MEDICAL GRAND ROUNDS

THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER

September 30, 1976

PHEOCHROMOCYTOMA

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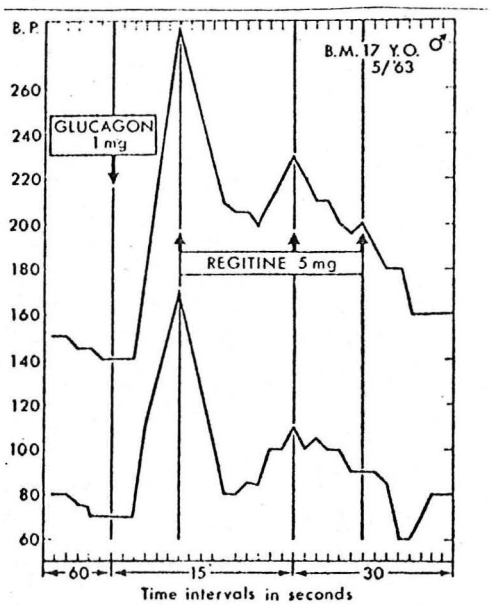


PHEOCHROMOCYTOMA

Pheochromocytomas are functionally active tumors of neural tissue which derive their name from a characteristic staining reaction with chromic acid. These tumors, though rarely a cause of hypertension, are important to recognize because they can usually be corrected permanently surgically, and when not recognized they can produce a myriad of dramatic clinical syndromes frequently resulting in untimely death.

An initial problem with pheochromocytoma involves the use of the chromaffin stain for the pathologic diagnosis. Chromic acid oxidizes catacholamines and indolamines (serotonin, etc.) to polymers that then incorporate chromium salts. Other oxidants such as iodate have also produced colored polymers from catecholamines. Epinephrine typically gives a dark brown stain whereas norepinephrine tends to give a yellow or yellow-brown stain. However, there are many technical problems with the use of the staining reaction to distinguish a pheochromocytoma from non-chromaffin paragangliomas. Functional tumors may not stain with the characteristic chromaffin reaction. The explanation may relate to: (1) differences in the nature and integrity of the protein granule retaining the catecholamine in cells from different tissues and tumors, (2) the concentration of the catecholamine within the cell, or (3) the susceptibility to depletion of the store of catecholamines prior to histologic preparation, primarily as a manifestation of anoxic changes. For these reasons, there is not an infallible correlation between chromaffin staining and catecholamine activity (Schwartz *et al*, 19[illegible]5). Chromaffin negative tissues can sometimes be shown to be producing catecholamines by the use of better criteria such as the demonstration of typical catacholamine granules in the tumor by electron microscopy (Figure 1). We have seen one patient at Parkland with a functional tumor that

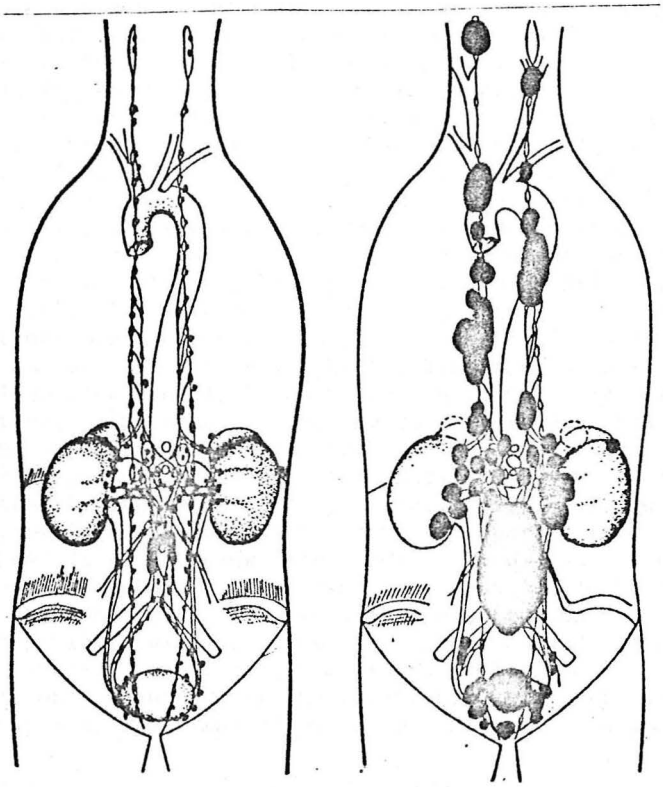
had chromaffin negative tumors removed on two separate operations but subsequently demonstrated a chromaffin positive metastatic lesion. Thus, the clinical characteristics of these tumors do not always correlate well with routine microscopic staining.

The general incidence of pheochromocytoma appears to be about 1 in 1,000 in the general population on the basis of a Mayo Clinic series of 15,984 consecutive autopsies (Minno *et al*, 1955). Two other series totaling about 5,000 cases together arrive at a similar figure of 1 in 1,000 autopsies (Blacklock *et al*, 1947; Berkheiser and Rappoport, 1951). The incidence of pheochromocytoma in hypertensive patients is about 0.5% (Smithwick *et al*, 1950). Since there is approximate incidence of hypertension in 20% of the adult American population, this again gives an incidence of pheochromocytoma in about 1:1,000. This is approximately the same incidence as primary hyperparathyroidism and emphasizes that many patients are never diagnosed.

This tumor has been called the "10% tumor" because about 10% of pheochromocytomas are malignant, about 10% are extra-adrenal, about 10% are bilateral or multiple, and about 10% are familial. The peak age for onset is between the fourth and sixth decade, though cases have been reported from the time of birth into the ninth decade of life (Hume, 1960). In a series of 76 cases from the Mayo Clinic (Gifford *et al*, 1964), there was no sex predilection in those cases with a paroxysmal history, whereas in those who had persistent hypertension, about two-thirds were women. Involvement of the right adrenal is somewhat more common than the left. There is widespread racial involvement.

Figure 2

Page and
Copeland, 1968



Chromaffin Tissue
-newborn

Extra-adrenal
Pheochromocytoma
-adult

Three catacholamines are found in human tissues--epinephrine, norepinephrine, and dopamine (Hume, 1960). These compounds are found in the chromaffin cells of the sympathetic nervous system which include (in the adult) the adrenal medulla, aberrant tissue along the sympathetic chain, and paraganglia. They are also present in the central nervous system, and norepinephrine and dopamine are found in the endings of the postganglionic fibers of the sympathetic system. The cells of the sympathetic nervous system and the related chromaffin cells take origin embryologically from the neural crest as primordial sympathetic ganglion cells which migrate out of the central nervous system to occupy a place behind the aorta. The sympathetic chain develops from these primordial chromaffin cells. In the embryo the chromaffin cells have a wide distribution in the adrenal medulla, the sympathetic ganglia, the paraganglia which lie along the sympathetic chain, and the organs of Zuckerkandl, which are a collection of chromaffin tissue lying along the abdominal aorta with particular concentration in the region of the inferior mesenteric artery. The organs of Zuckerkandl, which equal the size of the fetal adrenal at the time of birth, usually degenerate shortly after birth. The fetal adrenal and the organs of Zuckerkandl contain norepinephrine only--epinephrine appearing sometime after birth. In the adult, the great majority of chromaffin cells are concentrated in the adrenal medulla. However, numerous small discrete collections occur in association with the prevertebral sympathetic plexuses and the coeliac, mesenteric, renal, adrenal, testicular, ovarian, and hypogastric plexuses. In addition, small collections of chromaffin cells can be found along the aorta, particularly in the remnants of the organs of Zuckerkandl, in the walls of blood vessels, and scattered through various organs--especially the heart, prostate, and ovaries. These aberrant collections of chromaffin tissue may be the site for the development of a pheochromocytoma.

The existance of the enzyme phenylethanolamine-N-methyltransferase in the adrenal medulla for the methylation of norepinephrine and consequent production of epinephrine appears to be almost completely lacking in sympathic ganglia and nerves, so that principally norepinephrine (and dopamine) are found in these locations. This would account for the observation that while norepinephrine is present in normal amounts in the urine of patients who have undergone bilateral adrenalectomy, epinephrine is reduced (von Euler *et al*, 1955).

The clinical syndrome of the pheochromocytoma is dependent upon the proportion of epinephrine to norepinephrine produced. Epinephrine production is dependent on phenylethanolamine-N-methyltransferase activity in the tumor. Most pheochromocytomas produce norepinephrine in combination with epinephrine, though some tumors produce only norepinephrine, and rare tumors produce epinephrine alone. Epinephrine usually leads to the characteristic paroxysmal symptoms such as sweating, palpitation, nervousness, tremor, diarrhea, etc.; whereas, pure norepinephrine production leads to hypertension, resulting secondary manifestations such as visual disturbances, and constipation. However, even in the group with persistent hypertension, the hypertension is labile in character. The symptomatology of 76 cases of pheochromocytoma reported from the Mayo Clinic (Gifford *et al*, 1964) is shown below with subdivision of cases into paroxysmal and persistent pheochromocytoma. Particular attention should be given to the three most common symptoms--headache, excessive perspiration, and palpitation. All but one of the patients with paroxysmal hypertension and all but two of the patients with persistently functioning tumors had at least one of these three symptoms. However, only about 50% of those patients with sustained hypertension gave a history of typical superimposed paroxysmal attacks. In general, the

Symptoms Associated With Pheochromocytoma (76 Patients)

Symptoms	Paroxysmal function (37 patients)		Persistent function (39 patients)	
	Patients	Per cent	Patients	Per cent
Headache	34	91.9	28	71.8
Excessive perspiration	24	64.9	27	69.2
Palpitation with or without tachycardia	27	73.0	20	51.3
Pallor, usually of face	22	59.5	11	28.2
Nervousness or anxiety	22	59.5	11	28.2
Tremor	19	51.4	10	25.6
Nausea with or without vomiting	16	43.2	10	25.6
Weakness, exhaustion, or fatigue	14	37.8	6	15.4
Chest pain	12	32.4	5	12.8
Abdominal pain	6	16.2	6	15.4
Visual disturbance	1	2.7	8	20.5
Marked loss of weight	5	13.5	6	15.4
Raynaud's phenomenon	3	8.1	1	2.6
Dyspnea	4	10.8	7	17.9
Marked constipation	0	——	5	12.8
Grand mal	2	5.4	1	2.6
Warmth or flushing or both	4	10.8	3	7.7
Bradycardia (noted by patient)	3	8.1	1	2.6
Intolerance to heat	1	2.7	3	7.7
Dizziness or faintness	4	10.8	1	2.6
Paresthesia or pain in arms	4	10.8	0	——
Miscellaneous	*		†	

*Mentioned only once: Low back pain, cold hands, leg pains, peri-oral numbness, itching of scalp, gagging, hunger, and pounding in epigastrium.
†Mentioned only once: Tightness of throat and elevated temperature.

Table I

paroxysmal attacks can be quite variable. Some patients experience up to 25 paroxysmal attacks per day, whereas other patients may go for years between attacks. The attack itself may last from 30 seconds to one week, but generally lasts a few minutes to a few hours. Many patients experience an increase in frequency and duration of the attacks with time. The characteristic of the paroxysmal attack is its abrupt onset and rapid subsidence, usually within a period of minutes. These paroxysmal attacks may occur at any time of the day, with exercise, or with sleep or rest. Some patients, however, will note a characteristic precipitating factor for the attacks--for example, some patients will note that a certain posture precipitates the attack and that other things such as sneezing, pressing of the abdomen in a certain way, sexual activity, smoking, alcohol ingestion, urination, or anxiety will precipitate the paroxysmal attack.

Headache is the most common symptom of pheochromocytoma. The headaches tend to be associated with other paroxysmal symptoms, are abrupt in onset, severe, throbbing, generalized, and relatively short in duration, lasting from about 5 minutes to two hours (Lance and Hinterberger, 1976). However, the headache may not be distinguished from an ordinary tension or migraine headache. Excessive perspiration occurred either paroxysmally or more or less continuously and was a particularly troublesome symptom for many. The chest pain with

pheochromocytoma characteristically occurs at the height of an attack and not before the attack. This can help in distinguishing angina with resulting catecholamine discharge from pheochromocytoma with angina. Constipation characteristically occurs almost entirely with tumors which secrete predominantly norepinephrine. The tumors which secrete almost entirely epinephrine may paradoxically present with hypotension and shock, usually with associated profuse sweating, tachycardia, abdominal pain, nausea, and vomiting (Page *et al*, 1968). Similar syndromes of hypotension and shock have been described with hemorrhage into a pheochromocytoma resulting in necrosis of the tumor (Delaney and Paritzky, 1969; Sobonya *et al*, 1973).

In the Mayo Clinic series (Gifford *et al*, 1964), the duration of symptoms or hypertension at the time of diagnosis varied from three weeks to 32 years. The average was 3.7 years. There was no significant difference in this regard between paroxysmally functioning and persistently functioning tumors. The tumor itself was palpable in only 3 of 76 patients in the Mayo Clinic series, but in other series has been palpable in up to 14% of cases (Graham, 1951). A rise in blood pressure of considerable diagnostic significance may follow tumor palpation (Figure 3). Orthostatic hypotension in patients with persistently functioning tumors can be a valuable initial diagnostic clue.

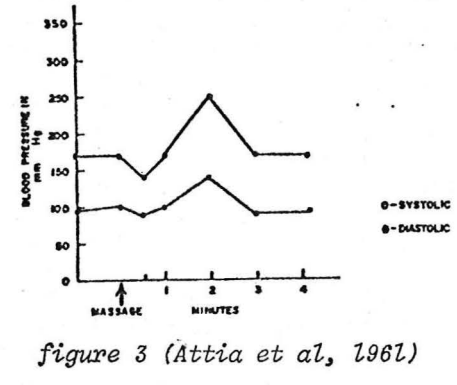


figure 3 (Attia et al, 1961)

Physical examination. Patients with pheochromocytoma are characteristically thin. In the Mayo Clinic series 41% of the patients with persistently functioning tumors were 10% or more below their standard body weights, and only one of the 39 patients was extremely obese. In general, the few truly obese patients with pheochromocytoma have paroxysmally functioning tumors. Although in one series over a third of the patients were 10% or more overweight, all but one of these obese patients had paroxysmally functioning tumors (Lee and Rousseau, 1967). Vasomotor instability manifested by livido reticularis, Raynaud's phenomenon, or both is not uncommon. Ophthalmoscopic examination reveals the usual changes of hypertension in patients with persistently functioning tumors. More than half of the patients in the Mayo Clinic series had Grade III or IV retinopathy at the time of diagnosis; whereas more than half of the patients with paroxysmal hypertension had normal ophthalmoscopic findings.

Laboratory findings. In the Mayo Clinic series, hyperglycemia was present in two-thirds and hypermetabolism (elevated basal metabolic rate) was present in three-fourths of the patients. These findings were encountered less frequently among patients with paroxysmal hypertension. Mild albuminuria was commonly seen in patients with persistently functioning tumors. In addition, an elevation of the BUN to greater than 40 mg % ml was present in approximately 20% of patients of both types. In the Mayo Clinic series there was a curious association of cholelithiasis in 30% of the patients with paroxysmally functioning tumors and 10% of the patients with persistently functioning tumors.

Tumor location. Location of pheochromocytoma has been summarized by Kaplan (1973) for pheochromocytoma in general and is shown in Table 2.

Location of Pheochromocytoma

Location	Percent
Intra-abdominal	97 to 99
Single adrenal tumor	50 to 70
Single extra-adrenal tumor*	10 to 20
Multiple tumors†	15 to 40
Bilateral adrenal tumors	5 to 25
Multiple extra-adrenal tumors	5 to 15
Outside abdomen	1 to 3
Intrathoracic‡	2
In neck	<1

*Sites: lumbar, paravertebral, epigastrium, bladder.
†More common in children and in familial syndrome with medullary thyroid cancer.
‡Usually in the posterior mediastinum.

