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Diagnosis of pheochromocytoma by pharmacologic tests : with emphasis on the role of the benzodioxans

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DIAGNOSIS OF PHEOCHROMOCYTOMA BY PHARMACOLOGIC TESTS

With Emphasis on the Role of the Benzodioxans

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INTRODUCTION:

Because in recent years the concept of the characteristic syndrome caused by the clinical entity pheochromocytoma has been so markedly changed, a vast amount of work has progressed toward the discovery of a reliable method for the diagnosis of this condition. The previous diagnostic criteria, although adequate for those tumors which were peri-adrenal in locale and manifested themselves by hypertensive crises, were wholly inadequate for all those which were extra-adrenal or were characterized by a sustained fixed hypertension resembling the clinical state of essential hypertension. This tumor which was considered to be rare up to as late as 1945, has been proved to be much more common than previously thought. It has been shown, as will be pointed out in this paper, that probably two-thirds of the reported cases have not demonstrated the classically characteristic syndrome that is considered diagnostic.

An attempt will be made to review briefly the historical background of our knowledge of the diagnosis of pheochromocytoma, its known pathology, and symptomatology, historical methods of diagnosis, and the more recent contributions to the diagnosis. This will include the theory, results and side actions of each test. Special emphasis will be placed upon the role of the Benzodioxans in our diagnostic armamentarium. An attempt will be made to evaluate the tests presented in the light of our present knowledge.

HISTORICAL:

Pheochromocytoma was first described by Manasse (1) in 1893. In 1903 Kohn (2) first described the chromaffin system, and in 1922, Labbe, Tinel, and Doumer (3) described the clinical syndrome of paroxysmal hypertension associated with pheochromocytoma.

INCIDENCE:

Although according to Goldenberg(4) only 134 cases had been reported to 1947, Smithwick (5) in a comprehensive study of hypertensive patients found that in 1,000 cases which were subjected to therapeutic lumbosacral sympathectomy for hypertension and both adrenals exposed for removal of any adrenal tumors, the incidence of pheochromocytoma was 0.5 per cent. This figure may be low, as it was shown in Ganem's (6) review that as many as eleven extra-adrenal pheochromocytomas had been reported. This is 8.2 per cent of all those reported to 1947, and of these some probably would have escaped detection by the surgical approach employed in Smithwick's series. That the tumor may be familial in nature is suggested by Calkin and Howard (7) in a report of three cases within the same family.

SYMPTOMS AND SIGNS:

The classical symptoms and signs of pheochromocytoma reviewed by Roth and Kvale (8) are well-known as paroxysmal attacks of sudden rise in blood pressure, tachycardia, great anxiety, severe

headache, subsequent pallor of the face in particular, numbness, tingling, and coldness of the hands and feet, sometimes nausea and vomiting, pain in the epigastrium extending over the precordial region, and excessive sweating. Drill (9) includes weight loss and blurring of vision among the manifestations. Holland and Strickland (10) point out that constipation is another annoying feature of the condition. The attacks last from a few minutes to several hours and are frequently followed by weakness and fatigue (8).

In 1946, Green (11) in a review of fifty-one cases pointed out that only fourteen of this number demonstrated paroxysmal hypertension while thirty-seven showed a chronic fixed hypertension. Goldenberg and Aranow (12), recognizing that pheochromocytomas are more frequently associated with persistent blood pressure elevation than with paroxysmal hypertension, report that the basal metabolic rates of those with the sustained type are in most cases elevated and associated with enlargment of the thyroid gland. It thus becomes apparent that cases diagnosed as essential hypertension should be viewed more critically.

The variable clinical pictures presented may be pointed out as indicative of the cause for confusion in diagnosis. Bartels and Wall (13) report four cases in which the manifestation of clinical types varied through typical episodic hypertension,

chronic progressive hypertension, mildly symptomatic and asymptomatic. Smith (14) reports one case in which blanching of the fingertips and paroxysmal hypertension were the only typical signs. In 1940, Phillips (15) reported one of two known intrathoracic pheochromocytomas that clinically masqueraded as a tumor of the left apical sulcus at the level of the first intercostal space with a Horner's syndrome.

It is thus apparent that the clinical syndrome which has been characteristically associated with pheochromocytoma must be altered to include a wide spectrum of symptoms and signs associated with hypertension either paroxysmal or fixed.

DIAGNOSIS:

Roth and Kvale (8) in their discussion of the progress of diagnosis of pheochromocytoma state that previous to 1945 and the recent search for more certain diagnostic methods, diagnosis of pheochromocytoma was based on; 1. Demonstration of a tumor by palpation or roentgenologic examination; 2. Localization of the tumor by perirenal air insufflation; 3. Demonstration of a pressor substance in the blood, and, 4. Observation of the attacks which characterize this clinical entity. The attacks were either spontaneous or induced by physical exertion, change in position, massage of the abdomen on the side of the tumor, administration of insulin, or epinephrine or the cold pressor test. The test proposed by Roth and Kvale (17) in 1945 was

another method of production of induced attacks by the use of histamine. Since that time other promising pharmacologic tests have been added to our diagnostic methods which the author will attempt to discuss briefly in the course of this paper.

