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PHEOCHROMOCYTOMA*

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PHEOCHROMOCYTOMA, a tumor of the chromaffin sympathetic nerve tissue, formerly considered to be very rare, seems to be now more frequently recognized than before, if one may judge from reports in the literature.

Recently it has been shown that these tumors produce the pressor catechols, epinephrine and norepinephrine in variable excess quantities and that these substances produce the hypertensive symptoms. Also in addition, pharmacological tests have been described, some stimulating the release of the pressor substances and others combating their effects, when they are present in excess amounts. From the use of these tests a more probable diagnosis was possible among the various hypertensives and enough tests have been performed to estimate their value. In addition, quantitative estimation of the catechols in the urine is now possible, not with too great a degree of accuracy but sufficiently accurate for a correct diagnosis. Also the more widespread use of retroperitoneal gas insufflation has definitely helped the location of the site of the tumor. Also, for this purpose aortograms and venograms have been done. Lastly,

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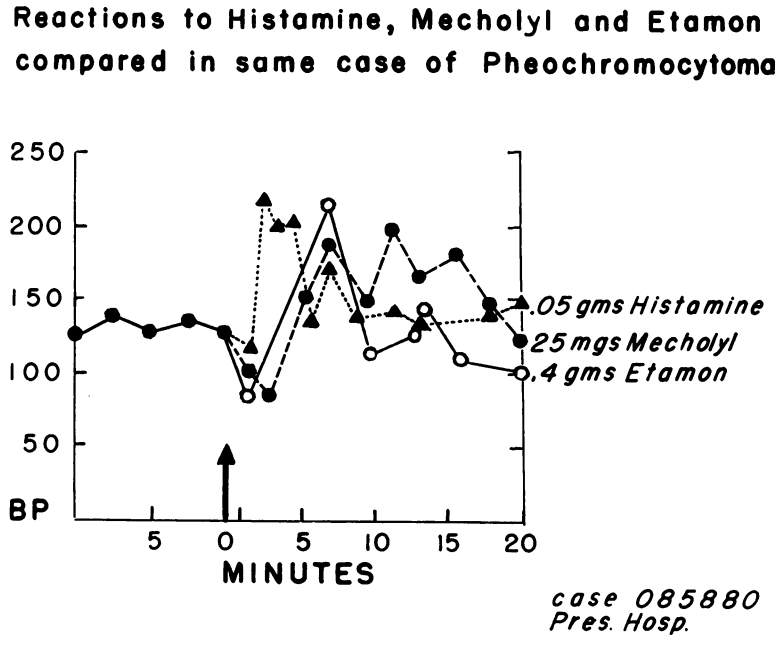

Chart 1. Blood pressure readings after injections of histamine, Mecholyl and Etamon given to the same patient at different times. From this it can be seen that histamine acts quicker and the effect is shorter.

experience with the chemical control of the symptoms has greatly improved the therapeutic operative removal.

From a survey of 139 cases in which the exact location of the tumor was stated, the occurrences were as follows: Right adrenal seventy-two, left adrenal forty-four, both adrenals thirteen, interthoracic four, intercerebral one, right aortic ganglia two, left inferior aortic ganglia, and Zuckerkandl's ganglia two. The tumor is most frequently seen in adult life, although the ages have ranged from sixteen months to eighty-two years. Only seven cases have been reported in children up to 1951. The ratio of sex occurrence was females seventy-two, males fifty-five. There is a family tendency in some cases and about 5 per cent have coincidental cutaneous neurofibromatosis, which also has a familial tendency. Of 121 cases in which race was mentioned only two occurred in Negroes. Other endocrine disorders occur with the syndrome, thyroid pathology, Addison's disease, adrenogenital syndrome and Cushing's adreno-cortical syndrome have been reported. About 16 per cent of the cases have multiple tumors, usually two, and only very rarely more. Most of the tumors are

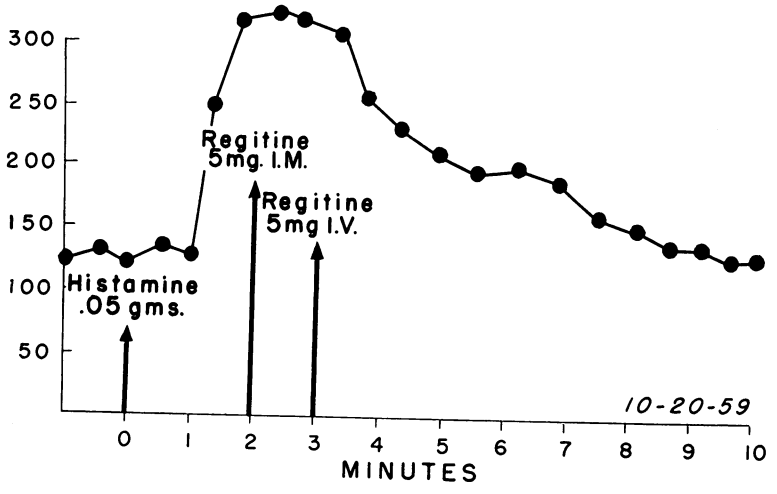

Chart 2. A case in which the reaction to a histamine injection was of such intensity that it was necessary to reverse the effect by intramuscular and intravenous injections of Regitine.

benign. Of the 8 per cent reported as malignant, some have hypertensive symptoms only at the onset, some during most of their existence and a few no hypertensive symptoms at any time.