Table 2

Diagnosis. A variety of pharmacologic tests for the diagnosis of pheochromocytoma have been reviewed (Orgain, 1955; Hume, 1960). The pharmacologic tests fall into two general categories: (1) those that stimulate a hypertensive response in a patient with paroxysmal hypertension and (2) those that produce a fall in the blood pressure in those patients with sustained hypertension. At the present time, these pharmacologic tests have very little to offer in the diagnosis of pheochromocytoma. In the past a stimulatory test was utilized when the blood pressure was less than 170/110 mm Hg and a blocking test when the blood pressure was higher. The stimulatory tests included injection of histamine, tyramine, mecholyl, benzodioxane, tetraethylammonium, and glucagon to cause catecholamine release. Catecholamines produced by the pheochromocytoma are taken up by the sympathetic nerve endings. Thus, the theory behind the stimulatory tests is that this increased store would lead to an increased blood pressure response on stimulation of catecholamine discharge by these agents. A cold pressor test should be done before any of the stimulatory tests to check for non-specific blood pressure lability. This is done by determining the maximal rise in the blood pressure while the patient holds one hand in ice water for one minute. The histamine test consists of rapidly injecting 0.025 mg of histamine base in 0.5 cc saline. Different criteria for a positive response have been proposed in the past, but in general an increase in the blood pressure (above the cold pressor level) of 50-60/25-30 mm Hg is considered positive (Orgain, 1955; Hume, 1960; Sheps and Maher, 1965). The side effects with the histamine test are considerable. The patient often notices flushing, a fall in blood pressure, a rise in pulse rate, significant bronchospasm which might precipitate acute bronchial asthma in a sensitive individual, a rise in cerebrospinal fluid pressure, and intractable histamine headaches. The tyramine test was developed to avoid some of these side effects, but it is not commercially available for parenteral administration at the present time. Its results are shown in Figure 4 (Engelman, 1964; Engelman, 1968). There is a false negative rate of 27% and a false positive rate of 3% in patients with pheochromocytoma in general. All of the pharmacologic tests have the ability to precipitate severe hypertensive reactions, and an occasional death of a patient has been reported with each test. In addition, there is considerable variation in the blood pressure response with these tests depending upon previous antihypertensive medications or other medications that the patient might have been taking.

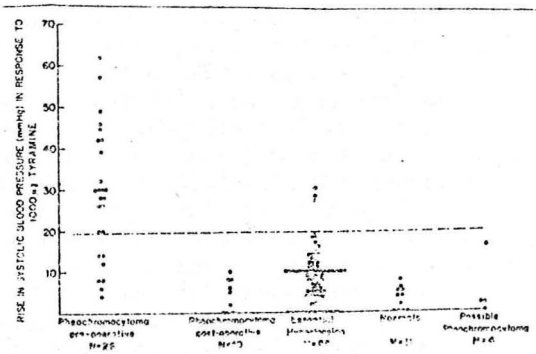


figure 4

The other stimulation test occasionally used is the glucagon stimulation test, originally reported by Lefebvre (1966) and popularized by Lawrence (1967) (Figure 5). The glucagon stimulation test, as with the other stimulation tests, must be compared with the results of the cold pressor test to

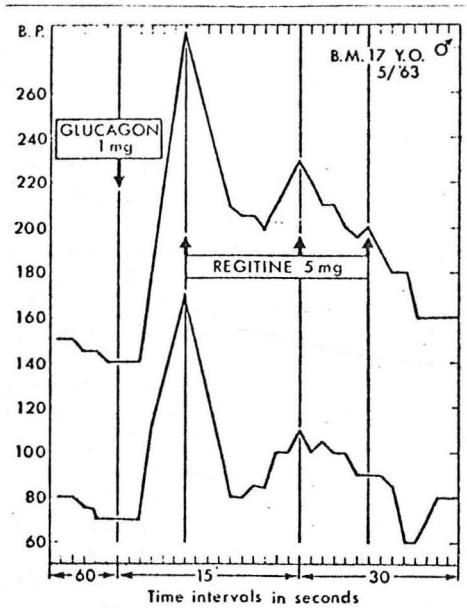


figure 5

determine the baseline response of the hypertensive patient. After the cold pressor test, the blood pressure is allowed to return to a basal state, and then 1 ml saline IV to check placebo response is followed by injection of 0.5 mg glucagon IV. 1.0 mg glucagon is given IV if there is no response. The 0.5 mg dose should always be given first because unusually severe hypertensive responses may result with 1 mg. Phentolamine should be available for instant administration into a good IV in the case of a severe hypertensive response. Some patients experience mild nausea, epigastric distress, pallor, perspiration, or tachycardia. Glucagon is not contraindicated in the presence of asthma, as is histamine. The blood pressure should be monitored at 15 to 30 second intervals for the first several minutes after injection of the test material, then at 1 minute intervals for at least 10 minutes. Essentially all patients who demonstrate a response to any of the stimulation tests have done so within 5 minutes. Lawrence (1967) originally reported that all 3 patients with pheochromocytoma that were tested with glucagon responded with a rise in the blood pressure greater than 20/10 mm Hg, although there was one possible false positive response at the time of the report in which the diagnosis was uncertain. The need for a cold pressor test was not described. 126 normal subjects or ambulatory nonhypertensive patients demonstrated no response to glucagon, as did 36 patients with essential hypertension in her series. In another series of German patients (Studnitz, 1970) 7 of 7 patients with pheochromocytoma responded in a positive fashion to glucagon, and 5 of these 7 did not respond to tyranine. However, other investigators (White *et al*, 1973; Sebel *et al*,

1974) have demonstrated that false positive pressure responses may occur in up to 20% of patients if a cold pressor test is not done in conjunction. A series of 12 patients with pheochromocytoma from the Mayo Clinic was studied, comparing the tyramine and glucagon stimulation tests (Sheps and Maher, 1968). Of these 12 patients, 6 demonstrated a positive response to glucagon; whereas only 4 of these 6 patients similarly responded to tyramine. One additional patient with pheochromocytoma responded to tyramine and did not respond to the 0.5 mg dose of glucagon. Simultaneous determinations of plasma catecholamines in these patients did not appear to enhance the sensitivity of the test. The major limiting feature of this test is its inability to consistently identify patients with pheochromocytoma, especially in those with Sipple's syndrome. Patients with sustained hypertension present no diagnostic problem, because they uniformly have elevations of 1 or more determinations of urinary catecholamines or their metabolic products. Thus, the overwhelming diagnostic need for patients with paroxysmal pheochromocytoma is an adequate stimulation test. Patients with Sipple's syndrome in particular have proved uniformly resistant to stimulation by tyramine and to histamine or only occasionally responsive to glucagon (Weiss, 1974).

The phentolamine (Regitine) test is the classical pharmacologic suppression test utilized in patients with sustained hypertension. However, at the present time this test is of no diagnostic use other than to give an initial diagnostic impression in patients who present with hypertensive crisis with marked swings in the blood pressure. False positive responses are not uncommon, whereas false negative responses are exceedingly rare.

Recently, a marked hypertensive response has been reported with intravenous infusion of saralasin, a selective angiotensin antagonist (Dunn *et al*, 1976) (Figure 6). With expected increasing use of this compound in the next few years to screen for angiotensinogenic hypertension, this potential complication should be carefully considered, since saralasin will be administered to patients who may be quite hypertensive, expecting a fall in the blood pressure. In this setting, fatal hypertensive responses might occur, as happened in the past when histamine was administered to patients with sustained hypertension.

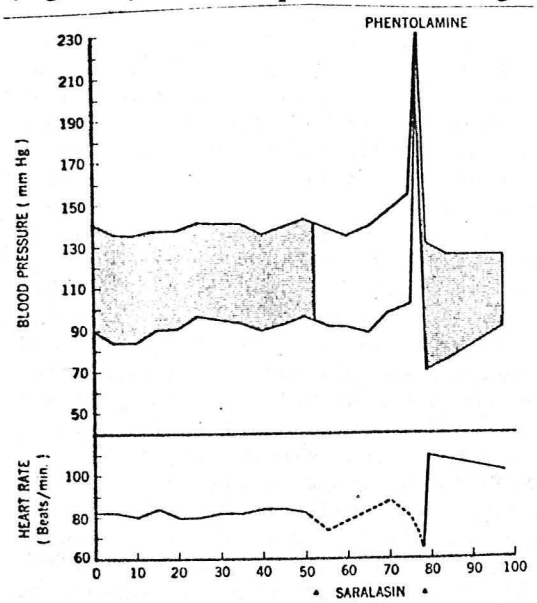
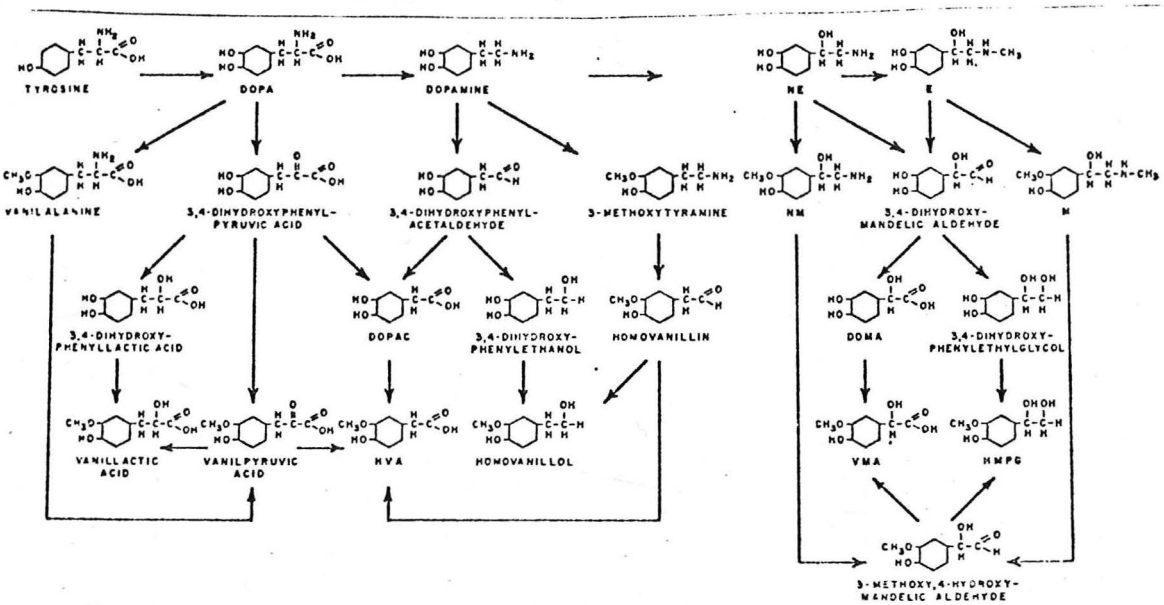


figure 6

At the present time the diagnosis of pheochromocytoma is almost entirely through the use of assays of catecholamines and their metabolites. In 1957 Armstrong reported the major catabolic pathways of catecholamines, and this has led to a rapid demise in the routine use of the various pharmacologic tests. In a normal individual only about 1-4% of synthesized norepinephrine or epinephrine is excreted unchanged into the urine (Kirshner *et al*, 1958; Goodall *et al*, 1959). Thus, quantitation of the major metabolites vanillylmandelic acid (VMA) and metaphrine plus normetanephrine



The major metabolic pathways of the catecholamines. DOMA = dihydroxymandelic acid; DOPA = dihydroxyphenylalanine; DOPAC = dihydroxyphenylacetic acid; E = epinephrine; HMPG = 3-methoxy-4-hydroxyphenylethyleneglycol; HVA = homovanillic acid; M = metanephrine; NE = norepinephrine; NM = normetanephrine; VMA = vanillylmandelic acid.

figure 7

(total metanephrines) is simpler. Pheochromocytomas differ widely in their size and catecholamine content (Crout and Sjoerdsma, 1964; Wocial and Januszewicz, 1974). In addition, the rate of turnover of catecholamines within the tumor also varies over a wide range. One end of the spectrum is represented by tumors with relatively small total stores of catecholamines. These tumors tend to produce only norepinephrine, to have a high rate of turnover of catecholamines (68 ± 16% of the total store/day), and to produce hypertension at a time when the tumor size may be small. At the other end of the spectrum are tumors which tend to have a high storage capacity for catecholamines, to have a low rate of turnover of the stored catecholamines (8.1 ± 2.4%/day), and to produce hypertension only after the tumor has grown to considerable size. However, there are a number of exceptions to these rules, and it would appear that the release of catecholamines may be highly erratic from time to time, as exemplified by an increased rate of release of free catecholamines at the time of a hypertensive attack. In addition, whether the hypertension is sustained or paroxysmal does not appear dependent on tumor weight. (See Figure 8, Wocial and Januszewicz, 1974.)

The major urinary determinations at the present time for the diagnosis of pheochromocytoma involve determinations of total metanephrines (free and conjugated), VMA, and free catecholamines (norepinephrine and epinephrine). Total catecholamine assays (free and conjugated) using flurometric methods are still used to some extent. However, these are influenced by a variety of substances which lead to false positive elevations. Dietary substances contain significant amounts of biogenic amines which may be measured in the

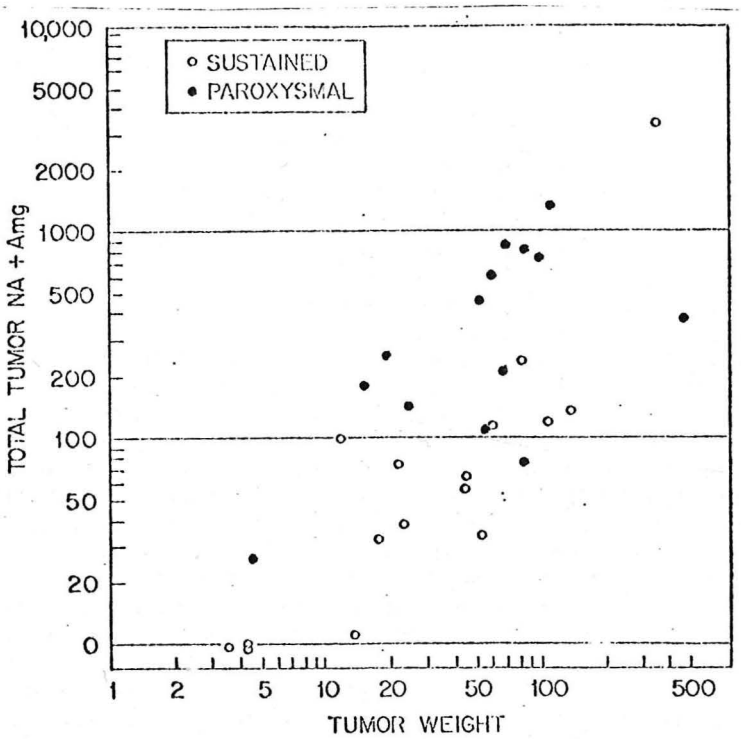


figure 8

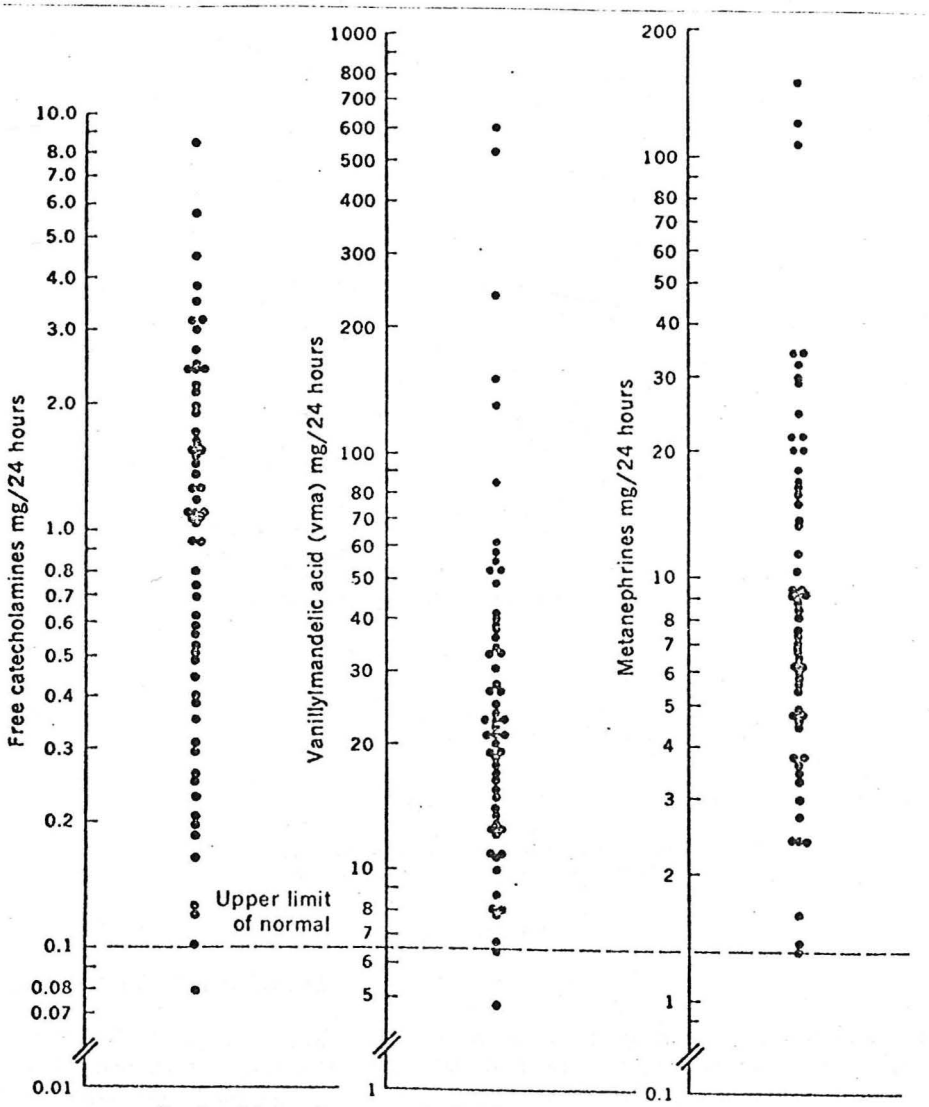
total catecholamine assays since conjugation of catecholamines occurs within the intestine before absorption (Haggendal, 1963; Kahane *et al*, 1967; Cardon and Guggenheim, 1970). Bananas, grain cereals, chocolate, tea, coffee, other fruits, and vanilla may cause an elevation in the conjugated catecholamine component. In addition, drugs such as glyceryl guaiacolate, PAS, methocarbamal, mephenesin, methyldopa, quinine and quinidine, tetracycline, chlorpromazine, chloral hydrate, nose drops, and bronchodilators may cause false positive elevations or interference with the fluorometric method. Urinary VMA has been determined by various methods employing diazotized p-nitroaniline which are usually advertised as VMA screening kits. This method is not recommended because of the high incidence of false positive reactions (24% of control patients--Gitlow, 1970) secondary to many of the same factors noted with the total catecholamine assays.