PATHOLOGY:

Pheochromocytoma is a tumor which arises from any of the widespread areas of the chromaffin system and is the cause of the only known clinically significant hypertension due to circulating epinephrine (4). The tumor arises from the pheochromoblast cell of the chromaffin system (16).

The chromaffin system as first described by Kohn (2), includes chromaffin cells along the entire length of the autonomic nervous system. They occur in the autonomic ganglia as nests known as chromaffin bodies or paragangliomas. Included also in the system are the adrenal medulla, Zuckerlands organ, and the carotid body. Brines and Jennings (18), contest the inclusion of the carotid body as it arises from a different embryologic anlage, and, since by 1943, the reported 275 carotid body tumors indicated that none of these patients had hypertension. Brines and Jennings (18) also include the argentaffin cells of the appendix and the intestine and the coccygeal body in the system.

Pheochromocytomas characteristically stain yellow with Zenker's Chromate Solution. Cytologically they are seen as

polyhedral cells arranged in nests or masses containing abundant cytoplasm but varying in size and shape. They often show hemorrhagic cysts (16).

Goldenberg's and Aranow's (12), experience suggests that the incidence of extra-adrenal tumors occur to a much higher percentage than the fifteen per cent stated in the literature. Tumors are usually solitary as shown by Brunschwig's and Humphries' (19) series of 103 autopsy cases in which the findings were right adrenal 43, left adrenal 34, bilateral 13, and extra-adrenal 13. Ganem (16) reported that in a review of 11 extra-adrenal pheochromocytomas 9 of these were of Zuckerland's organ. McKieth (20) states that 9.7 per cent are bilateral and 9.0 per cent are malignant. Burrage (21) states in his review of 52 cases that less than 6.0 per cent were malignant.

Chromaffin cells do not necessarily produce epinephrine as some tumors of the organ of Zuckerland have been demonstrated to have no adrenaline or other pressor substance (16). The normal adult adrenals yield about 8.0 mg. of pressor substance, and as much as 2,300 mg. of pressor substance has been reported contained in one pheochromocytoma (18). Both the normal adrenal medulla and pheochromocytomas have been shown by Tullar (22) and Auerbach and Angell (23) to contain not only epinephrine but also nor-epinephrine, the corresponding primary amine, in varying amounts. Some pheochromocytomas have been shown to contain nor-epinephrine predominately up to as high as 97.0

per cent (12). Detection of tumors in this category will be discussed later in this paper.

PREVIOUS TESTS USED AS DIAGNOSTIC AIDS:

Aside from observation of spontaneous and induced attacks of hypertensive crises in those patients subject to this clinical form of pheochromocytoma, other methods have been in use to diagnose the condition and localize the tumor. Brunschwig and Humphries(19) have observed that although a flat plate of the abdomen followed by intravenous and retrograde pyelogram may suffice, the best method of localization is achieved by perirenal air insufflation.

The demonstration of epinephrine in the peripheral blood of patients is a prodigious pharmacologic proceedure. This has been claimed only once and is open to criticism (4).

Other possible avenues through the use of blood values have proved to lack constancy. The insulin tolerance test has been reported as yielding a hyperglycemic reaction in a case reported by Burrage and Halsted (21), and as remaining normal in three cases reported by Calkins and Howard (7). Serum potassium and urea clearance tests have also been found to be elevated in some cases (16), but the value of these findings as a diagnostic aid is questionable. The cold pressor test may or may not yield a pressor response (21) (24).

The impetus to suspect pheochromocytoma in persistent

hypertensive cases brought about by the changing concept of the syndrome caused by pheochromocytoma through the work of such men as Smithwick (5) and the knowledge that between 10 per cent (19) and 15 per cent (4) of the known pheochromocytomas are extra-adrenal, has brought about a search for further and more dependable diagnostic methods.

RECENT TESTS USED AS DIAGNOSTIC AIDS:

The recent work on diagnostic aids in pheochromocytoma has been based upon two opposing general concepts. The earliest work was done with the intent of finding a reliable method for inducing hypertensive attacks in patients suspected of having paroxysmal hypertension or who had experienced known hypertensive crisis. These tests are the Histamine test of Roth and Kvale (7), the Mecholyl test (Methacholine Chloride), proposed by Guarneri and Evans (25), and the Tetraethylammonium Bromide test of LaDue, Murison, and Pack (26). The other concept of proof of pheochromocytoma by use of the adrenolytic drugs to demonstrate the hypertension that is due to circulating pressor substance, was advanced by Goldenberg, Snyder and Aranow (4). At about the same time Hecht and Anderson (27) were experimenting with the effects of other adrenolytics. The following is a brief review of the various tests proposed by these authors.