It had been the accepted explanation that the occurrence of hypertension in these cases was due to an excess secretion of epinephrine. Holton,[1] however, reported that they secrete both epinephrine and norepinephrine. These observations were confirmed by Goldenberg and his co-workers[2] and they have shown that in a fairly large number of cases the norepinephrine excretion may range from 50 to 90 per cent of the total catechols present. A continued study by them again showed a marked difference in the effect of these substances in normal humans. With epinephrine there was an increase in cardiac output with a fall of over-all peripheral resistance. They postulated that there was a vasodilation of the vascular bed of the muscles which outweighed the vascular constriction of the skin, mucous membranes and the splanchnic area. They found an uniform increase in the heart rate. There was an elevation of the glycogenolytic rate and of the basal metabolism. With norepinephrine, in contrast, there was little change in cardiac output, but a constant significant rise in over-all peripheral resistance. There was less or little effect upon the pulse rate, the glycogenolytic rate and the basal metabolism. They found that when both catechols were simultaneously

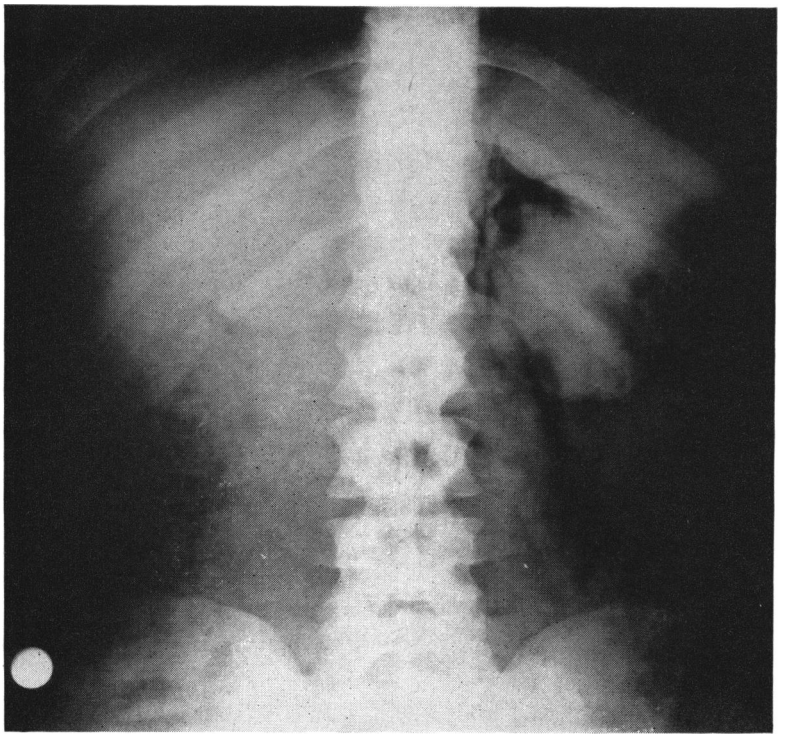

Chart 3. An air insufflation x-ray in a case of a pheochromocytoma arising from the left adrenal and growing in front of the left kidney. The low density of this tumor is beautifully brought out by the perfect circle of air outlining the tumor and that the upper pole of the kidney can be seen through the much less dense tumor. Most pheochromocytomas are of similar low densities and often give a negative shadow so to speak, rather than the denser positive shadows seen with adrenocortical tumors.

infused in equal amounts, their cardiovascular actions were antagonistic rather than augmentive. The vasoconstrictor action of norepinephrine was either nullified or over-balanced by the over-all vasodilator action of epinephrine. The clinical effects of their studies were striking. A normal subject receiving an infusion of norepinephrine, sufficient to produce a well marked increase in both diastolic and systolic blood pressure was mostly completely unaware of his blood pressure changes, and resembled in this respect a patient with essential hypertension. Whereas in contrast, infusions of epinephrine were almost always accompanied by headache, palpitations and an unpleasant feeling of anxiety and sweating. From these studies it can be reasoned that the secretion of various amounts