In view of the ease and specificity of methods for determining both VMA and metanephrine by spectrophotometric methods, the older determinations of total catecholamines and fluorometric VMA should be abandoned. VMA, which constitutes about 35% of the daily catecholamine excretion (Kirshner *et al*, 1958), is best determined by organic extraction, conversion to vanillin, and spectrophotometric determination (Pisano *et al*, 1962). Drugs such as Leritine, nalidixic acid, levodopa, lithium, and nitroglycerin cause an increase in the measurement, whereas chlofibrate and MAO inhibitors cause a decrease. Total metanephrines (free and conjugated, normetanephrine and metanephrine), which

constitute about 50% of the daily catecholamine excretion (Kirshner *et al*, 1958), are measured by hydrolysis of conjugates, column adsorption (Amberlite CG-50), elution, conversion to vanillin with sodium metaperiodate, and spectrophotometric determination (Crout *et al*, 1961). For both of these VMA and metanephrine determinations using spectrophotometric measurement of vanillin, Crout recommends that optical density be determined with the spectrophotometer at 333, 347, and 360 mμ. The absorption peak of vanillin is at 347 mμ. Urine of patients without pheochromocytoma may contain a compound (presumably p-octopamine) which can be oxidized by periodate to p-hydroxybenzaldehyde by periodate, which absorbs maximally at 330 mμ. Because the contribution to absorbance from p-hydroxybensaldehyde is significant at 347 mμ, Crout *et al* recommend determination of vanillin at 360 mμ, which is 80% of the peak absorbance of vanillin. In those patients demonstrating an increase at 360 mμ, the samples should also be read at 347 mμ to confirm that the predominant peak is vanillin and is not an interfering substance with a maximal peak at 333 mμ. Thus, when the metanephrine reports contain a comment about interfering substances, this generally means that the peak measurement was at 333 mμ and that the increases at 347 and 360 mμ were attributed to this. When this happens the determination should be repeated, taking care to have the patient off of as many medications as possible, and determinations of free catecholamines should be done. In general, the metanephrine determination is most commonly done since it is positive in the greatest percentage of patients and is the simplest technically to do. There are very few interfering factors for this determination. Chlorpromazine and MAO inhibitors cause an increase. X-ray contrast media containing methylglucamine can decrease the metanephrine (Johnson, 1972). This decrease is caused by the fact that methylglucamine is eluted from the Amberlite column with metanephrines and then consumes the periodate, preventing oxidation of the metanephrines to vanillin. The methylglucamine can be separated by adsorbing the metanephrines on QAE Sephadex A-25 acetate. However, it is usually simpler to just wait for at least 3 days for the contrast media to be cleared before repeating the determination. Methylglucamines are present in several commonly used radiopaque dyes including Renovist, Renographin, Hypaque-M 75%, Hypaque-M 90%, Cardiographin, Gastrographin, Urographin, and Conray. However, in Hypaque Sodium the sodium salt of diatiazoate instead of the methylglucamine salt is used, and so this contrast agent will not interfere with the metanephrine determination.

Free catecholamines (norepinephrine and epinephrine) have been commonly determined by the trihydroxyindole fluorometric method (Crout, 1961). Dietary substances such as bananas which contain catecholamines lead to only trivial increases in the free catecholamines while causing large increases in conjugated catecholamines measured in total catecholamine assays (Crout and Sjoerdsma, 1959). Tetracycline, quinidine, quinine, chloral hydrate, and methyldopa will cause a false positive increase. More specific determinations of the free catecholamines utilizing some of the methods which have been validated for plasma assays enables removal of these drug effects. An extensive but poorly documented listing of all factors which will interfere with the determinations of free catecholamines, VMA, and total metanephrine as determined above has been listed by Young *et al* (1972). However, many things listed may cause such slight changes as to be insignificant clinically. It is specifically worth noting that the following do not generally lead to diagnostic confusion about the possibility of pheochromocytoma with any of the three assays: thiazides, reserpine, guanethidine, hydralazine, Regitine, phenoxybenzamine, barbiturates, aspirin (Gitlow, 1970).

Several large series have demonstrated the utility of these three assays in the diagnosis of pheochromocytoma (Figures 9,10; Table 3a,b).



Results of three urinary assays in 64 patients with proved pheochromocytoma. Upper limits of normal per 24-hour urine specimen are: free catecholamines 0.1 mg, VMA 6.5 mg, and metanephrines 1.3 mg. (Sjöerdsma A, et al: *Ann Intern Med* 65:1302, 1966.)

figure 9 (NIH Experience)

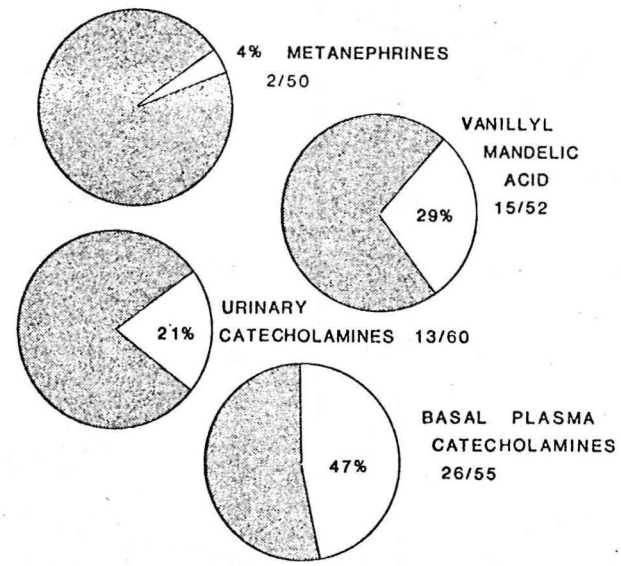
Vanillyl-mandelic Acid	Patients With Pheochromocytoma (%)	Patients Without Pheochromocytoma (Noncomatose) (%)
> 5.0 µg/mg creatinine	96.4	0
< 5.0 µg/mg creatinine	3.6	100

Table 3a

Total Metanephrines	Patients with Pheochromocytoma (%)	Patients without Pheochromocytoma (Noncomatose) (%)
> 2.2	100	2
< 2.2	0	98
> 4.5	82	0
< 4.5	18	100

Table 3b

(Gitlow, Mt. Sinai Experience)



Comparison of false-negative biochemical studies for MN, VMA, UCA, and basal plasma catecholamines.

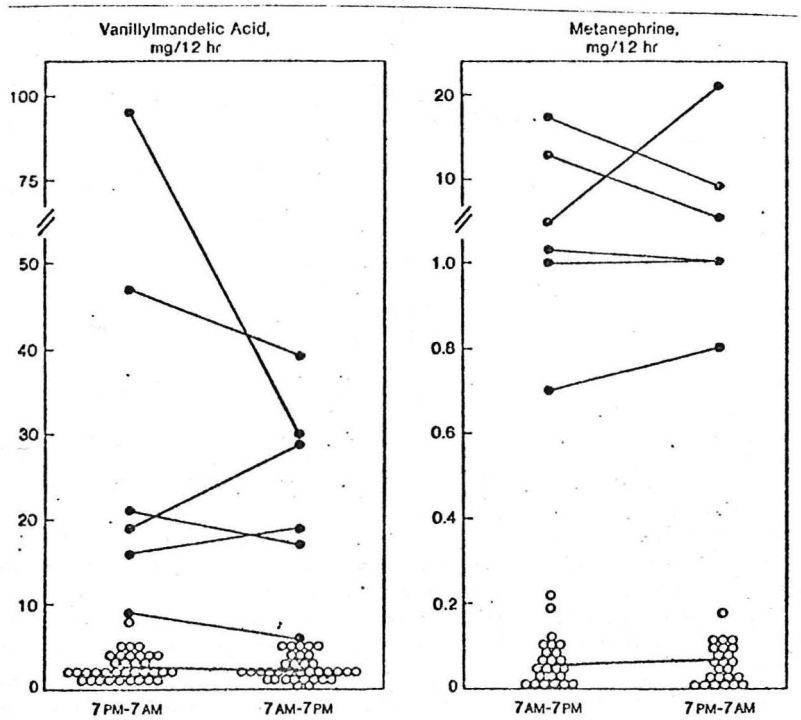
figure 10

(Mayo Clinic Experience)

Thus, in general, the metanephrine is most accurate and easiest to do, but in occasional patients the VMA or free catecholamines may be the only test which does not give a false negative result. The free catecholamines, especially, are helpful in identifying an occasional patient with a small pheochromocytoma with very rapid secretion of free catecholamines into the systemic circulation and little intra-tumor metabolism.

In general the excretion of VMA and metanephrine is relatively constant throughout a 24-hr period of time. In general, Gitlow (1970) has found it most useful to express the 24-hr urine results in terms of µg/mg creatinine. For VMA the upper limits of normal was 3.5 µg/mg creatinine and 5 µg/mg creatinine was diagnostic. Of course, these values should be adapted to the normal range of the particular assay used.

For metanephrine, a value of 1-1.5 µg/mg creatinine is the upper limits of normal and greater than 2.2 µg/mg creatinine is considered diagnostic of pheochromocytoma. Accurate testing for pheochromocytoma can still be accomplished with less than a 24-hr urine, though when urinary free catecholamines are determined, a full 24-hr urine is collected because there is a diurnal rhythm so that the excretion rate is higher during the day and lower during the time of sleep (Townshend and Smith, 1973). This might lead to occasional false positive results if morning samples were utilized and the results expressed as µg free catecholamines/mg creatinine. However, patients with pheochromocytoma lose the diurnal variation, and so there is no problem with false negative results if urine samples are taken at night. Sullivan and Soloman (1975) have demonstrated that 12-hr collections of VMA or metanephrine suffice for the diagnosis of pheochromocytoma. (Figure 11)



Diurnal variations of urinary catecholamine metabolite excretion. Patients with essential hypertension are represented by open circles, patients with pheochromocytoma by closed circles.

figure 11

At Parkland Hospital, we have utilized the spot metanephrine determination extensively for screening purposes. A strong correlation can be found between simultaneously collected 24-hr urine and single-voided urine samples in terms of micrograms metanephrine/mg creatinine (Kaplan *et al*, 1976) (Figure 12).

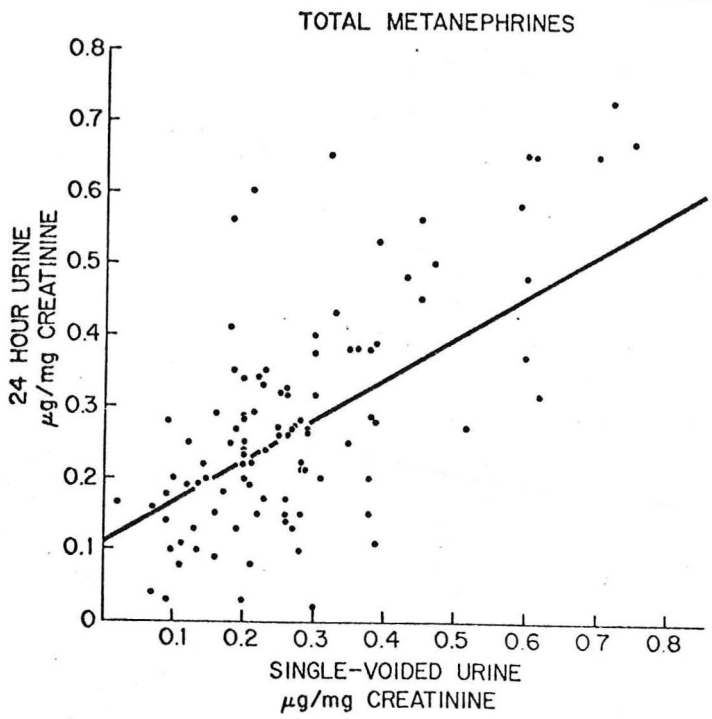


figure 12

The mean metanephrine level in single-voided urines from 500 consecutive patients diagnosed as having essential hypertension was 0.35 ± 0.35 (2 standard deviations) with a range of 0.06 to 1.18 μg/mg creatinine. Even though there is a diurnal rhythm of free catecholamine excretion (Townshend and Smith, 1973), this appears not to be a problem with metanephrine determinations. Four-hour fractional excretion of metanephrine over a 24-hr period of time was determined in seven patients with pheochromocytoma and 10 hypertensive patients without evidence of pheochromocytoma (Kaplan *et al*, 1976). There is little variation in the metanephrine excretion rate expressed as μg/mg creatinine regardless of the time during which the 4-hr fractional urine was taken. These results are shown in Table 4. The simultaneous total metanephrine excretion (mg/24 hours) is also shown.

TABLE: TOTAL METANEPHRINE EXCRETION IN PATIENTS WITH AND WITHOUT PHEOCHROMOCYTOMA

	24 hour Specimen	Fractional specimens (µg/mg creatinine)					
	(mg/24 hr)	0800-1200	1200-1600	1600-2000	2000-2400	2400-0400	0400-0800
Non-pheochromocytoma patients (No.=10)							
Mean ± SD	0.42±0.16	0.31±0.08	0.35±0.12	0.33±0.10	0.35±0.06	0.26±0.11	0.29±0.09
Range	0.20-0.56	0.16-0.41	0.21-0.48	0.23-0.46	0.21-0.51	0.14-0.39	0.11-0.39
Pheochromocytoma patients							
1	5.0	4.1	4.4	3.4	3.9	- 5.5 -	
2	11.2	9.6	8.7	6.7	5.4	- 9.7 -	
3	3.8	2.8	3.5	3.7	2.9	- 3.0 -	
4	77.0	92.0	90.0	72.0	83.0	98.0	90.0
5	12.5	6.1	8.4	4.1	8.2	5.1	3.6
6	143.0	102.0	110.0	98.0	88.0	112.0	105.0
7	8.6	9.2	8.6	9.4	7.8	6.9	7.8

Table 4

From this data, it would appear that the spot metanephrine test is the most reliable and easiest of all screening tests for pheochromocytoma. It must be noted, however, in view of the failure of 24-hr urinary metanephrine, VMA, and free catecholamine determinations to detect 100% of cases with pheochromocytoma that the false negative rate of the spot metanephrine will certainly be somewhat greater than with these determinations. However, in patients with paroxysmal hypertension, the spot metanephrine, if taken during a hypertensive episode, may be most accurate in identification of a pheochromocytoma. Therefore, when patients with "labile hypertension" are noted to be hypertensive, a spot metanephrine should be obtained at that time. It may also be helpful to instruct the patient to collect a urine sample when he has an "attack." All urine for free catecholamine, metanephrine, and VMA determinations should be immediately acidified to pH 2 and then stored in a refrigerator until the time of assay. For 24-hr collections, 10 ml of 6N hydrochloric acid is sufficient; whereas, with spot urines, lesser amounts of acid must be added--depending on the volume. It should also be noted that the urinary excretion of VMA, HVA, and total metanephrines is age related. The following age-adjusted values are given in Table 5.

