressor amines and catecholamines were found to be normal also. By filling the bladder with air in increments of 20 to 30 ml., the blood pressure could be elevated to 210/132, with sweating and headache. The symptoms were due to the mass reflex produced by filling of the bladder in a paraplegic patient.

Correlation of Results of Pharmacologic Tests and Tests for Pressor Amines with Failure to Find Pheochromocytoma at Operation

In our laboratory 13,834 pharmacologic tests were carried out on 12,713 patients. Tumors were diagnosed and removed at operation from 66 patients. No tumors were found in an additional 16 patients who underwent exploratory operation because of one positive test, or for clinical reasons, or who had a positive test but died before any operation. Eight of these 16 patients reacted positively to 1 Regitine test, but of these 8, 6 subsequently had a negative result from one or more Regitine tests before operation. Two of the 8 had high values for pressor amines (positive finding) because of epinephrine in nose drops. Of the other 8 patients, 2 had positive results of the test for pressor amines but the results of the Regitine tests were negative; 3 had a positive result from one histamine test but negative results were obtained on other histamine tests before operation. The false-positive results to the histamine tests were due in 1 patient to Regitine taken by mouth for 2 months, in 1 to sedation for headache, and in 1 to a severe migraine headache.

The tests on the other 3 patients gave negative results, but exploratory operations were carried out for clinical reasons.

In contrast, recently 1 patient who had taken various drugs and frequently had some attacks with hyperventilation before he arrived for the pharmacologic and chemical tests had negative results of histamine and Regitine tests and normal levels of catecholamines in both the plasma and urine on 5 different days during a period of 21 months. We did find, however, that 2 minutes after exercise and hyperventilation (that is, 2 minutes after bending and standing for 2 minutes and hyperventilating for 5 minutes) the blood pressure rose from 150/116 to 194/120. Following this procedure the pressor amines rose from 3.0 to 9.8 μg. per liter of plasma when the blood pressure was 194/120. Urine collected half an hour later contained 40 μg. per 100 ml. A 32-Gm. tumor was removed.

Catecholamines

Turning to urinary catecholamines, in 1950 Engel and von Euler18, 19 indicated that the biologic assays of catecholamines reported by Holtz and associates20 and later by Helmer21 and themselves could be used in the diagnosis of pheochromocytoma. In 1951 Goldenberg and Rapport 22, 23 modified the von Euler test
and made it a chemical method for determination of catecholamines in the urine, which they consider the best test. Numerous methods are now available for determining catecholamines.

At present we are using the von Euler and Floding methods for determining catecholamines in the urine as modified by Sobel and Henry. In a series of 290 specimens of urine from 287 patients without pheochromocyotoma the average concentration of total catecholamines was 9.4 μg per 100 ml. The average 24-hour output was 118 μg. In 4 of our patients with proved pheochromocyotoma, the catecholamines in the urine 30 minutes after injection of histamine ranged from 42 to 2,649 μg per 100 ml. After removal of the tumor, the patient who excreted 2,649 μg per 100 ml. (48.0 μg per mg of creatinine) excreted 6 μg per 100 ml. (6.6 μg per mg of creatinine) 30 minutes after the histamine test.

The fact still remains, however, that a pheochromocyotoma may not secrete continuously, and normal levels of catecholamines may be obtained. On the other hand there are reports of excretion of normal levels even when attacks have occurred spontaneously or have been induced with histamine. Also, patients using vasoconstrictor substances have shown increased levels of catecholamines. With the finding of norepinephrine in banana...

**Figure 7**

*Variations in blood pressure during operation for removal of a pheochromocyotoma.*

ROTH, FLOCK, KVALE, WAUGH, OGG

as, more excretion of norepinephrine may be explained on this basis.