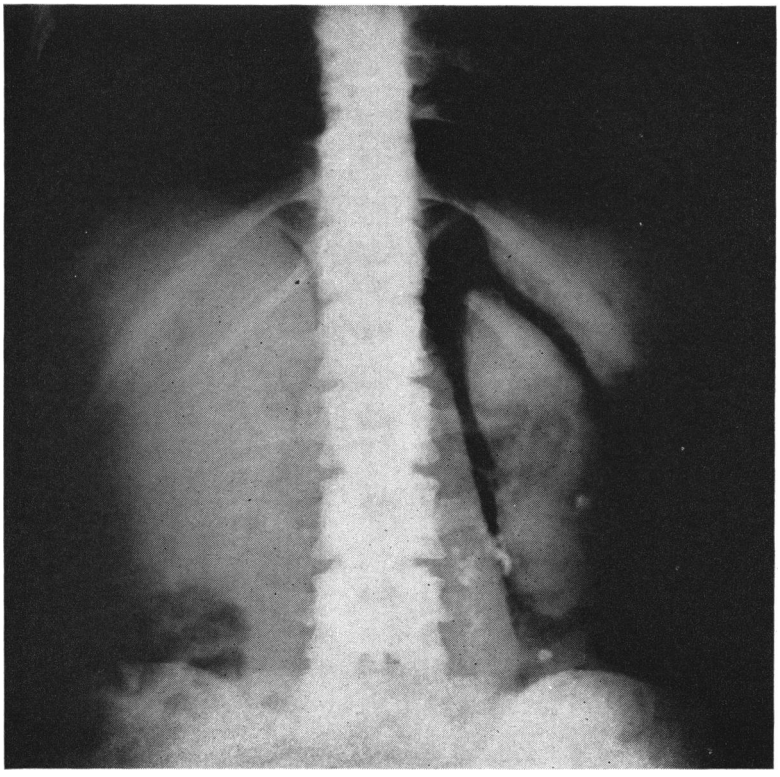

Chart 4. An air insufflation x-ray showing a large and somewhat denser tumor above the right kidney. The air outlines the left kidney beautifully but the fascial spaces on the right are pressed upon firmly by the tumor so that the air does not infiltrate very well.

of these active principles may produce a wide range of clinical phenomena. Such has occurred with these tumors and the variables were without explanation until these experiments were reported.

Symptoms

The symptoms may be simply classified into the silent, the paroxysmal, and the continuous hypertensive.

The Silent: An individual may go through life with a pheochromocytoma and never experience any effect of its presence. It may be discovered accidentally by x-ray, at operative exploration or at autopsy apparently unrelated to the cause of death. Fatal intraperitoneal hemorrhage has occurred with right adrenal tumors, also without any other symptoms.

These tumors from section and assay contain both pressor catechols but in some fashion, whether in the absence of a trigger release mechanism or some reason of the situation of the tumor, the individual gives no history of any relating symptoms.

In some, without symptoms, death may occur with a slight trauma. Again a pressor attack may occur with an operative procedure unrelated to the tumor. Not infrequently an anesthesia has precipitated the pressor attack in an unsuspected case. The occurrence of such pressor attack, if possible should cause abandonment of the operative procedure until the cause of the pressor attack has been ascertained.

The Paroxysmal: The first description of the syndrome was that of "paroxysmal hypertension." This is not always indicative of a chromaffin tumor. Similar crises have been described in eclampsia, lead poisoning, essential hypertension, nephritis, aortitis and various diseases of the nervous system such as epilepsy, traumatic or vascular damage to the brain or the meninges and also in tabes dorsalis. Tumor apparently has not occurred with these disorders. However most people who have a tumor with paroxysmal symptoms have been treated usually under various diagnoses until the true cause was ascertained. These were essential hypertension, cardiac neuroses, hyperthyroidism, diabetes mellitus and renal tumor.

The paroxysmal hypertension occurs in 30 to 40 per cent of the known tumor cases. When the attacks occur they are acute, unpredictable, and lasting from a few minutes to several hours. The palpitation and headache may overshadow the other symptoms. There is apprehension, anxiety and restlessness. The extremities may become cold and pale. There is an increase in the pulse and a marked rise in both systolic and diastolic pressure. The attack ceases with marked sweating, fall of blood pressure and a feeling of exhaustion. There is often a rise in the blood sugar and the appearance of glycosuria. Hypermetabolism is present as well as some changes in the electrocardiograph. With a complete picture of such a clinical phenomenon in an apparently normal individual, the diagnosis is often tenable and then with specific tests the presence of a secreting tumor may be proven. The attacks are most often similar each time, but may slowly increase in frequency, severity and duration, progressing with the growth of the tumor.

A differential diagnosis of tumor from psychoneurosis and hysteria offered difficulties in the past until the specific tests were devised. In

children there have appeared paroxysmal crises associated with metabolic reactions, but with no tumor present. Some of these resemble the disturbances in the diencephalon described by Penfield.[3] As a rule since paroxysmal hypertension was the symptom first described and apparently "labeled" as pheochromocytoma, the large number of these cases are those in which provocative tests have been frequently used and these cases are not usually missed.