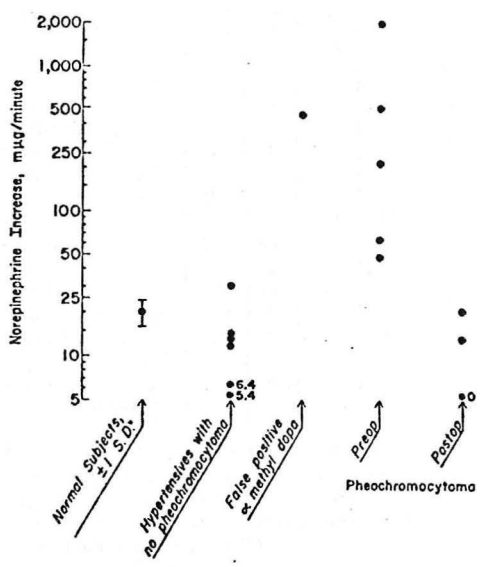
Urinary Excretion of VMA, HVA, and Total Metanephrines in Children

Age (years)	VMA Mean	VMA SD	HVA Mean	HVA SD	Total metanephrines Mean	Total metanephrines SD
<1	6.9	3.2	12.9	9.6	1.6	1.3
1 to 2	4.6	2.2	12.6	6.3	1.7	1.1
2 to 5	3.9	1.7	7.6	3.6	1.2	0.8
5 to 10	3.3	1.4	4.7	2.7	1.1	0.8
10 to 15	1.9	0.8	2.5	2.4	0.6	0.5
15 to 18	1.3	0.6	1.0	0.6	0.2	0.2

All values are given as micrograms per milligram of creatinine.
From Gitlow SE, et al: *J Lab Clin Med* 72:612, 1968.

Table 5

Harrison *et al* (1967) have proposed utilizing a tilt test (Figure 13) with measurement of the increase in urinary norepinephrine before and during the tilt in hopes of providing a gentle, safe stimulation test that would also utilize urinary measurements. Urine is collected for 3-hr periods of time while the patient is being well hydrated first with the patient supine and second with the patient tilted 70° head up. Five of six patients with pheochromocytoma had an increase above the normal range. The sixth patient had extremely high baseline norepinephrine excretion and showed no increase. However, there was no diagnostic confusion with this patient. As with the pharmacological stimulation tests, the theory is that the catecholamines liberated by the tumor are taken up by the sympathetic nerve endings, thus increasing the tissue stores and allowing a greater reflexly stimulated release from this highly saturated labile pool. In addition, with the tilt test, it is possible that renin released in response to the tilt may stimulate catecholamine release, analagous to the response seen with saralasin, a known weak angiotensin agonist. Further studies with this test have not been reported. Of particular importance would be to demonstrate its utility in patients with pure paroxysmal hypertension and Sipple's syndrome.



Logarithmic Scale Showing the Increase in Free Norepinephrine Excretion after Tilt in Each of the Groups under Study. The exaggerated responses of the patients with pheochromocytoma are apparent. The normal values shown are those of the 15 normal subjects described by von Euler et al.*

figure 13

Familial pheochromocytoma. There are 4 familial syndromes, of which pheochromocytoma is a part: (1) simple familial pheochromocytoma, (2) pheochromocytoma with neurofibromatosis, (3) pheochromocytoma with von Hippel-

Lindau disease, and (4) pheochromocytoma in association with medullary carcinoma of thyroid and hyperparathyroidism.

In all of these 4 cases, with the possible exception of pheochromocytoma with neurofibromatosis, the genetic lesion best fits a two-mutation model, with inheritance of the first mutational event in an antosomal dominant fashion and occurrence of the second mutational event in one or more somatic cells leading to one or more tumors (Knudson and Strong, 1972). In non-familial pheochromocytoma, the first mutational event is not hereditary. In those cases of multiple non-familial pheochromocytoma, it is proposed that the first mutation occurs as a germinal event. In those cases with single, sporadic pheochromocytoma, both mutations occur in somatic cells.

Familial pheochromocytoma in general differs strikingly from sporadic pheochromocytoma in its location, as noted in Table 6 (Steiner, 1968). Familial cases are characterized by bilateral involvement in about 50% of cases, with an additional 10% of cases having extra-adrenal involvement. It occurs in a variety of racial and ethnic groups. The incidence of extra-adrenal tumors in the familial cases is not significantly different from that in the sporadic ones.

(1) Simple familial pheochromocytoma comprises about 60% of familial pheochromocytoma. Sustained hypertension is common--occurring in about 2/3 of cases (Hume, 1960; Knudson and Strong, 1972). The incidence of sustained hypertension in pheochromocytoma, with and without medullary thyroid carcinoma, is shown in Table 7 (Steiner, 1968). Simple familial pheochromocytoma is more common in children, the modal age of onset being age 20 as opposed to age 40 for nonfamilial pheochromocytoma. Since familial cases are more often multiple and since they occur earlier, it is not surprising that about 40% of childhood cases are multiple.

Location and Histologic Nature of Pheochromocytoma in 83 Familial and 463 Non-Familial Cases[1,2]

	Total number	%	Number benign	Number malignant
Familial Cases	83			
Adrenal only	75	90	74	1
Unilateral	35	42		
Bilateral	40	48		
Extra-adrenal	8	10	7	1
Extra-adrenal alone	3	4		
Extra-adrenal and unilateral adrenal	4	5		
Extra-adrenal and bilateral adrenal	1	1		
Non-Familial Cases	463			
Adrenal only	392	85	371	21
Unilateral	371	80		
Bilateral	21	5		
Extra-adrenal	71	15	65	6
Extra-adrenal alone	59	12.5		
Extra-adrenal and unilateral adrenal	10	2		
Extra-adrenal and bilateral adrenal	2	0.5		

[1] In two of the 85 reported cases of familial pheochromocytoma, no data were provided concerning the location and nature of the tumors.

[2] The data of the non-familial cases were derived from Hermann and Mornex (51).

Table 6

Incidence of Sustained Hypertension in Pheochromocytoma Patients with and without Medullary Thyroid Carcinoma

	Cases with sustained hypertension	
	No.	%
Sporadic pheochromocytoma		
A. Pheochromocytoma alone[1]	285/434	66
B. Pheochromocytoma with associated thyroid carcinoma	0/14	0
Familial pheochromocytoma		
A. Pheochromocytoma in families not afflicted with thyroid carcinoma	32/51	63
B. Pheochromocytoma in families afflicted with thyroid carcinoma	5/35	14
1) Pheochromocytoma and associated thyroid carcinoma	2/22	
2) Pheochromocytoma without associated thyroid carcinoma	3/13	

[1] Data derived from Hermann and Mornex (50).

Table 7

PHEOCHROMOCYTOMA: SIMPLE FORM. COMPARISON OF AGE DEPENDENCE FOR SINGLE, MULTIPLE, AND FAMILIAL TUMORS

	AGE AT DIAGNOSIS (YEARS)							
	0–9	10–19	20–29	30–39	40–49	50–59	>59	Total
Nonfamilial*:								
Single	11 (3%)	25 (8%)	81 (25%)	73 (23%)	61 (19%)	45 (14%)	24 (8%)	320
Multiple	5 (11%)	17 (37%)	7 (15%)	8 (17%)	3 (7%)	6 (13%)	0	46
Familial†	7 (15%)	17 (37%)	6 (13%)	6 (13%)	7 (15%)	3 (7%)	0	46

* [21]: from 507 cases, age at diagnosis and negative family history were ascertained for 320.
† [22]: families A, D–K, M–O, T, U, Y, A1; [23]: with follow-up on family X; [24].

Table 8 (Knudson and Strong, 1972)

The common age distribution of pheochromocytoma in the multiple nonfamilial and simple familial patients supports the two-mutation model. The simple familial pheochromocytoma gene is inherited dominantly with almost 100% penetrance. In some cases, however, the offspring may be diagnosed before the parent.

(2) Pheochromocytoma with neurofibromatosis. Between 4-25% of patients with neurofibromatosis will have pheochromocytoma, and these patients constitute 5-8% of unselected pheochromocytomas (Chapman *et al*, 1959; Knudson and Strong, 1972). However, the modal age of onset is essentially similar to single nonfamilial pheochromocytoma, being 40-45 years of age, thus demonstrating genetic heterogeneity from simple familial pheochromocytoma. (Table 9)

PHEOCHROMOCYTOMA WITH NEUROFIBROMATOSIS OR WITH VON HIPPEL-LINDAU DISEASE: AGE AT DIAGNOSIS

	AGE AT DIAGNOSIS (YEARS)				
	0–19	20–39	40–59	>59	Total
Neurofibromatosis*	2 (3%)	24 (40%)	30 (51%)	3 (5%)	59
Von Hippel-Lindau†	4 (17%)	16 (66%)	4 (17%)	0	24

* [47, 63–74].
† [75–80].

Table 9 (Knudson and Strong, 1972)

The tumor is bilateral in only about 10% of cases, and the average age of onset in these cases is 60 years. It is very rare for the tumor to appear in childhood. There are no cases of familial pheochromocytoma with neurofibromatosis.

(3) Pheochromocytoma in association with von Hippel-Lindau disease. These tumors usually appear at about age 30-35 (Table 9), slightly less than single nonfamilial pheochromocytoma. These patients have hemangioblastomas of the cerebellum, retina, and spinal cord; cysts of the pancreas, epididymis

and kidney; and renal cell carcinoma, in a variable fashion (Melmon and Rosen, 1964). There is association of pheochromocytoma and von Hippel-Lindau disease in the same family, with occasional members having both diseases (Knudson and Strong, 1972).

(4) Pheochromocytoma with medullary carcinoma of the thyroid and hyperparathyroidism constitutes about 30% of all familial cases of pheochromocytoma. It appears to have a distinctly different gene from simple familial pheochromocytoma (Knudson and Strong, 1972; Steiner *et al*, 1968; Keiser *et al*, 1973). The differences from simple familial pheochromocytoma include: (1) a later age of onset (mode of 30-35 years), (2) a rarity of sustained hypertension, and (3) fewer extra-adrenal tumors (Marks and Channick, 1974). There is a high degree of penetrance, but death from medullary carcinoma of the thyroid may prevent this expression. These tumors are bilateral in a very high percentage of cases, about 65% in two series (Keiser, 1973; Khairi, 1975) and probably 100% in the series by Steiner (1968). In this series 9 of 10 patients had demonstrable bilateral pheochromocytomas, and the other patient remained hypertensive postoperatively--after removal of one tumor.

A subgroup of these patients has been described in which marfanoid habitus, neuromas, hypertrophied corneal nerves, skeletal defects (kyphosis, pes cavus, high arched palate, scoliosis, lordosis, valgus deformities of the knees or toes, asymmetry of the skull), and gastrointestinal tract abnormalities are seen (Khairi, 1975; Schimke, 1968).

Summary of Clinical Features in 41 Patients with MEN Type 3

Clinical features	Number of patients with findings			Number of patients with inadequate information
	Positive	Probable	Negative	
Family History	14	2	15	10
Neuroma	41			
Oral	37		4	
Ocular	24		16	1
Others	4		36	1
"Bumpy" Lips	35	2		4
Pheochromocytoma	19	4	18	
Unilateral	7			
Bilateral	12			
Medullary Thyroid Carcinoma	38		2	1
Marfanoid Habitus	26	5		10
Hypertrophied Corneal Nerves	23			18
Skeletal Defects	24		4	13
Gastrointestinal Tract Abnormalities	23		10	8

Table 10
Khairi et al., 1975

Combination of Tumors in 41 Patients with MEN Type 3

Combination	Patient	
	Number	Percent
Neuroma, Pheochromocytoma, Medullary Thyroid Carcinoma and "Bumpy" Lips	20	48.7%
Neuroma, Medullary Thyroid Carcinoma and "Bumpy" Lips	18	43.9%
Neuroma and Pheochromocytoma	3	7.3%

Table 11
Khairi et al., 1975

Gastrointestinal Tract Abnormalities in 41 Patients with MEN Type 3

Present	23
Intestinal ganglioneuromatosis	14
Persistent diarrhea	9
Diverticulosis	6
Megacolon	4
Intestinal hypertrophy	3
Abnormal gastrointestinal motility	2
Digestive trouble	1
Absent	10
Inadequate Information	8

Table 13
Khairi et al., 1975

Location of Neuromas in 41 Patients with MEN Type 3

Site	Number of patients
Oral	37
Lips	29
Tongue	34
Buccal Mucosa	6
Gingivae	1
Palate	1
Pharynx	1
Ocular	24
Eyelids	19
Conjunctiva	6
Cornea	3
Others	4
Skin	2
Nasal Cavity	1
Larynx	1

Table 12
Khairi et al., 1975

These cases have resulted in the division of those patients with pheochromocytoma-medullary carcinoma of the thyroid-hyperparathyroidism into Multiple Endocrine Neoplasia (MEN), Type II (Sipple's Syndrome) and MEN, Type III (with neuromas, etc.). Since there is no overlap of these two syndromes within the same family, support for this division can be advanced. However, the clinical characteristics of the pheochromocytomas with both are highly similar (Siqueira-Filho *et al*, 1975), and the almost identical age at diagnosis for the two suggests genetic homogeneity of the pheochromocytoma (Table 14, Knudson and Strong, 1960). For purposes of discussion, all cases will be lumped under the heading of Sipple's syndrome.

PHEOCHROMOCYTOMA-MEDULLARY CARCINOMA OF THYROID SYNDROME: COMPARISON OF AGE AT DIAGNOSIS FOR FAMILIAL AND NONFAMILIAL CASES

CATEGORY	AGE AT DIAGNOSIS OF PHEOCHROMOCYTOMA (YEARS)				
	0–19	20–39	40–59	>59	Total
Without mucosal neuroma:					
Nonfamilial*	0	16 (67%)	5 (21%)	3 (13%)	24
Familial†	4 (9%)	25 (57%)	13 (30%)	2 (5%)	44
With mucosal neuroma:					
Nonfamilial‡	1 (8%)	10 (83%)	1 (8%)	0	12
Familial§	1 (8%)	6 (50%)	4 (33%)	1 (8%)	12

* [22]: cases 1, 3–8, 10, 13, 17, 21–23, 29–30, 33–36, 40–41; [31–36].
† [22]: families I, B, C, L, P, R, U, W, F; [37]: followup on family C; [38–44]; C. S. Hill, personal communication, 1969: followup on case reported in [44]; [45].
‡ [48–53].
§ [48, 51, 54, 55].

Table 14

With the advent of calcitonin determinations for detection of family members affected with Sipple's syndrome, these cases pose the greatest diagnostic and therapeutic problem in the area of pheochromocytoma at the present time. It would appear that many of these cases progress from an early stage of bilateral adrenal medullary hyperplasia to a later stage of bilateral nodular medullary hyperplasia to a final stage of overt pheochromocytoma.