**Surgical Aspects and Precautions**

Various hazardous conditions may occur before, during, and after operation, and certain precautions should be taken. Before operation we have found that many active tumors are stimulated by the fall in blood pressure after the hypodermic administration of as little as 50 mg. of meperidine hydrochloride (Demerol) and 200 grains of phenobarbital (Luminal). Alarmlingly high blood pressures may ensue that can be counteracted by an intravenous injection of Regitine, which should be at hand. With the induction of anesthesia the blood pressure again may rise to excessive heights (fig. 7). It has been our custom to take the blood pressures at minute intervals during the operation and to give Regitine when needed in order that the level of blood pressure may be safe for the surgical procedures being performed. Whenever the tumor is stimulated by manipulation, the blood pressure may rise and Regitine may or may not be necessary. When the tumor is removed, a sudden fall in the blood pressure takes place. It is wise to wait a few minutes before proceeding with the operation to determine whether the blood pressure rises again. The fall after removal of the tumor may stimulate secretion from another tumor, if one is present, that will increase the blood pressure. We have looked for and found additional tumors because of such observations. If the fall in blood pressure is maintained for several minutes, norepinephrine (levarterenol, Levophed) is administered. The amount of norepinephrine required and the length of time that this substitution therapy is necessary varies from patient to patient. Little or no prediction can be made. It may be necessary to give norepinephrine at intervals from 6 to 72 hours, and in a couple of instances none was needed.

Another precaution can be suggested for general surgery. If a hypertensive reaction occurs during any operative procedure, the presence of a pheochromocyotoma might be suspected. Regitine could be administered to
confirm the diagnosis of pheochromocytoma, and the use of this drug could protect the patient until the pheochromocytoma is removed. Bartels and Cattell have reported 4 fatalities during lumbar sympathectomy, repair of an incisional hernia, a thoracic operation, and a gastrectomy due to unsuspected pheochromocytoma. In our experience a hypertensive crisis occurred in the course of an operation for removal of the gallbladder; the adrenal gland was explored, a pheochromocytoma found and removed, and then the gallbladder was removed at the same operation.

Discussion

The correct diagnosis of pheochromocytoma is still difficult, and the surgical excision is a hazardous procedure unless the blood pressure is controlled during and after the operation. Thus pheochromocytoma is a challenge to the clinician, to the physiologist, to the biochemist, and to the surgeon.

The greatest obstacle to the successful diagnosis of pheochromocytoma from pharmacologic and chemical tests is previous medication. For determinations of the pressor amines in the plasma and urinary catecholamines of patients with paroxysmal hypertension, stimulation of the adrenal tumor is often necessary for the increased excretion indicative of pheochromocytoma. No one test is infallible, and knowledge concerning the drugs used or the manner in which the blood and urine are collected, or both, is necessary to avoid a false-positive or false-negative result from the test.

The Regitine test following the histamine test is a good index of the amount of Regitine necessary to control the blood pressure during operation and gives some indication of the amount of norepinephrine (Levophed) to be prepared for use following removal of the tumor.

The most frequently asked questions are (1) how many patients are screened to find the large number of adrenal tumors, and (2) how many deaths have occurred during operation? To July 1, 1959, we have carried out 13,834 pharmacologic tests on 12,713 patients, 694 tests for pressor amines on 526 patients, and 305 tests for catecholamines on 293 patients. Seventy-six pheochromocytomas have been diagnosed and successfully removed from 66 patients at the Mayo Clinic. No untoward effects or deaths have occurred in our cases during the pharmacologic tests, during operation, or immediately after operation.

Summary

Today pharmacologic and chemical tests are helpful in screening a relatively large number of patients for pheochromocytoma and are a definite aid to a correct diagnosis. No one test is infallible, and knowledge concerning the drugs used or the manner in which the blood and urine are collected, or both, is necessary to avoid a false-positive or false-negative result from the tests.

Summario in Interlingua

In nostre dies, tests pharmacologique e chimico es de adjuta in examinar relativamente grande numeros de patientes pro deteger pheochromocytoma. Illos es definitemente utile in establist le correcte diagnose. Nulle test individual es infallibile. Un detaliat cognossentia del drogas usate e del maniera in que le sanguine e le urina es colligite debe esser disponibile ai on vole evitat risultatos false-positive o false-negative.

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