The Persistent Hypertension: It is most likely that by the time a diagnosis is arrived at, persistent hypertension is the more frequent type of hypertension seen with a tumor. This is supported by Green[4] who has shown that over 70 per cent of his collected cases had more or less continuous hypertension. It is in the large group of persistent hypertensives seen that a special effort must be made to exclude pheochromocytoma. What hypertensives should arouse the suspicion of pheochromocytoma? First, hypertensives who have at times symptoms suggestive of crises; second, all those hypertensives who have an elevated basal metabolism; third, a hypertensive who also has at times an elevated blood sugar and glycosuria; and fourth, those hypertensives in addition who have associated severe sweating. The presence of most or all of these symptoms requires the use of a specific test to eliminate pheochromocytoma.

A persistent hypertension may occur with no suggestive symptoms and still in a rare case be associated with tumor and cured by the removal of the tumor. Certainly before any severe operative attempt at correction, as a lumbo-dorsal sympathectomy, is undertaken, all persistent hypertensives should be given a trial run with Benzodioxane or Regitine.

Specific Tests

Provocatives: Histamine: Roth and Kvale[5] reported the use of intravenous 0.05 histamine base to precipitate the secretion of an excess amount of pressor substance in pheochromocytoma. They showed that with tumor, after a short initial drop, there was a marked rise in systolic and diastolic pressure with all the symptoms of a pressor attack. The reaction is short and the blood pressure returns to its former levels. Repetition produces similar results. The test should be given only in a patient without sedation. This test when properly performed, when tumor is present, is very reliable and its value has been repeatedly confirmed. A few cases have given a negative reaction and later proven to have tumor, with as

yet no clear explanation. In hypertensives without tumor, especially in psychoneurotics, a reaction has been seen resembling that of tumor but with a slower rise and of more sustained and prolonged duration. The possibility of excess catechols causing such a reaction awaits investigation. In some tumor cases with severe reactions due to the size of the tumor, the use of histamine must be guarded and Regitine must be available to prevent a catastrophy.

Mecholyl bromide, introduced by Guaraneri and Evans[6] in doses of 25 mgm. subcutaneously will incite a paroxysm of hypertension in patients with pheochromocytoma. The accuracy of this test has been confirmed by others as well as by ourselves. H. Aranow, Jr.[7] modified the test for safety purposes by including .001 gm. atropine sulfate parenterally previous to the test to prevent serious reactions that may occur unless the parasympathetic effectors are previously blocked.

Etamon (tetraethyl ammonium bromide) reported by LaDue and his co-workers[8] produces a paroxysmal rise in the blood pressure in pheochromocytoma. The advantage of the test is that the extent of the rise may be controlled by changing the position of the patient. It is a longer acting agent than histamine and has been stated by Roth to be less reliable.

We have found all three provocatives reacting as described in cases where tumor was proven and that after removal of the tumor, all three had no reaction. We have had a greater experience with histamine and because of the experience believe that it may be more reliable. The variables of the reaction are shown in the accompanying chart.

Antagonists: Benzodioxane (piperoxan) introduced by Goldenberg,[9] the first used, has had a wide use and its value established. It is of importance in distinguishing persistent, essential hypertension from the continuous hypertension seen with pheochromocytoma. In a patient with the tumor, the drug is introduced intravenously and has a predominately depressor effect in which both systolic and diastolic blood pressure falls significantly and rapidly and soon returns to or above its previous reading. In patients with blood pressure elevation due to other reasons besides pheochromocytoma, there occurs no change or a pressor change in which the blood pressure rises. In these there may also occur flushing and tachycardia. The accuracy of Benzodioxane has been well established. There have been several cases reported in which a positive reaction was obtained and no pheochromocytoma found. Cases have been

reported with no reaction in paroxysmal hypertensives with tumor when injected in the quiescent state. This is the expected reaction in those instances. Conley and Junkerman[10] reported a negative reaction in a continuous hypertensive and a proven tumor. It may be assumed that other pathological conditions may be present that have influence upon the pressure changes. Since the depressor effect of Benzodioxane is only effective when the elevated pressure is due to the presence of excess catechols and to date excess catechols in the blood in quantities have been seen only in association with pheochromocytoma, the specificity of the test must be recognized.

Dibenamine (NN dibenzyl betachlorethyl amine) was first used for study on man by Hecht and Anderson.[11] This drug was shown to have marked sympatholytic effect upon the muscle nerve endings in the smaller arterioles. This marked over-all depressor effect may last for twenty-four to forty-eight hours. During the period of depressor effect, the sympathetic system may be unresponsive to the necessary pressor catechols to prevent a complete collapse. This drug has not been used for diagnosis because it has a depressor effect in both normals and in the hypertension of pheochromocytoma. Its use has been mostly confined to the therapeutic control in operative procedures.