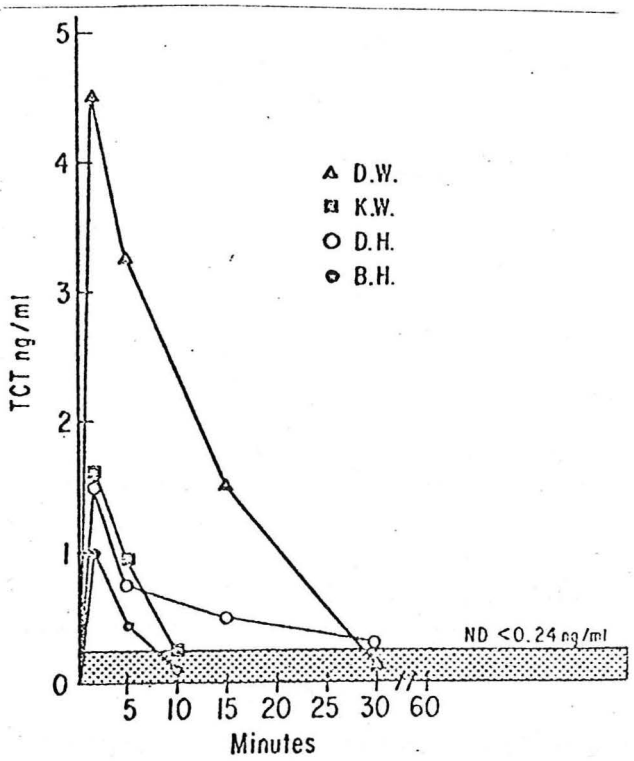
Adrenal medullary hyperplasia is a poorly understood entity at the present time. Vaquez (1904) noted adrenal adenomas and suggested that hypersecretion of adrenalin might lead to hypertension. However, the fundamental differentiation between the adrenal cortex and medulla had not been recognized. By the 1930's, this functional distinction had been determined and several cases were reported which may well have represented early reports of adrenal medullary hyperplasia. One such case is that of Piotrowski and Ody (1935) in which a patient with a syndrome compatible with pheochromocytoma had removal of the right adrenal with some improvement of the hypertension. Pathologic examination of this adrenal revealed both medullary and cortical hyperplasia. Leriche *et al* (1935) also reported a similar case. Several other authors also reported that cases of paroxysmal hypertension in which slight adrenal enlargement was found occasionally had improvement of paroxysmal symptoms and hypertension with adrenalectomy. Autopsy findings were compatible with hyperplasia of the medulla. One early report clearly demonstrating the case of a patient with adrenal medullary hyperplasia was by Drucker *et al* (1957). A 17-year-old girl presented with a typical pheochromocytoma syndrome with blood pressure of 220/110. Abdominal exploration revealed no gross abnormalities in the adrenal glands. However, the left adrenal was removed for pathologic evaluation and was found to have medullary hyperplasia. With removal of only the left adrenal, there was no change in the paroxysmal nature of the hypertension. Subsequent reoperation with removal of the right adrenal resulted in cure of the paroxysmal symptoms of hypertension, though it is interesting to note that the the blood pressure remained somewhat elevated (145-160/105-120 mm Hg) with a persistent pulse rate of 130/minute. This leaves some doubt as to whether an occult site of pheochromocytoma remained. Subsequent to these two operations, urinary catecholamines were said to be within normal limits. In 1962 Montalbano and others reported a 23-year-old white man with a typical paroxysmal pheochromocytoma syndrome. The Regitine, histamine, and catacholamine determinations were all characteristic of pheochromocytoma. Laparotomy revealed enlargement of the left adrenal but no abnormality in the right adrenal. The right adrenal was biopsied and confirmed to be normal. Thus, the left adrenal only was removed. It demonstrated localized medullary enlargement with much more medullary tissue on the left than on the right. The hypertension was cured by this operation for at least a period of one year. Bialestock (1961) reported two children: (1) a 5-year-old white boy with severe hypertension (blood pressure 260/175) and a history of left CVA. The hypertensive work-up revealed a question of right renal artery stenosis. However, the urinary catecholamine determinations were normal. Because of the severe nature of the hypertension, right nephrectomy was done with no change in the blood pressure. The patient subsequently died and at autopsy the adrenals were grossly normal, but had bilateral medullary hyperplasia. (2) Another 11-year-old boy in the same series presented with severe hypertension (blood pressure 250/180) and died shortly after presentation without any diagnostic evaluation. At autopsy there were no abnormalities other than adrenal medullary hyperplasia.

The most carefully documented case of adrenal medullary hyperplasia at the present time appears to be that of Carney *et al* (1975) from the Mayo Clinic. A 12-year-old girl with normal blood pressure, marfanoid habitus, hyperparathyroidism, and known medullary carcinoma of the thyroid was evaluated. The urinary VMA was elevated on two occasions to 5.6 to 5.7 (normal = 0.25 - 3.25 mg/24 hr). Total urinary catecholamines and urinary normetanephrine were normal. Glucagon and histamine stimulation were negative. A bolus nephrotomogram suggested a left suprarenal mass. Laparotomy revealed enlargement of the adrenal glands bilaterally. The left adrenal was biopsied and noted to have a somewhat prominant medulla. Because of this finding, bilateral adrenalectomy was done. The following pathologic findings were noted: (1) adrenal weight to body weight ratio equalled 2×10^{-4} (normal = 0.8 to 1.4×10^{-4}), (2) the corticomedullary ratio was 4:1 (adult control = 10:1 and age matched control = 6:1), (3) 20% of the cells were typical pheochromocytes with cellular and nuclear hypertrophy and giant nuclei. The nuclei appeared somewhat more open, the nucleoli were somewhat more prominant, and mitotic figures were common. (4) Catecholamine content was 9.12 mg/gland (normal range of 0.8 - 4.4 mg/gland). (5) Medulla was noted in all regions of the gland; whereas, in most adrenal glands the adrenal medulla is noted mainly in the head with some being noted in the body and none in the tail of the gland. (6) Electron microscopy revealed evidence of increased synthesis suggested by increase in the rough endoplastic reticulum and Golgi apparatus. Thus, cases of adrenal medullary hyperplasia pose a diagnostic and therapeutic dilemma. They can be very difficult to diagnose without doing histologic examination of the adrenals and, in some patients, they can lead to a severe hypertensive crisis which may present at the time of surgery for medullary carcinoma of the thyroid. In other patients, the pheochromocytoma may well be quiescent until late in adult life.

In addition to bilateral medullary hyperplasia and bilateral nodular hyperplasia, other patients with Sipple's syndrome have small intra-adrenal pheochromocytomas (1-2 cm) which may be multiple on both sides. The exact functional characteristics and location of the tumor is relatively constant in some families. This can be of considerable importance at the time of operation in decisions about the need for bilateral adrenalectomy and to provide guidance about locations to search for a tumor. For example, all 10 cases in the family of Steiner *et al* (1968) were bilateral, and in one family, both affected members had pheochromocytoma arising from chromaffin tissue at the aortic bifurcation (Cook, 1960). In other families, however, some members have unilateral tumors and others have bilateral ones.

Other general aspects of Sipple's syndrome have been reviewed (Keiser, 1973; Steiner, 1968; Khairi, 1975). The great majority of patients with pheochromocytoma in this syndrome will have medullary carcinoma of the thyroid at the time of presentation of the pheochromocytoma. Fortunately, this can aid greatly in the identification of the syndrome since almost all of the cases have paroxysmal pheochromocytoma which may be very difficult to diagnose by urinary metanephrine, VMA, and catecholamine determinations or by histamine, tyramine, or glucagon stimulation. Medullary carcinoma of the thyroid can be diagnosed with great accuracy by the use of pentagastrin (Sizemore *et al*, 1975; Wells *et al*, 1975; Hennessy, 1974) or calcium infusion (Jackson *et al*, 1975) with determination of stimulated plasma calcitonin concentration. Pentagastrin stimulation (Figure 14) appears to be somewhat superior and easier to do, and so in general it is the initial procedure of choice (Sizemore *et al*, 1975;

Hennessy, 1974). However, in those patients with strong clinical suspicion of Sipple's syndrome who do not stimulate with pentagastrin, the 4-hr calcium infusion (15 mg calcium/kg) should be done. With pentagastrin stimulation (0.5 µg/kg IV push) samples should be determined at 0,1,2,5,10,15 minutes since the response is exceedingly rapid and usually maximal within the first five minutes. An occasional patient who does not demonstrate a rise in peripheral calcitonin may do so if the inferior thyroidal veins are selectively catheterized (Figure 15). Obviously, this procedure is reserved for those in which there is other strong evidence that they have Sipple's syndrome. Some patients note mild epigastric pain, nausea, or vomiting with pentagastrin.

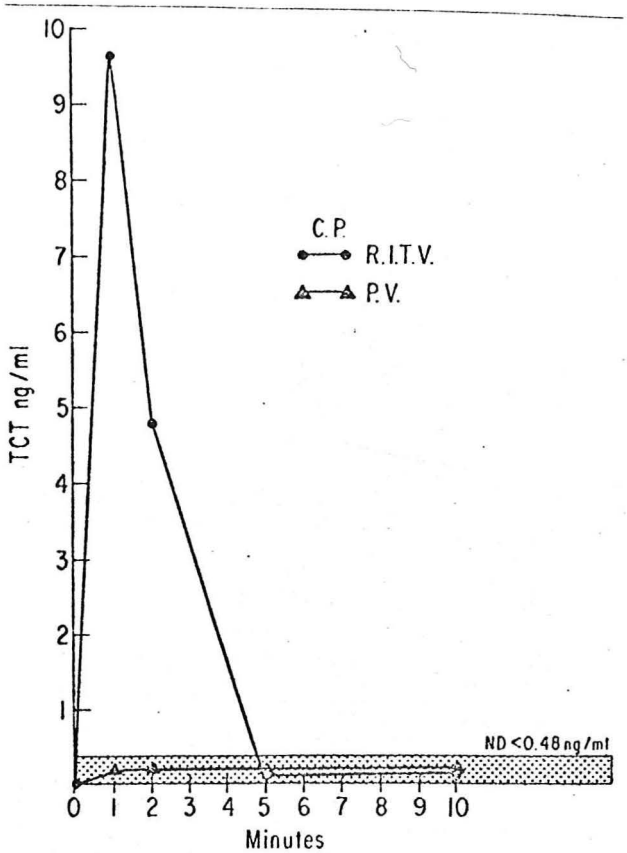


Thyrocalcitonin response to pentagastrin stimulation in four children (D.W., K.W., D.H., and B.H.) with a family history of multiple endocrine neoplasia type II.

figure 14

(Wells et al, Ann Surg 182:362, 1975)

Sampling during calcium infusion (Figure 16) is less critical and is usually done at 30-60 minute intervals since the rise is less rapid and is well maintained. EKG monitoring should be done. The combination of these two tests should enable the diagnosis of MCT in almost 100% of adult patients.

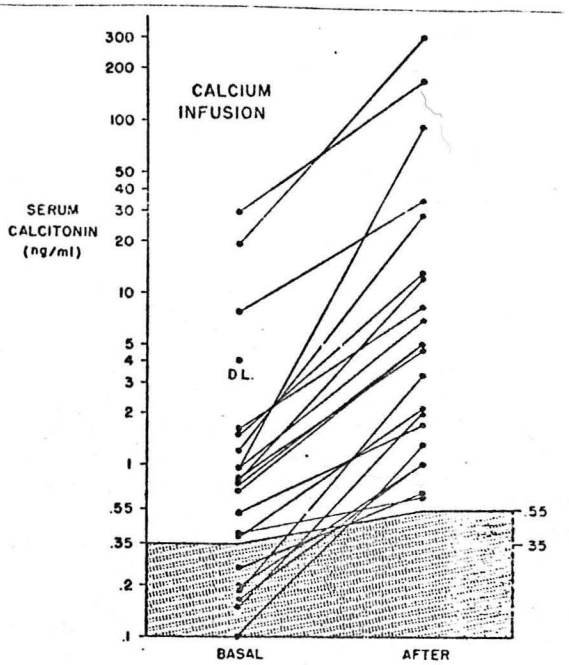


Thyrocalcitonin response to pentagastrin stimulation in patient C.P. Note the absence of TCT elevation in the peripheral blood following pentagastrin stimulation. An elevated TCT level is only detected in the right inferior thyroid vein.

figure 15

About 20-30% of cases with Sipple's syndrome first manifest their pheochromocytoma with a severe hypertensive reaction at the time of a surgical procedure. The issue of pheochromocytoma should, thus, be well delineated before surgical approach of the MCT. In those patients with MCT with a history of paroxysmal hypertension or attacks and equivocal laboratory evidence for pheochromocytoma, arteriography and adrenal venography (if an excellent venographer is available) is then indicated. Urinary determinations of metanephrine and VMA will be most helpful if urine can be obtained during the time of a hypertensive response (unassociated with surgery or other stressful procedures), and the results expressed in terms of µg/mg creatinine. If a severe (life-threatening) hypertensive reaction has been well documented, adrenal exploration is warranted, even if these radiographic procedures are negative. In a similar situation but with no laboratory evidence to suggest pheochromocytoma, adrenal arteriography and possibly venography should be done to search for an occult pheochromocytoma. If these are negative, the decision about adrenal exploration would depend on the strength of the historical evidence suggesting pheochromocytoma.

figure 16



Serum calcitonin concentrations in the 22 members with positive tests in the three families. The maximum normal basal level is 0.35 ng/ml with the maximum normal observed after calcium infusion being 0.55 ng/ml (*shaded areas*). Serum calcitonin concentration is on logarithmic scale.

As mentioned earlier, the tyramine test is of no diagnostic help in Sipple's syndrome, and the histamine and glucagon tests are of limited usefulness. It is difficult to determine from the literature what percentage of patients with Sipple's syndrome and normal urinary catecholamines, VMA, and metanephrine will respond to histamine and glucagon testing. It appears that less than 25% of all patients with Sipple's syndrome respond to glucagon and that 25-50% respond to histamine (Sheps, 1968; Siqueira-Filho *et al*, 1975; White *et al*, 1973; Sheps and Maher, 1966), though the false positive rate with histamine is about 10% (Sheps and Maher, 1966). However, since the histamine test is potentially so much more dangerous, it is still best to utilize the glucagon test initially. Both of these tests should be used only in those patients who have excellent historical evidence, but negative laboratory and arteriographic evidence to guide the decision about adrenal exploration. Some investigators have claimed greater diagnostic specificity of these stimulation tests if plasma catecholamines are simultaneously determined (White *et al*, 1973). However, the evidence presented is meager, and other investigators have found it of no help (Cremer *et al*, 1968). Nonetheless, until this point is better settled, it is probably advisable to simultaneously determine plasma catecholamines, in hopes that these might strongly confirm a positive blood pressure response. In this syndrome the importance of bolus nephrotomography should be emphasized (Pickering *et al*, 1975) since the tumors are occasionally relatively large in spite of being quiescent.

Some patients with pheochromocytoma and hypercalcemia do not have Sipple's syndrome. In these cases the pheochromocytoma itself appears to be producing PTH or a PTH-like material, or possibly the high catecholamines stimulate PTH production. The hypercalcemia returns to normal after removal of the pheochromocytoma (Swinton *et al*, 1972; Finlayson and Casey, 1975; Kukreja *et al*, 1973). Against the theory of catecholamine stimulation of PTH production is a recent report of normal PTH concentrations in ten patients with pheochromocytoma and normocalcemia (Miller *et al*, 1975).

Several different syndromes of pheochromocytoma are notable:

Pheochromocytoma of the bladder is a very rare tumor, comprising less than 1% of all bladder tumors and less than 1% of all pheochromocytomas (Bourne and Beltaos, 1967; Scott and Eversole, 1960). The classical distinguishing feature of pheochromocytoma of the bladder is the precipitation of the typical paroxysmal attacks with the onset of micturition. This occurs in about 80% of cases and has occasionally resulted in micturition syncopy. Hematuria occurs with 50-60% of these tumors and other characteristics of bladder tumors are usually present. These tumors are not visible in 20% of cases at the time of cystoscopy. A typical paroxysmal attack may be precipitated during massage of the bladder and/or adnexa. There is a much higher incidence in women. Other than the precipitation by micturition, the clinical syndrome and the diagnostic tests are similar to pheochromocytoma in general. Intravenous pyelography may demonstrate a filling defect in the bladder which occasionally may be confused with a ureterocele (Cabanas *et al*, 1973). Ring calcification in the tumor has also been confused with schistosomiasis (Kolawole *et al*, 1975). A few cases of malignant pheochromocytoma of the bladder have been reported (Deklerk *et al*, 1975; Javaheri *et al*, 1975). In general these are said to be less invasive than other malignant pheochromocytomas. Because the pheochromocytoma arises from the paraganglia relating to autonomic nerves in the bladder, it is typically within the muscle coat and invades the mucosa, serosa, and perivesicle tissues. It may thus be difficult to recognize the full extent of invasion by external inspection. For this reason, a generous margin of tissue should be removed at the time of excision. One case of pheochromocytoma of the bladder has been associated with renal cell carcinoma (Deklerk *et al*, 1975). This case is reminiscent of the association of von Hippel-Lindau disease with its association of pheochromocytoma and renal cell carcinoma, and it may represent a case of incomplete penetrance.