Regitine (C7337) reported by Grimson and co-workers,[12] is used both for its diagnostic help and as a therapeutic aid at the time of operative removal of the tumor. It produces a more pronounced and more prolonged reduction in blood pressure than Benzodioxane when used for diagnostic purposes. Its therapeutic effect is more effective than Dibenamine because it is less toxic and more easily controlled. False positive tests have occurred in cases with uremia. The administration of Regitine may be intramuscular or intravenous.

Experience with these three drugs has shown the value of both Benzodioxane and Regitine each within a specific area and it is most probable that they will be in continued use, unless supplanted by the estimation of the catechols in the urine.

Demonstration of Pressor Substances: The first report was that of Ernould and Picard in 1934[13] who claimed they identified a pressor substance chemically in the blood of a pheochromocytoma. Beer et al.[14] demonstrated pharmacologically a pressor substance in the blood of a tumor case during a hypertensive crisis. These two methods have not been of value in the diagnosis and some doubt has been raised as to the

interpretation of the tests. The tests as described were also too difficult for ordinary use.

More recently the identification of the pressor substances and a fair quantitative estimation of the various catechols have been done upon the urine in normals, the urine of ordinary hypertensives and the urine of the pheochromocytomas, both paroxysmal and with sustained hypertension. The use of various methods has been investigated by Goldenberg[15] who after experimenting with bio-assay and pharmacological methods, used an alum hydroxide extract and concentration of the 24-hour specimen of urine and by florometric determination found that in normal people it was not simple to separate the two catechols but estimated that roughly 10 per cent appeared as epinephrine and 90 per cent plus as norepinephrine and that the total was somewhere between 20 and 50 gamma (micrograms) in twenty-four hours. In essential hypertension he found excretions up between 75 and 100 gamma in twenty-four hours. The important great difference appeared in the sustained hypertension due to pheochromocytoma in which excretions varied from 600 to 2700 gamma in 24 hours. The paroxysmal cases varied, according to attacks or not, from 110 gamma to a top of 580. A report of this study is to be shortly made by Goldenberg. The simplification of the test for the excretion of the catechols in the urine and the preliminary report of the amounts eliminated in the various conditions if verified by experience, offer a simple and real positive diagnosis of the syndrome and will probably see the abandonment of the present chemical tests.

Radiography: In any hypertensive, the visualization of a tumor in the adrenal or in the area of a sympathetic ganglion strongly suggests the possibility of a chromaffin tumor. With a characteristic history and with positive specific tests, the visualization of a tumor is the next important step. A large tumor may show a shadow upon a plain abdominal film but this is rare with pheochromocytoma because they are usually of very low specific density, almost similar to cysts. Also most all the cases of pheochromocytomas do not have much fat, the syndrome producing loss of weight. Calcification is not frequently seen in these tumors. Pyelography has shown displacement of the kidney downwards by a tumor mass and in some a flattening of the upper pole of the kidney. Retroperitoneal gas as a diagnostic aid in localization of these tumors has now been used for years. First used perirenally through the flank by ourselves[16] and others in many cases, it has been used from the first to identify the

tumors on a film clearly. More recently the use of gas by the presacral route, introduced by Rivas,[17] has popularized the method. In a small tumor there is no better method than that of retroperitoneal gas. It must be stressed, however, that the demonstration of a pheochromocytoma is often of an ovoid or circular shadow less dense than the other tissues and the opposite of the adrenal cortical tumors which most often are dense like renal tissue. Extra- adrenal pheochromocytomas have been outlined by retroperitoneal gas. In several cases in which the tumor was near the aorta and under pressure, failure of the gas to infiltrate into that region suggested the probable site of the tumor. Interpretation of retroperitoneal gas insufflation films needs experience in order to be correct. Laminographic x-rays have successfully shown these tumors. We have had many confusing shadows with hypertension in cases with negative specific tests. Exploration of some of these showed the shadows to have been due to a retroperitoneal spleen displacing the kidney or a pancreatic cyst across the pole of the kidney and several times a retroperitoneal lipoma. Aortograms, first used to show an adrenal tumor by dos Santos, have been used by others and ourselves and have been of less value to date than retroperitoneal insufflation gas x-ray. Venograms have been reported as used by Goodwin.[18] Most of these tumors have been almost cystic and of no uniform pattern of vascularity and, with expansion of a venous system without the tumor and from our vascular studies, we have not had the assurance in interpretation that is present in the round or ovoid mass defined by gas. The intrathoracic tumors have been all clearly shown by x-ray, the lung conveniently supplying the contrasting air. Because of the possibility of an intrathoracic tumor being present, all cases of suspected pheochromocytoma should have such films made.