Pheochromocytoma and pregnancy. Schenker and Chowers (1971) have reviewed a series of 89 cases of pheochromocytoma occurring during pregnancy. As might be expected, pheochromocytoma is commonly confused with toxemia of pregnancy or with eclampsia if it presents at the time of childbirth. However, it can be distinguished from toxemia by the lack of protenuria and fluid retention. Catastrophic syndromes at the time of delivery may also be confused with rupture of the uterus. The symptomatology with pregnancy is essentially the same except that an increased percentage of convulsions (10%) is noted with pregnancy (Table 15). The classical paroxysmal attacks may be precipitated by postural changes, the mechanical effect of the gravid uterus in the last trimester of gestation, uterine contractions during labor, and increased fetal movements. It is particularly important to diagnose these cases correctly since the maternal death rate is 58% in undiagnosed cases, and the fetal death rate is 56%. When the pheochromocytoma has been diagnosed, the maternal mortality rate is only 18% and the fetal mortality rate is also decreased to 18%. The placenta contains large amounts of catechol-0-methyltransferase, thus acting as a barrier against

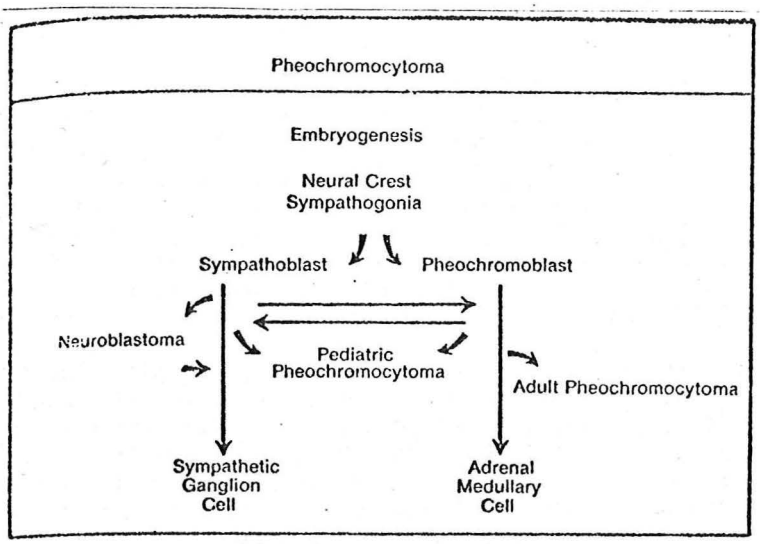
Symptoms and signs	No. of cases	Per cent
Paroxysmal or sustained hypertension	73	82
Headaches	59	66
Palpitation	32	36
Sweating	30	33
Blurred vision	16	17
Anxiety	14	15
Convulsions	9	10
Dyspnea	9	10
Others	6	7

Table 15

the circulation of excess catecholamines into the placenta. Thus, the high fetal death rate is probably associated with catecholamines in the mother's circulation causing decreased uterine blood flow. A few fetuses do demonstrate the effects of some passage of catecholamines into the fetal circulatory system.

In general, when the diagnosis of pheochromocytoma is confirmed, the tumor is removed immediately regardless of the state of pregnancy. However, some patients can be controlled chronically with Dibenzyline and propranolol therapy (Brenner *et al*, 1972; Griffith *et al*, 1974). Labor and vaginal delivery have been followed by maternal and/or fetal death due to sudden discharge of catecholamines into the circulation, probably the result of mechanical interference with the tumor. For this reason, delivery should be done by caesarian section. If the diagnosis is not made until near the time of delivery, the fetus can be delivered by caesarian section, and then the pheochromocytoma can be removed. In the few cases that were treated with Dibenzyline during the first trimester of therapy, there has been no demonstrated teratogenic effect as yet.

Pediatric pheochromocytoma is one of two important neural crest tumors in children. The relationship between the two is suggested in Freier *et al*, 1973 (Figure 17). These tumors are characterized by a much higher percentage of norepinephrine secreting or persistently functioning tumors (90%). In addition, familial forms of pheochromocytoma are much commoner in children



Embryogenesis of neural crest cells.

figure 17

(40%) and multiple and bilateral pheochromocytomas are much commoner (Stackpole *et al*, 1963; Hume, 1960; Freier *et al*, 1973). The incidence of bilateral or multiple pheochromocytomas varies from 30-60% depending upon the series (Stackpole *et al*, 1963) (Table 16). The symptomatology in children

Incidence of single and multiple intra-adrenal and extra-adrenal pheochromocytomas (totaling 140 tumors) as found in 100 children

	Single		*Multiple (2 or more)*	
Site	*No. of patients*	*No. of tumors*	*No. of patients*	*No. of tumors*
Intra-adrenal	49	49	(bilateral) 20	40
Extra-adrenal	19	19	(extra-adrenal only) 4	12*
Intra and extra-adrenal	—	—	8	20†
Total	68	68	32	72

*One patient with 6 tumors.

†Two patients with 3 tumors and one with 4 tumors.

Table 16

is somewhat different than in adults in that nausea and vomiting, weight loss, polyuria and polydipsia, visual disturbances, and convulsion are more predominant as presenting symptoms (Stackpole *et al*, 1963) (Table 17). In addition, in 11% of cases there was a reddish-blue mottled cyanotic discoloration of the hands with edema, or swelling, and severe constipation. Some degree of retinopathy was seen in 77% of the patients. Because the great majority of tumors are persistently functioning tumors, the diagnosis is somewhat more straightforward than in the adult with paroxysmal attacks. However, the management is more complicated. In pediatric pheochromocytoma the mortality rate averaged about 45% until 1954; whereas, since then it has averaged 13%. The occurrence of multiple pheochromocytomas complicates the surgical management, and the commonest cause of death after operation is an undiscovered tumor left behind. There is a 2:1 male to female ratio until the age of puberty, at which time the sex ratio becomes equal. It should be noted that about 50% of all children who present with hypertension will have some secondary form of hypertension. Thus, children with hypertension should be evaluated very carefully for pheochromocytoma. Because of the higher familial occurrence of pheochromocytoma in children, the families of these patients should also be carefully evaluated. In view of the high incidence of multiple pheochromocytoma, some surgeons have concluded that all childhood cases of pheochromocytoma should have venous sampling with determination of plasma catecholamines for an attempted preoperative localization of the tumor(s). However, in children as well as in adults, the

Signs and symptoms in 95 children with pheochromocytomas*

	No.	*%*
Hypertension	95	100
Sustained 84 (88%)		
Intermittent 11 (12%)		
Headache	71	75
Sweating	64	67
Nausea and vomiting	46	48
Weight loss	36	38
Visual disturbances	35	37
Abdominal pain	30	32
Polydipsia and Polyuria	29	31
Convulsions	21	22
Acrocyanosis	21	22

*In 5 cases (Cases 1, 13, 51, 81, and 94) the clinical history was not given in sufficient detail for signs and symptoms.

Table 17

tumors are located within the abdominal cavity in all but 1 or 2% of patients. Since the abdomen can be more easily explored completely in children, it would appear that this procedure need not be done routinely.

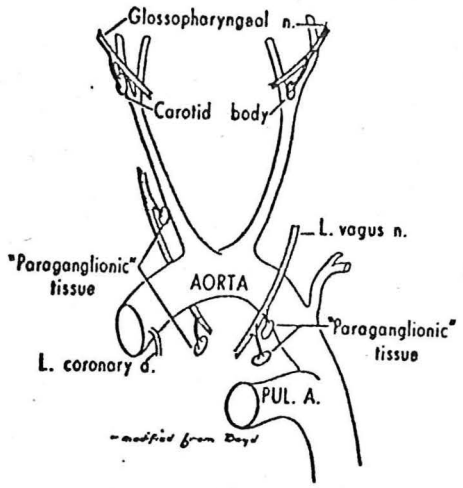
Malignant pheochromocytomas. A series of 41 cases of malignant pheochromocytoma has been reported by Schönebeck (1969). For a pheochromocytoma to be characterized as malignant, it must demonstrate metastases at sites where aberrant chromaffin tissue does not occur. The reason for this criterion for diagnosis is that it is impossible to distinguish benign from malignant pheochromocytomas histologically (Symington and Goodall, 1953). Benign pheochromocytomas which never metastasize may be characterized by considerable dysplasia and by other criteria of malignancy such as vessel invasion. Malignant pheochromocytomas are more frequently extra-adrenal. In Shönebeck's series about 50% of cases in which the site of origin could be established were extra-adrenal. Initially, the symptoms in both benign and malignant cases are largely related to the production of catecholamines and, therefore, are similar. In the malignant cases the signs and symptoms of metastases are added--for example, a pathologic fracture. The distribution of metastases is shown in Table 18. (Schönebeck, 1969). Malignant pheochromocytomas are more likely to produce increased amounts of dopamine and its primary metabolite, homovanillic acid (HVA). In adults with pheochromocytoma, increased HVA excretion has proved a reliable indicator of malignancy. However, in children this is not true (Gitlow *et al*, 1972). Increased excretion of homovanillic acid can also be seen in cases of neuroblastoma and malignant melanoma. In those cases in which the tumor cannot be completely excised, palliation can sometimes be obtained with radiation therapy. The prognosis of malignant pheochromocytoma is variable. Most patients in the older series died within three years after the time of diagnosis. More recent case reports have indicated longer survivals of metastatic pheochromocytoma than the earlier cases. For example, Traub and Rosenfield (1970) reported a malignant pheochromocytoma with pleural metastases with a 20-year survival. Palmieri *et al* (1961) reported a case that survived at least 8 years. Scharf *et al* (1973) followed a case for 11 years. In addition, occasional cases may not present with the initial metastasis until many years later. One case reported by Jaffe did not present with the initial metastasis until 12 years after removal of the primary tumor. It is possible that this longer survival is due to a more aggressive approach to the medical therapy of these patients with sympathetic blocking agents and to possible beneficial effects of high dose radiation therapy in some cases. Metastatic pheochromocytoma must be considered in the differential diagnosis of a miliary, pulmonary infiltrate (Tu and Bottomley, 1974; James *et al*, 1972). In some patients resection of individual metastases may be justified because tumor growth is often slow and the management of the patient's hypertension may be appreciably improved. In general, metastatic pheochromocytomas are radiation resistant. In some localized tumors, particularly metastatic bone lesions with pathologic fractures, intensive radiation with tumor doses in excess of 3500 to 4000 r may be of definite value (James, 1972).

Distribution of metastases in 41 cases of malignant pheochromocytoma

Localisation	26 autopsy cases	15 non-autopsy cases	%
Skeleton	12	6	44
Liver	12	3	37
Lymph-node	11	4	37
Lungs	9	2	27
CNS	4	0	10
Pleurae	4	0	10
Kidneys	2	0	5
Pancreas	1	0	2
Omentum	1	0	2

Table 18

Paragangliomas. Difficulty exists in trying to distinguish the function of pheochromocytomas and paragangliomas on the basis of the chromaffin stain, as discussed earlier. Therefore, the concept of functional non-chromaffin paragangliomas is somewhat arbitrary. These functional paragangliomas are exceedingly rare. Those tumors that appear to be derived from chemoreceptor tissues such as the carotid body and aortic bodies are called chemodectomas (Figure 18, Hewitt *et al*, 1972). This term has also been used in a non-specific fashion for paragangliomas. Paragangliomas are exceedingly widespread in their distribution, occurring in the: (1) glomus jugulare, (2) vagus nerve, (3) ganglion nodosum, (4) mediastinum, (5) lungs, (6) retroperitoneal region, especially in the area of the organs of Zuckerkandl, (7) elsewhere throughout the abdomen, and (8) extremities. Glomus jugulare tumors present with decreased hearing, otitis, tinnitus, pain, headache, vertigo, and history of multiple miringotomies. The glomus jugulare is a highly vascular collection of nests of epithelioid cells located in or near the adventitia of the bulb of the jugular vein, immediately below the bony floor of the middle ear. One case has been reported (Figure 19, Matsuguchi *et al*, 1975) of a norepinephrine secreting glomus jugulare tumor with cyclic changes in the blood pressure so that each cycle occupied approximately 10 minutes. Carotid body tumors present with a typical pheochromocytoma syndrome. However, the major



Locations of chemoreceptor tissue. (From Boyd, J. D.: Contri. Embrol. Carnegie Inst. 26: 1, 1937, reproduced by courtesy of the Carnegie Institute of Washington.)

figure 18

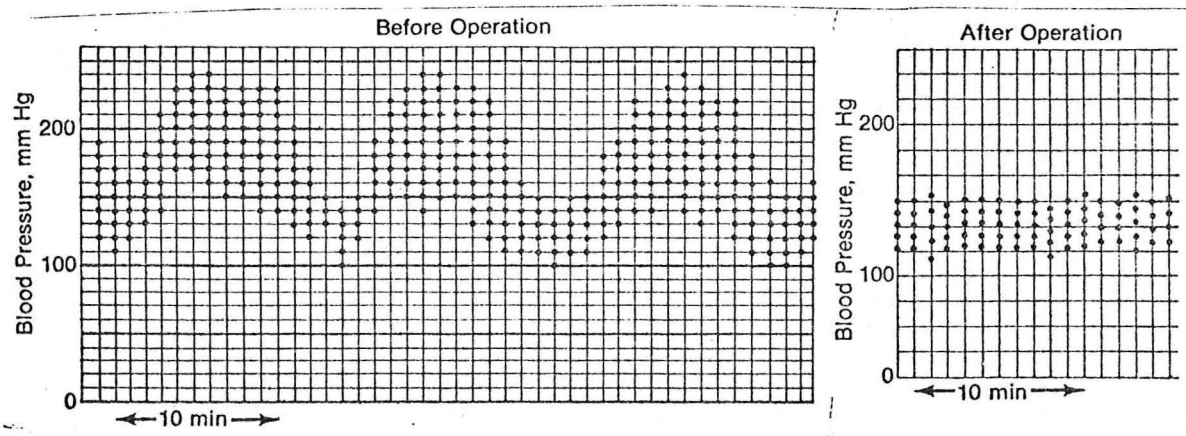


Fig 1.--Cyclic change of blood pressure recorded by automatic continuous sphygmomanometer every minute. Cyclic change of blood pressure was not seen after operation.

figure 19

clinical feature suggesting the diagnosis of this tumor is to find a mass in the neck (Hewitt *et al*, 1972). One case of chemodectoma of the right adrenal, mediastinum, and carotid body which occurred as three separate tumors over a period of 25 years has been reported (Revak, 1971). This patient had a family history of thyroid carcinoma, as has been reported in another patient (Albores-Saavedra and Duran, 1968). In one of these cases, medullary carcinoma of the thyroid was definitely not the associated thyroid carcinoma; whereas, in the other the tumor type of the thyroid carcinoma is unclear. If a mass is not present in the neck, the diagnosis of carotid body chemodectoma may be quite difficult and may only be suspected after doing selective venous sampling. Arteriography, however, will usually provide a definitive localization of these tumors. Functional non-chromaffin paragangliomas of the organs of Zuckerkandl have also been reported (Attia *et al*, 1961). Tumors of these paraganglia are more likely to become malignant (38%) than are tumors of other paraganglia.

Cardiovascular manifestations of pheochromocytoma. Patients with pheochromocytoma may present with myocardial infarction, myocarditis, cerebrovascular disease, peripheral vascular disease, and hypotension (Radtke *et al*, 1975).

Myocardial infarction and myocarditis. Frank myocardial infarction may occur with pheochromocytoma. However, a myocardial infarction-like syndrome may also occur in which there is focal myocarditis, subpericardial hemorrhage, pulmonary edema, ST segment elevations in the EKG, and elevation of cardiac enzymes. In these cases normal coronary arteries have been demonstrated by coronary arteriography. Catecholamines, particularly norepinephrine, are known to have a toxic effect on the myocardium and this may account for many of the changes. The cardiomyopathy may be remarkably reversible with pharmacologic blockade and later removal of the tumor.

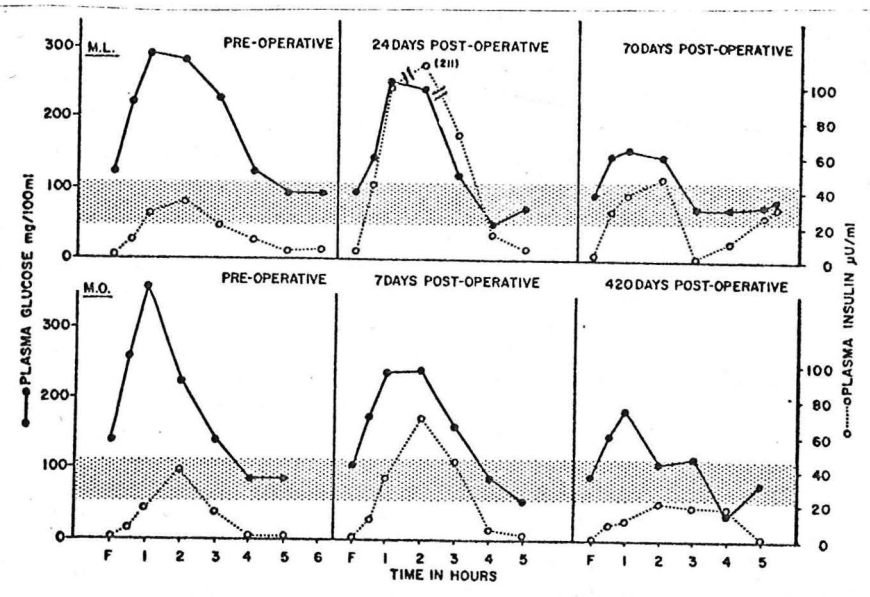
Peripheral vascular disease. Many patients may experience intense vasomotor phenomena with pheochromocytoma. Peripheral cyanosis, livido reticularis, and Raynaud's phenomenon are occasionally noted. Some patients have experienced such severe vasoconstriction that ulceration and sloughing of the skin may occur. In other patients, intermittent claudication which cannot be explained by subsequent arteriographic findings may occur. Arterial spasm may be confused with arterial emboli. Secondary to intense vasoconstriction, the peripheral pulses may be weak to palpation, and there may be difficulty in hearing the blood pressure at the time of presentation.

Cerebrovascular manifestations. Visual changes occur in about 20% of patients with sustained hypertension. Occasional patients may become almost totally blind (cortical blindness) during a paroxysm of hypertension. Cerebrovascular accidents may occur during hypertensive crisis. A variety of other manifestations of cerebrovascular insufficiency are common.

Hypotension. Hypotension may result from: (1) orthostasis, (2) tachyarrhythmias, (3) epinephrine excess (Page *et al*, 1969), and (4) massive infarction of the pheochromocytoma with necrosis and subsequent hypotension (Delaney and Paritzky, 1969; Sobonya *et al*, 1973). Hypotension may also be noted with intense peripheral vasoconstriction in the sense that no blood pressure can be obtained in the arm. However, if intra-arterial pressure from a large vessel is monitored at this time, it obviously will be quite high.

Pheochromocytoma and diabetes. Insulin secretion is increased by beta receptor stimulation and inhibited by alpha receptor stimulation. In addition, glycogenolysis is induced by β-receptor stimulation. Thus, patients with

pheochromocytoma are occasionally confused with diabetic patients with hypertension. Patients noted to have diabetes who present with hypertension at less than age 40 or who present with significant hypertension early in the course of diabetes should be especially suspect for pheochromocytoma. In the Mayo Clinic series of 76 patients (Gifford *et al*, 1964), 23.5% of patients with paroxysmal function and 34.5% of patients with persistent function had an elevated blood sugar above 109 mg %. There is a somewhat higher percentage of elevated blood sugar in those patients with persistently functioning tumors. Spergel *et al* (1968) have also suggested that there is a resistance to the hypoglycemic action of endogenous insulin. Immediately after removal of the tumor in two patients, the response of plasma insulin levels to glucose and tolbutamide was exaggerated, but resistance to the hypoglycemic effects of insulin continued (Figure 20). Over a period of time carbohydrate metabolism



Serial Plasma Glucose and Plasma Insulin Responses to 100 Gm of Glucose Given by Mouth to Two Patients with Pheochromocytoma. The stippled bar represents the normal range of the fasting glucose values.

figure 20

reverted toward normal. In some patients the glucose intolerance may disappear shortly after surgery (Colwell, 1969); whereas, in other patients such as those described by Goldner (1947), the glucose intolerance may persist for up to 2 years after the time of surgery. In those patients with genetic diabetes which first becomes manifest in association with a pheochromocytoma, glucose intolerance may persist permanently after removal of the pheochromocytoma.

Gastrointestinal complications of pheochromocytoma. Gastrointestinal complaints such as nausea and vomiting are common symptoms with pheochromocytoma, particularly in childhood pheochromocytoma (Hunter and Martel, 1973).

Chronic constipation is a feature of persistently functioning pheochromocytoma. Occasional cases of infarction and hemorrhage of the small bowel and colon have been recorded. Intestinal ileus may be observed without demonstrable infarction. Non-specific abdominal pain was seen in about 15% of both paroxysmally functioning and persistently functioning patients in the Mayo Clinic series (Gifford *et al*, 1964). The gastrointestinal effects probably result by several mechanisms. The most prominent mechanisms would be a direct inhibitory effect of norepinephrine upon the smooth muscle of the GI tract and a vasoconstrictive effect of norepinephrine upon the intestinal vasculature. In addition, occasional large pheochromocytomas may compress the GI tract. Patients with multiple endocrine neoplasia type III have a variety of gastrointestinal disturbances such as intestinal ganglioneuromotosis, diverticulosis, and megacolon (Khairi *et al*, 1975).

Pheochromocytoma and adrenocortical hyperfunction. Patients with adrenocortical hyperfunction consistent with Cushing's syndrome have been reported. Neff *et al* (1942) reported the case of an infant who showed features consistent with Cushing's syndrome but who was found to have only a pheochromocytoma at the time of surgery. With the advent of assays for ACTH it became clear that some pheochromocytomas and nonfunctional paragangliomas could produce ACTH (Meloni, 1966; Williams *et al*, 1960; Schteingart *et al*, 1972). With ectopic ACTH production, bilateral adrenal hyperplasia with marked increases in plasma cortisol, 24-hr urinary 17-hydroxy-corticosteroids, and often 24-hr urinary 17-ketosteroids will be present. As with all patients with the ectopic ACTH syndrome, the patients are likely to have a hypokalemic alkalosis. Cope *et al* (1952) has described one case of simultaneous occurrence of pheochromocytoma and an adrenal cortical adenoma without physical features of Cushing's syndrome, but with evidence that the adenoma was functioning. Cushing's syndrome may also result from direct production of cortisol by the pheochromocytoma itself (Mulrow *et al*, 1959). This may be unrecognized until the postoperative period when the patient develops signs of adrenocortical insufficiency secondary to long-standing suppression of the contralateral adrenal. Administration of ACTH has been reported to precipitate a hypertensive crisis, which was fatal in two patients who were being tested to evaluate Cushing's syndrome. Therefore, this testing should be avoided (Moorhead *et al*, 1966). Patients may also present with Cushing's syndrome who have Sipple's syndrome. Medullary thyroid carcinomas have been shown to produce an ACTH-like substance (Goldberg and McNeil, 1967; Melvin *et al*, 1970). Interestingly, Steiner *et al* (1968) described one case that appeared to have simultaneous occurrence of Sipple's syndrome and Cushing's disease (pituitary ACTH production). In addition to Cushing's syndrome patients with pheochromocytoma often have evidence of secondary aldosteronism. This may be produced by renal artery stenosis secondary to extrinsic pressure of the tumor, or it may be due to β-receptor mediated renin release stimulated by the catecholamine excess (Kitajima *et al*, 1975; Rosenheim *et al*, 1963; Ishibashi *et al*, 1975).

Miscellaneous associations with pheochromocytoma. Pheochromocytoma has been associated with Down's syndrome (Kuni, 1973), with Noonan's syndrome (Becker *et al*, 1969), and with a patient with primary hypogonadism and a bicuspid aortic valve (Page, 1974). One patient with intrapericardial pheochromocytoma was reported who had a typical pheochromocytoma syndrome that could not be located after laparotomy. This patient also had physical and radiological signs of mitral valve disease secondary to compression of the valve by the tumor. This tumor undoubtedly arose from chromaffin tissue accompanying

the heart and great vessels or the sympathetic innervation of the heart (Besterman, 1974). A significant association of pheochromocytoma with rare brown fat tumors (hibernomas) also appears to exist (English *et al*, 1973). Brown fat occurs in small amounts in fetal life and tends to disappear in childhood though small amounts usually remain between the scapulae, in the axillae, and in the abdomen around both kidneys and adrenals. In animals the function of brown fat is the production of heat; its function or metabolic significance in man is unknown. Hibernomas are rare, benign tumors which can present in any location in which fetal brown fat occurs. They have also been seen in the thorax and neck and thigh. Awareness of the association of brown fat tumors can be important in an angiographic search for pheochromocytomas since they are highly vascular tumors which may be confused with the pheochromocytoma.

Differential diagnosis of pheochromocytoma. Most patients with hypertension and one or more of the symptoms of pheochromocytoma turn out not to have that diagnosis. Conditions that may simulate pheochromocytoma are shown in Table 19 (Kaplan, 1973). Particular problems arise with intracranial lesions since they have been reported to cause an increase in catecholamine metabolite excretion. Evans *et al* (1972) have reported a patient with astrocytoma mimicking the features of a pheochromocytoma with paroxysmal hypertension up to blood pressure levels of 190/150 mm Hg, tachycardia to 180 beats per minute, and elevated urinary catecholamine and catecholamine metabolite levels during the time of the episodes and occasionally during asymptomatic periods. There was a positive intravenous phentolamine test, inducing a fall of 50 mm Hg systolic and diastolic pressure on two occasions. Gabriel and Harrison (1974) have also described a case of supratentorial meningioma in a patient who had episodic hypertension responsive to alpha and beta blockade associated with excess urinary excretion of VMA. One case has been reported of a patient with a stroke who had hypertension with very elevated VMA and urinary norepinephrine levels which subsequently resolved (Mazey *et al*, 1974; Table 20). Abdominal exploration revealed evidence of pheochromocytoma. Patients with acute intermittent porphyria that present with hypertensive crisis may be confused with pheochromocytoma, as might patients that have an encephalopathic form of lead poisoning. A rare patient that presents with hypertensive rebound secondary to clonidine withdrawal might also be mistaken for a patient with pheochromocytoma. Another fairly common clinical setting which may be confused with pheochromocytoma is a hypertensive response occurring during surgery, head injury, or during some other stress. Catecholamine, VMA, and metanephrine excretion may increase in this setting into the range associated with pheochromocytoma (Franksson *et al*, 1954; Gitlow, 1970). Gitlow (1970) has claimed that the VMA does not increase as much as the free catecholamine or metanephrine in this setting. However, the reason for this is unclear, and the clear elevations in VMA in a patient after a stroke (Table 20)

Conditions That May Simulate Pheochromocytoma

- Anxiety with hyperventilation
- Menopause
- Hypoglycemia
- Angina
- Acute pulmonary edema
- Eclampsia
- Migraine and cluster headaches
- Thyrotoxic storm
- Brain tumor
- Carcinoid
- Porphyria
- Lead poisoning

Table 19

CATECHOLAMINE EXCRETION AFTER STROKE

No. of Days After Stroke	VMA, mg/24-hr	Norepinephrine, µg/24-hr	Epinephrine, µg/24-hr
5	10.1	255.5	51.3
6	20.6	245.7	45.5
42	8.3	142.1	10.2
43	7.6	108.0	8.8
77	6.9	121.8	13.4
78	8.9	135.0	14.0
29 weeks	5.8	--	--
normal	5.0	100.0	20.0

Table 20

point out the fact that there must be many exceptions to this rule. When confusion exists in these clinical settings and the danger to the patient would appear to be life-threatening, it is best to proceed to bolus nephrotomography and arteriography, if necessary.

Children with neuroblastomas may occasionally be confused with pheochromocytoma. However, the great majority of these cases have normal blood pressure, whereas childhood pheochromocytoma is characterized by sustained high blood pressure (Voorhess, 1974). Interestingly, the blood pressure is usually normal even when the 24-hr urniary norepinephrine is in the same range as in patients with pheochromocytoma. Most patients with neuroblastoma have characteristic large increases in homovanillic acid (HVA), the major metabolite of dopa, and VMA (Voorhess, 1974; Gitlow, 1970). However, the VMA may be normal in from 3-15% of cases. Neuroblastoma is a highly malignant tumor in early life with peak incidence before the age of 3 years. These tumors have the capacity to regress spontaneously and also to differentiate and mature to ganglioneuroblastomas and then to benign ganglioneuromas. Both neuroblastomas and pheochromocytomas may occur in more than one member of a family.

Asymptomatic pheochromocytomas have been described (Louis *et al*, 1972; Taubman *et al*, 1974). In two of these cases, the tumors were producing large quantities of dopa, and it was postulated that this is what kept the patient normotensive--similar to what is found with neuroblastoma. These patients are poorly understood at the present time. It is possible that the more indolent forms of paroxysmal pheochromocytoma closely resemble these patients and that poorly understood factors initiating a hypertensive episode change the metabolic characteristics of the tumor or cause a massive release of catecholamines. It is possible that these patients contribute to the discrepancy between the autopsy incidence (1:1000) of pheochromocytoma and the frequency with which the diagnosis is made, though the similar incidence in cases undergoing sympathectomy, as explained earlier, would argue against this.

Localization of pheochromocytoma. The IVP with nephrotomography remains a useful initial method of localization of the pheochromocytoma. With plain IVP in the Mayo Clinic series of 76 patients (Gifford *et al*, 1964), the IVP

accurately diagnosed and localized about 23% of cases. Pickering *et al* (1975) have published considerably more optimistic figures. The following four procedures were compared for the localization of adrenal cortical tumors and pheochromocytoma: (1) conventional excretory urography (50 ml IV Renovist II), (2) excretory urography with tomography (50 ml IV Renovist II and tomography), (3) infusion excretory tomography with tomography (300 ml IV infusion Reno-M-DIP), and (4) bolus nephrotomography (80 ml rapid IV 90% Hypaque-M). The results are shown in Tables 21 and 22. All films were reviewed to see if tumors were missed at the time of the original interpretation. There was a 10-15% increase in the yield after this review. 48% of pheochromocytomas were identified with routine urography and 91% were identified by bolus nephrotomography--a considerable improvement over previously reported results. The major data missing from this paper, however, is a comment about false positive results. It also appears that the skill of the radiologist in appreciating subtle factors such as slight depression or rotation of the kidney is of considerable importance. The bolus nephrotomogram appeared to be superior to the infusion nephrotomogram by virtue of its greater ability to demonstrate tumor vascularity during the vascular phase of the procedure.

Adrenal Tumors Identified by Excretory Urographic Methods Before and After Review

	No. of Patients Examined	Tumors Seen Before %	After %	Total No.	%
Without tomography					
Conventional excretory urogram	47	40	13	25	53
With tomography					
Excretory urogram	27	70	11	22	81*
Infusion excretory urogram	64	77	9	55	86
Bolus nephrotomogram	33	82	15	32	97

* $P < 0.02$.