Therapy

The treatment of pheochromocytoma is complete removal of the tumor or tumors if more than one is present. If completely removed, the patient is relieved of all symptoms and signs. The success of the operation is due to the planning of the procedure. Two adrenolytic agents have been used for the therapeutic effect in the operative handling: Dibenamine and Regitine.

Dibenamine has been used in amounts of 5 to 7 mgm. per kilo of body weight given in an infusion of 300-500 cc. of saline slowly for one hour. The action is a sympatholytic effect up to forty-eight hours.

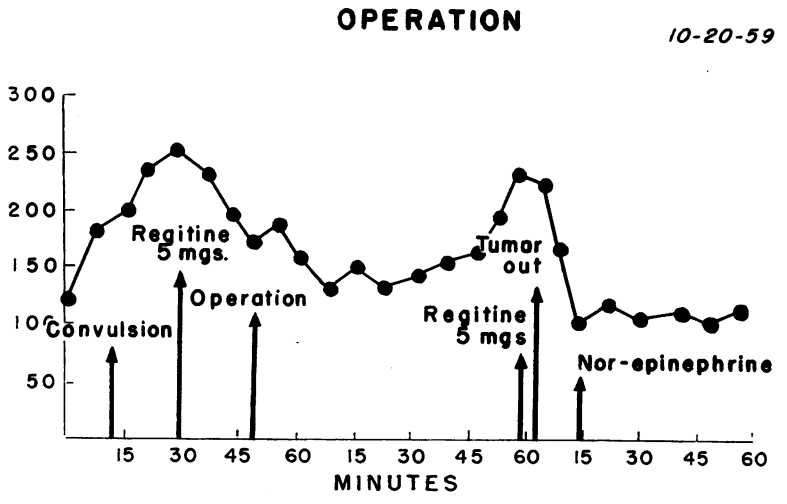

Chart 5. The operative chart of the removal of the tumor seen in chart 3. This large tumor with a severe paroxysmal type syndrome had severe convulsions on beginning of the anesthesia which were controlled by Regitine and later the drop in blood pressure after removal of the tumor was controlled by norepinephrine.

It has been used with severe cases of hypertension with pheochromocytoma, preoperatively to condition the patient for operation. During the prolonged action of lowered pressure, the patient is free from hypertensive crises, rests and improves with nourishment. So used, marked improvement has occurred in severe cases where emaciation and exhaustion have been present. The beneficial effect of Dibenamine has been reported by Spear and Griswold, [19] by Hoch,[20] by Cahill and Montieth[21] and others. Side effects of the drug may occur and cause cessation of the treatment; partial hemiplegia and loss of sensation have occurred, both temporary. Tetany has occurred, relieved by calcium gluconate. It has been customary to proceed with the operative effort at the later part of the period of the depressor effect. While this effect is still present, manipulation of the tumor is possible, without the sometimes fatal effect of excess catechols. However, operation during the maximum pressure effect eliminates a diagnostic aid, namely the rise in pressure that occurs in the handling of a tumor of pheochrome tissue. In addition the use of Dibenamine has a major risk, in that on removal of the tumor a marked fall in blood pressure usually occurs and this fall may be reversed by norepinephrine, but in the presence of Dibenamine, such reversal is not

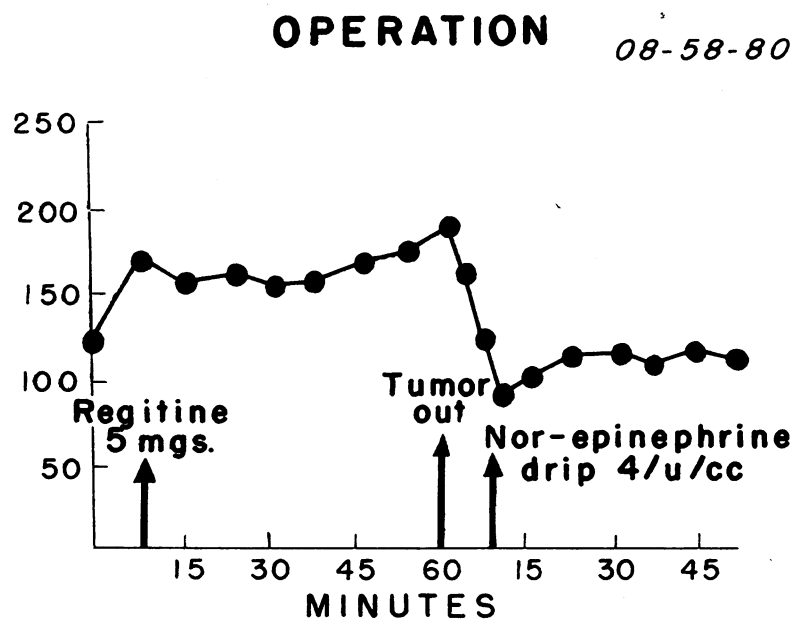

Chart 6. The operative chart of the case with x-ray in chart 4. A less severe case in a woman after childbirth in which one injection of Regitine and post-removal norepinephrine were needed.

possible and death may occur. Because of these effects, there is a necessary regulation of the timing in the injection of Dibenamine in relation to the operation. Enough effect must be present to allow manipulation of the tumor, but not too much to prevent the use of sustaining drugs. Use of Dibenamine is probably too risky compared with the safety and effects of the other adrenolytic drug, Regitine.