Table 21

Tumor Types Identified by Urographic Methods After Review

	Pheochromocytoma	Cortical Adenoma	Cortical Carcinoma	Total
Without tomography				
Conventional excretory urogram				
Examinations	23	14	10	47
Tumors seen, %	48	29	100	53
With tomography				
Excretory urogram				
Examinations	15	7	5	27
Tumors seen, %	73	86	100	81
Infusion excretory urogram				
Examinations	38	18	8	64
Tumors seen, %	79	94	100	86
Bolus nephrotomogram				
Examinations	11	11	11	33
Tumors seen, %	91	100	100	97

Table 22

In the past, presacral retroperitoneal pneumography was utilized to attempt to localize the pheochromocytoma. However, this procedure can be quite dangerous and with the advent of arteriography, it is no longer used. At the present time arteriography is the major diagnostic tool used for the localization of pheochromocytoma (Rossi *et al*, 1968; McGarity *et al*, 1971). The routine use now of the transfemoral route has made the procedure considerably safer than the translumbar route utilized in the past. Localization of the tumor is quite valuable to the surgeon in view of the appreciable incidence of bilateral and extra-adrenal pheochromocytomas. Small extra-adrenal tumors may be difficult to locate by palpation at the time of surgery because their consistency is somewhat soft due to their extreme vascularity. A large volume of contrast media is generally injected into the aorta at the level of the T-12, L-1 vertebral bodies

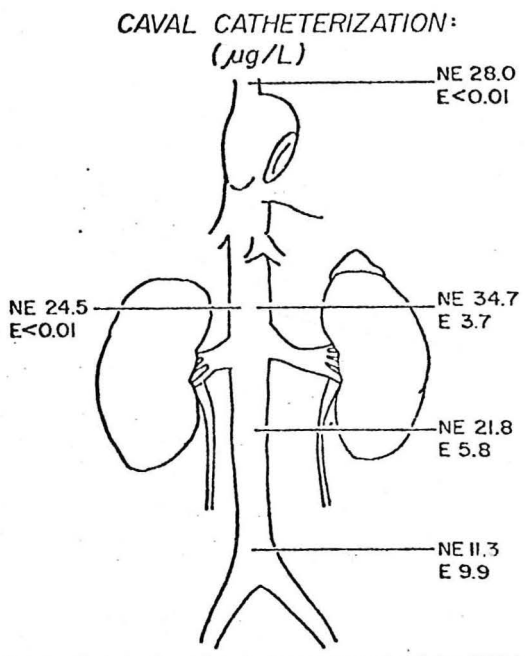
in order to fill the small vertebral vessels, which may be feeding a pheochromocytoma. If the aortogram does not give sufficient radiographic detail, or if a suprarenal artery appears to be hypertrophic, but no tumor stain can be identified in the capillary phase, selective catheterization of the inferior phrenic artery, middle suprarenal, or renal artery is done. The inferior phrenic artery supplies the superior suprarenal, and it arises from the aorta or from the iliac artery. The middle suprarenal artery usually arises directly from the aorta while the inferior suprarenal artery arises from the aorta or from the renal artery. In a review of arteriographic results by Rossi *et al* (1968), the major factors felt to lead to false negative arteriography were: (1) the amount of contrast medium in the aortagram was not sufficient for visualization of small arteries; (2) the tip of the catheter was placed below the renal arteries preventing adequate filling of the vessels above; (3) selective catheterization was not performed.

Some investigators contend that thoracic and pelvic arteriorgraphy should be done in conjunction with abdominal aortography in order to detect those patients who have extra-adrenal or multiple pheochromocytomas (Campbell *et al*, 1974). This would appear to be particularly applicable to children with pheochromocytoma but not necessarily true for all cases of pheochromocytoma. Certainly in those cases where a diagnosis is not made with the abdominal aortogram and selective arteriograms, it is prudent to look in these other sites. Meaney and Buonocore (1966) have stated that the occurrence of a hypertensive response during selective arteriography may help localize a pheochromocytoma even if it is not visualized. However, Rossi *et al* (1968) reported that 8 of 52 cases without pheochromocytoma were noted to have wide fluctuations in the blood pressure during the arteriographic procedure. Thus, it would appear that simply finding a hypertensive response during an arteriogram does not serve to identify a patient with pheochromocytoma. The mechanism by which the injection of contrast material precipitates a rise in the blood pressure with pheochromocytoma is unclear. Usually, the rise in blood pressure will occur within ten seconds after the completion of injection. It would, thus, seem that the contrast material produces a direct release of catecholamines stored in the sympathetic nerve endings or stimulates the tumor directly to release catecholamines.

Adrenal venography has also been utilized for the localization of pheochromocytoma (Nakada *et al*, 1973). A small percentage of pheochromocytomas will be so small that they will not be demonstrable by arteriography but will still be intra-adrenal. This technique would seem to be most useful for these few patients. However, it must be noted that the technique of adrenal venous catheterization, particularly of the right adrenal vein, is quite difficult and, thus, requires the assistance of an expert angiographer. In addition, an occasional complication of adrenal venography is the development of necrosis of the adrenal or of the pheochromocytoma subsequent to injection of too much contrast material or injection at too rapid a rate. This complication may be particularly threatening in the patient with pheochromocytoma. There has been one experience at Parkland Hospital after adrenal venography of not having satisfactorily evaluated the adrenals at the time of surgery because hemorrhage in the adrenals subsequent to the venography made them appear to be enlarged bilaterally, suggestive of bilateral pheochromocytomas. Bilateral adrenalectomy was done, but no tumor could be found with histologic examination. Thus, selective adrenal venography for the identification or localization of pheochromocytoma appears to have a rather restricted place.

In contrast to selective adrenal venography, regional venous sampling for the localization of pheochromocytoma has proved quite helpful in patients who

have recurrent pheochromocytomas after the first operation or in those patients in which a pheochromocytoma cannot be localized by arteriography before the first operation. The sites of venous sampling are depicted in Figure 21 (Harrison and Freier, 1974). It should be emphasized that no attempt should be made



Caval catheterization values in Case 1. Norepinephrine (*NE*) levels suggest a lesion near the hilum of the left kidney and this proved to be true. Increased content is also apparent in the superior vena cava sample.

figure 21

to selectively catheterize either of the adrenal veins. There are considerable fluctuations in adrenal vein catecholamine content from moment to moment, and criteria for abnormality of catecholamine content in the adrenal veins have not been established. Thus, it is mandatory that these samplings from the inferior vena cava be done just above the renal veins on both sides. Several limitations to regional venous sampling, however, must be realized. The superior vena cava sampling may be quite high, thus suggesting the possibility of a pheochromocytoma in the region of the neck or head. However, since the azygous vein empties in this area, the increased catecholamine content may actually be coming from the abdomen. In addition, a pheochromocytoma has occasionally been localized to the wrong side with the samples taken just above the renal veins because of venous streaming from one of these veins toward the other side of the inferior vena cava.

Pheochromocytomas have also occasionally been noted with sonography, with an optimistic prediction that any tumor at least 3 cm in size should be able to be detected (Birnholz, 1973). In addition, one case has been reported in which the tumor was seen during the flow (vascular) phase of a renal scan (Petrocelli and Wetzel, 1975). Neuroblastomas have been visualized with 99 m TC-Diphosphonate scanning (McCartney *et al*, 1976), but pheochromocytomas have not yet been reported to take up this scanning agent.

Medical Therapy: Therapy of pheochromocytoma. Treatment of the hypertensive crisis is best accomplished with nitroprusside or Regitine (phentolament) (Gitlow *et al*, 1971). Propranolol should be given IV if the pulse rate increases excessively secondary to the alpha blockade. It should be noted that propranolol should never be given by itself to patients with pheochromocytoma because the ensuing beta blockage then leads to a relative increase in alpha receptor activity, causing significant elevations in the blood pressure. Any of the catecholamine depleting antihypertensive agents such as reserpine, guanethidine, methyldopa, or clonidine can lead to an increase in blood pressure response in the patient with pheochromocytoma since a state of denervation hypersensitivity may be established which is then sensitive to a sudden catecholamine release by the tumor. Thus, it is essential that the diagnosis of pheochromocytoma be established relatively early in the course of the hypertension, and exceedingly labile or refractory hypertension should be considered an indication for further work-up for a pheochromocytoma. If significant doubt exists about the diagnosis, and the blood pressure is markedly elevated, a brief trial of Dibenzyline (phenoxybenzamine) therapy should be given until the test results are back. With mild hypertension and a suggestive history, diuretics alone should be utilized while test results are pending. Regitine has traditionally been the mainstay of treatment of hypertensive crisis, and a marked fall in the blood pressure with Regitine is of considerable initial diagnostic significance for pheochromocytoma. However, nitroprusside now appears in general to be a more useful agent since it does not present the problem of reflex tachycardia, and it can be titrated somewhat more precisely because of its exceedingly brief duration of action (Csanky-Treels *et al*, 1976). At the time that the patient with pheochromocytoma presents with severe hypertensive crisis, it is not at all uncommon for the blood pressure to be exceedingly labile because intense vasoconstriction is occurring in the setting of decreased plasma volume in many cases. Therefore, the patient may alternate between severe hypertension and hypotension. Nitroprusside or phentolamine therapy should be titrated very carefully during the initial phase and if excessive lability of the blood pressure is encountered, it is probably advantageous to slightly expand volume with saline, plasma, or albumin. Once it becomes apparent that a dramatic response to Regitine has occurred, and the diagnosis of pheochromocytoma seems quite likely, it is best to initiate oral Dibenzyline (phenoxybenzamine). This oral preparation will then begin acting within a period of a few hours to smooth the blood pressure control. Dibenzyline is a very long-acting alpha blocker which appears to be absorbed to some extent into fat, which may explain its very long duration of action. For this reason, it generally can be given only once or twice per day. Generally, treatment can be begun with 20-30 mg/day and progressively increased. Some patients with pheochromocytoma require 150 mg/day. The most common side effects indicating excessive toxicity are nasal congestion, sedation, orthostatic hypotension, excessive dryness of the mouth, and visual symptoms such as diplopia. Many patients experience mild side effects in order to attain good blood pressure control. Dibenzyline commonly leads to a reflex tachycardia which can be easily treated by the addition of propranolol (10-40 mg qid). Medical therapy with Dibenzyline plus propranolol can be continued for many years in those patients who have malignant pheochromocytoma or multiple pheochromocytomas which cannot be adequately localized and removed.

Surgical treatment. Surgical mortality in pheochromocytoma was reported to be as high as 25-45% in the pre-1950 era (Apgar and Papper, 1951). More recent series such as a series of 46 cases from the Cleveland Clinic (Deoreo *et al*,

1974) have reported no mortality and only minimal surgical morbidity. This striking decrease in mortality rate has been accomplished through a number of developments: (1) a realization that preoperative preparation of the patient with an alpha blocker such as Dibenzyline greatly diminished the extent of the intraoperative hypertensive crises and allowed restoration of the decreased plasma volume which is characteristic of many patients with pheochromocytoma, (2) improvement in the anesthetic agents utilized, (3) development of techniques to localize most tumors prior to surgery, (4) development of better pharmacological agents to control the blood pressure, arrhythmias, etc., and (5) a general improvement in surgical and monitoring techniques. In the series of patients from the Cleveland Clinic, a decreased plasma volume was noted in most patients (Deoreo *et al*, 1974; Figure 22). The plasma volume has been adjusted for height, not weight. Other determinations of plasma volume which have been based upon body weight (Sjoerdsma *et al*, 1966) have not shown a decrease as commonly. However, the clinical experience with patients with pheochromocytoma tends to indicate that most patients, indeed, have a decreased plasma volume. The exact duration of preoperative preparation with Dibenzyline, often in combination with propranolol, depends upon the individual patient, but in general it requires at least several days and, optimally, about 2 weeks. The hematocrit can be followed serially with Dibenzyline therapy to gauge the extent of plasma volume expansion before surgery. Those patients that have the greatest fall in hematocrit are probably those patients who would be most likely to require blood or plasma volume expanders at the time of surgery. In general, patients with more severe sustained hypertension are more likely to have a decreased plasma volume. Some groups have contended that two units of blood should routinely be given to all patients with pheochromocytoma immediately preoperatively (Deoreo *et al*, 1974). However, there is no data which supports this contention, and it would appear at the present time that blood need not be given routinely preoperatively. Blood and plasma volume expanders should be given readily during the period of surgery, especially immediately after the pheochromocytoma is removed.

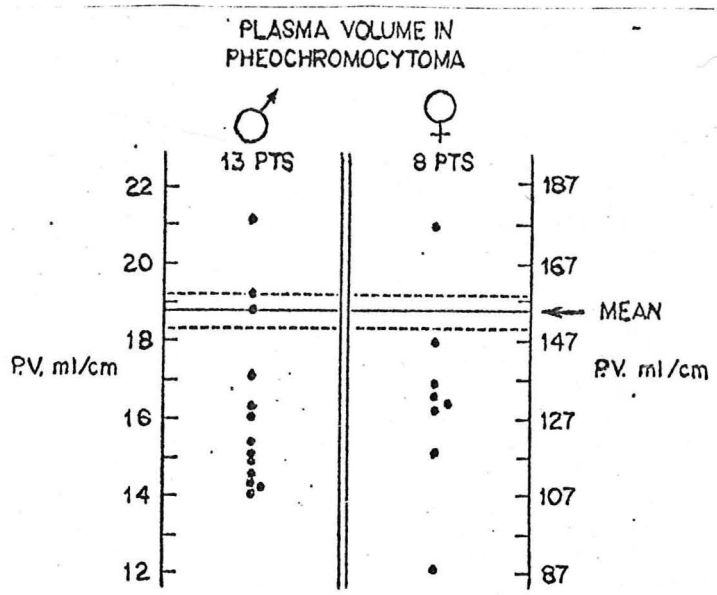


figure 22

Newer anesthetic agents have contributed to the decrease in the mortality rate and ease of patient management. Crout and Brown (1969) reported a series of 14 patients from Parkland Hospital managed with methoxyflurane (Penthrane). In 12 cases they noted a remarkable freedom from ventricular arrhythmias with this anesthetic agent in comparison to halogenated hydrocarbons such as halothane.

A newer anesthetic agent, Ethrane (enflurane), appears equally effective to methoxyflurane but is somewhat less toxic (Kopriva and Eltringham, 1974; Ortiz and Diaz, 1975). It, thus, appears to be the anesthetic agent of choice at the present time. At one time it was contended (Gitlow *et al*, 1971; Cooperman *et al*, 1967) that halothane was an ideal anesthetic agent, even though it resulted in a high incidence of ventricular arrhythmias, because it had an inherent property of lowering the blood pressure. However, with the use of nitroprusside for the intraoperative control of blood pressure, it would appear that this theoretical advantage is no longer tenable and that Ethrane is the anesthetic agent of choice. At the time of surgery the patient should have EKG, central venous and intra-arterial pressure monitoring, and a foley catheter should be placed to accurately monitor urinary output. Anesthesia is best induced in all patients with thiopental. All blood losses during surgery should be immediately replaced and a sufficient volume of lactated Ringer's solution should be given to maintain a urine flow of 60-100 ml/hr. Other volume expanders such as plasma or albumin may be given at the time of surgery.

At the time of removal of a pheochromocytoma there is usually a marked fall in the blood pressure and if the patient has not had satisfactory preoperative and operative restoration of plasma volume, there may be profound hypotension requiring large amounts of volume replacement in combination with vasoconstrictors such as phenylephrine or norepinephrine. For example, Salo and Laaksonen (1972) report that a patient who had not been prepared preoperatively required a total of 7,450 ml of fluid during the hypotensive crisis that arose after removal of the tumor with the administration of norepinephrine for two days to support the blood pressure. Thus, these problems can be dramatically prevented by proper preparation of the patient in the preoperative period. One problem which has ensued, however, with the use of preoperative Dibenzyline preparation has been the failure of the blood pressure to remain elevated if another smaller pheochromocytoma is left behind at the time of surgery. In the series of patients reported by Crout and Brown (1969), all patients responded with a hypertensive response during the time of anesthesia. Thus, preoperative Dibenzyline therapy did not totally block all effects of catecholamine release by the tumor and/or sympathetic fibers. However, two of 11 patients who had second pheochromocytomas did not have a rise in their pressure after removal of the first tumor. For this reason, it is mandatory that the surgeon very carefully explore the entire abdomen for other pheochromocytomas. In general, even in the face of preoperative alpha blockade with Dibenzyline, palpation of a second pheochromocytoma in the abdomen will result in a rise in the blood pressure. This, then, facilitates localization of other tumors.

If postoperative hypotension occurs, a common cause is intra-abdominal hemorrhage. Preoperative preparation with Dibenzyline ameliorates the vasoconstrictor response at the time of surgery, thus leading to persistent oozing of blood from the operative site. Ventricular arrhythmias during the time of surgery are usually best treated with intravenous propranolol or lidocaine. However, with Ethrane anesthesia these arrhythmias have been distinctly less common. Postoperatively, the patient should be followed with serial determinations of urinary catecholamine metabolites for the possibility of recurrence of a pheochromocytoma. A significant percentage of patients with previous sustained hypertension from the pheochromocytoma will have a mild sustained hypertension postoperatively, probably secondary to renal damage (Sander *et al*, 1971). This hypertension can then be managed with the usual drugs for essential hypertension.

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