Regitine C-7337 (2(N-p-tolyl-N-(m hydroxy-phenyl)-amino methyl)-imidazoline hydrochloride) introduced clinically by Grimson and his co-workers,[12] given intravenously an hour or two before operation, in a 5 mgm. dose and then given intravenously during operation in a dosage of 0.08 to 0.33 gm. for each kilogram of body weight, to prevent paroxysms of hypertension, tachycardia, respiratory depression or convulsions or other effects of epinephrine intoxication, has apparently to date been the most satisfactory adrenolytic agent in operative procedures. It definitely has been safer and more satisfactory than Dibenamine. After the tumor is removed under Regitine administration, and the pressure falls, a reversal of this fall is possible by the administration of norepine-

phrine because Regitine will completely suppress the effect of epinephrine, but only partly the effect of norepinephrine.

The anesthesia problems in these chromaffin tumors[22] have been largely concerned with four important elements: adequate relaxation, the possibility of pneumothorax, the physiological effect of excessive secretion of epinephrine or norepinephrine during the manipulation of the tumor, and the sudden circulatory depression following its removal; no matter what the anesthestic regime, anoxia is to be avoided. Anoxia appears to be as potent a stimulant to medullary secretion as is tumor manipulation. Agents, which in the presence of epinephrine produce serious ventricular arrythmias are to be avoided. Cyclopropane, chloroform, and ethyl chloride are unwise choices for anesthesia. Basal avertine, ether and oxygen have been most frequently used.

Surgical removal of these tumors has been done successfully by all routes. These have included flank extraperitoneal approach without or with rib resection, either bilateral when the tumor has not been properly located, or unilateral if located. Thoracico-abdominal approach, as well as rib-flap retroperitoneal incisions, enjoyed a vogue for a while. Because of the possibility of these tumors being multiple (16 per cent) and because of their variable locations, the transverse, transperitoneal upper abdomen has in our hands been the most satisfactory approach. This has been especially so in the past in which with an original flank approach multiple tumors required two operative procedures for their removal. Experience since has enabled us to remove all the tumors at one stage with the transperitoneal approach. The value of adequate exposure is obvious, and with a wide exposure the blood supply to and from the tumor is easily severed before manipulation of the tumor. In large tumors, especially on the right side and if close to the vena cava, soft occlusion clamps may be necessary on the cava, above and below the tributary veins, before the tumor is handled. After removal of the tumor, the blood pressure often falls to surprisingly low levels, and this may be prevented by using an increasing amount of norepinephrine intravenously (.4 mgm. norepinephrine in 1000 cc. of saline). In two cases of pheochromocytoma associated with Cushing's disease, the patients were prepared in addition with high salt intake and desoxycortisone, which was the only adrenal steroid available at that time, and the operative procedure was successful. These tumors are usually in a fairly vascular bed and if large, control of hemostasis may be difficult and may require blood replacement.

CHART 7—PHEOCHROMOCYTOMA

Name	*Hosp. No.*	*Age*	*Year*	*Side and Type*	*Results*
J.B.	59936	59	1924	R—malignant	DIED—no operation
E.W.	312177	33	1932	L—benign	DIED—no operation
S.P.	438208	53	1934	R— "	DIED—postoperative
D.P.	542008	27	1938	L— "	" "
G.K.	41024	61	1939	R— "	" " spontaneous tumor hemor.
E.C.	600888	49	1940	R— "	cured
J.S.	657128	48	1941	R also Cush.	"
P.H.	690134	29	1942	R+Zuckerkandl	"
H.A.	623060	25	1943	R	no operation
D.B.	815439	10	1946	R+Zuckerkandl	DIED operation
J.L.	716125	13	1944	L+Retroperit.	cured
P.D.	844975	12	1946	R+Thoracic	"
K.G.	857560	42	1947	R	"
M.E.	965960	49	1949	L	"
H.B.	967974	41	1949	L	"
R.H.	085580	31	1952	R	"
A.G.	102059	26	1952	L	"

A chart summary of 17 cases of pheochromocytoma at the Presbyterian Hospital showing that in the beginning the disease was unrecognized and of course no attempt to save the patient by operative intervention was made. Next the disease was not diagnosed but operative attempts were made to correct a hemorrhage or a collapse without correction of cause. Later the condition was recognized and corrected with only one death in 1946 and none since. Specific diagnostic tests were used and chemical control of the operative procedures was used.

The tumors are bright pink red, soft, elastic and cystic. The weights vary according to size; and the tumors contain varying amounts of norepinephrine and epinephrine. After recovery has been accomplished and discharge is contemplated, a histamine test has been routine to show that no tumor tissue had been overlooked.

SUMMARY

The diagnosis of pheochromocytoma may be made by: (a) History and specific tests; (b) estimation of catechols in the urine; (c) demonstration and location of the tumor by gas insufflation x-rays.

The only successful treatment is operative removal. This has been made successful by: (a) An adrenolytic agent to prevent hypertensive

crisis on handling the tumor; (b) a replacement sustaining hypertensive substance to correct the hypotensive state that follows a removal.

The risk in these patients is in the operative procedure phase. The removal of the tumor cures the pressor syndrome and the prognosis is good in the large number of benign lesions.

REFERENCES

1. Holton, P. Noradrenaline in adrenal medullary tumours, *Nature 163*:217, 1949.
2. Goldenberg, M., Pines, K. L., Baldwin, E. de F., Greene, D. G. and Roh, C. E. Hemodynamic response of man to norepinephrine and epinephrine and its relation to the problem of hypertension, *Amer. J. Med. 5*:792-806, 1948.
3. Penfield, W. Diencephalic autonomic epilepsy, *Arch. Neurol. Psychiat. 22*: 358-74, 1929.
4. Green, D. M. Pheochromocytoma and chronic hypertension, *J. Amer. med. Assoc. 131*:1260-65, 1946.
5. Roth, G. M. and Kvale, W. F. A tentative test for pheochromocytoma, *Amer. J. med. Sci. 210*:653-60, 1945.
6. Guarneri, V. and Evans, J. A. Pheochromocytoma; report of a case with a new diagnostic test, *Amer. J. Med. 4*:806-13, 1948.
7. Aranow, H., Jr. Symposium on cardiovascular diseases; differential diagnosis of pheochromocytoma, *Med. Clin. N. Amer. 34*:757-67, May 1950.
8. LaDue, J. S., Murison, P. J. and Pack, G. T. Use of tetraethylammonium bromide as a diagnostic test for pheochromocytoma, *Ann. intern. Med. 29*:914-21, 1948.
9. Goldenberg, M., Snyder, C. H. and Aranow, H., Jr. New test for hypertension due to circulating epinephrine, *J. Amer. med. Assoc. 135*:971-76, 1947.
10. Conley, J. E. and Junkerman, C. L. Lack of specificity of piperoxan hydrochloride test for adrenal medullary tumors, *J. Amer. med. Assoc. 147*:921-23, 1951.
11. Hecht, H. H. and Anderson, R. B. Influence of Dibenamine (N_1N=dibenzyl=β=chlorethyl-amine) on certain functions of the sympathetic nervous system in man, *Amer. J. Med. 3*:3-17, 1947.
12. Grimson, K. S., Longino, F. H., Kernodle, C. E. and O'Rear, H. B. Treatment of a patient with a pheochromocytoma; use of an adrenolytic drug before and during operation, *J. Amer. med. Assoc. 140*:1273-74, 1949.
13. Ernould, H. and Picard, E. Un cas de sympathome sympathogonique avec hypertension artérielle paroxystique, *Rev. belge Sci. med. 6*:223-51, 1934
14. Beer, E., King, F. H. and Prinzmetal, M. Pheochromocytoma with demonstration of pressor (adrenalin) substance in the blood preoperatively during hypertensive crises, *Ann. Surg. 106*:85-91, 1937.
15. Goldenberg, M. Personal communication.
16. Cahill, G. F. Tumors of the adrenal and use of air insufflation in their diagnosis, *Radiology 37*:533-44, 1941.
17. Rivas, M. R. Roentgenologic diagnosis; generalized subserous emphysema through a single puncture, *Amer. J. Roentgenol. 64*:723-34, 1950.
18. Goodwin, W. Unpublished data.
19. Spear, H. C. and Griswold, D. The use of Dibenamine in pheochromocytoma, *New Engl. J. Med. 239:* 736-39, 1948.
20. Hoch, G. F. Pheochromocytoma with paroxysmal hypertension, *J. Urol. 61:* 473-76, 1949.
21. Cahill, G. F. and Montieth, J. C. Use of Dibenamine and norepinephrine in the operative treatment of pheochromocytoma, *New Engl. J. Med. 244*:657-61, 1951.
22. Papper, E. M. and Cahill, G. F. Anesthetic problems in hormonal disorders of the adrenal glands, *J. Amer. med. Assoc. 148*:174-79, 1952.