Histamine test: The purpose of the histamine test is to induce the characteristic attack at will by a dependable method

since none of the other known methods was considered dependable (8). Best and Taylor (28) state that there is some indication that histamine increases the output of adrenaline from the adrenal gland. Whether the histamine test is dependent upon this supposition is not clearly understood. It was shown by Roth and Kvale (7) that subcutaneous injection of 0.05 mg. of histamine produced a pressor response in patients with pheochromocytoma. This response in one case has been reported by Burrage and Halsted (21) to have percipitated such a dramatic and extreme rise in blood pressure as to endanger the life of the patient through rupture of a cerebral vessel, pulmonary edema or shock from release of too much adrenaline. Furthermore, they point out that the myocardium which is already over-stimulated by high blood levels of pressor substance shows electrocardiographic changes, expecially inversion of T waves, during attacks of hypertension. On the other hand Roth and Kvale (29) in a series of 200 hypertensive patients and fifty other patients with other clinical conditions elicited no untoward effects from the histamine test which would seem to indicate that the test is not hazardous. Guarneri and Evans (25) report a series of 22 cases in which five patients showed sufficient blood pressure elevation to indicate that that they were hyper-reactors and one patient who showed a definite positive test for pheochromocytoma. This case was not operated in the absence of clinical symptoms. No follow up on this case could be found by

the author.

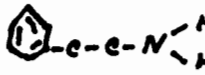
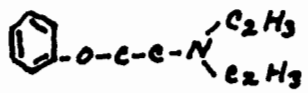
Mecholyl test: The mecholyl test introduced by Guarneri and Evans (25) produces a severe hypertension resembling the paroxysmal attack of hypertension due to pheochromocytoma. This was substantiated by Taliaferro (30). In addition to the hypertension all individuals tested, both normal and with hypertensive vascular disease, exhibited nausea, salivation, epiphora, sweating and dyspnea (25).

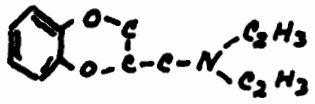
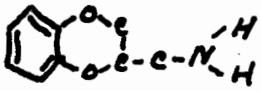
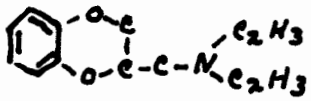
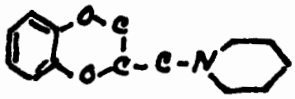
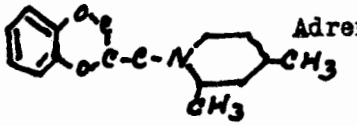
Tetraethylammonium bromide test: This drug was tested by LaDue, Murison and Pack (26) in 1947. The effect was found to be pressor as with the histamine and mecholyl tests, but much more persistent thus prolonging the period of hypertensive crises. They state that the advantage of the test is the ability to control abnormally high blood pressure response by having the patient sit in an upright position or by tilting on a bed or tilt table. The disadvantage according to Roth and Kvale (8) is the large number of false negative and false positive responses.

The other approach to the search for a dependable diagnostic aid in pheochromocytoma is based upon the thesis that if hypertension is due to circulating epinephrine it will be abolished or significantly decreased by the intravenous administration of adrenolytic compounds. Most adrenolytics are sympatholytic also (4). The Benzodioxans in doses under 10 mg. per kilogram

and Dibenamine are adrenolytic but not sympatholytic (4) (27). Calkins, Dana, Seed and Howard (31) believe the adrenolytic drugs inhibit the effect of epinephrine and allied pressor agents by occupying the epinephrine specific receptor. The majority of the epinephrine inhibitors (e.g. benzodioxan, ergotoxine, yohimbine and the phenoxyethylamines) appear to combine reversibly with the receptor thereby competing with epinephrine. They point out that dibenamine combines irreversibly with the receptor and cannot be overcome by an excess of pressor agent. The possible basis for this competition is a common chemical configuration C-O-C-C-N which is observed in all the competitors and may correspond to H-O-C-C-N in epinephrine.

Benzodioxan test: The benzodioxans have received the greatest attention of the adrenolytics studied, and of these 933F (Pipericylmethyl Benzodioxane) has been the one most thoroughly investigated. Goldenberg has been the foremost investigator in this field and has published many articles concerning his work. The benzodioxans are derived from the simplest aromatic sympathomimetic amine, phenylethylamine. Their chemical descriptions and the quantity of each drug required to produce an adrenolytic action in man is shown in the following table from Goldenberg (4).

Phenylethylamine		Sympathomimetic
B-diethylaminophenetole 928F		Adrenolytic, 10 mg/kg.

2-methoxy-B-diethyl-amimophenetole 930 F		Adrenolytic, 10 mg/kg.
Aminomethylbenzodioxane 946 F		Adrenolytic, 5 mg/kg.
Diethylaminomethyl Benzodioxane 883 F		Adrenolytic, 1 mg/kg.
Piperidylmethyl Benzodioxane 933 F		Adrenolytic, 1 mg/kg.
(2,4-dimethylpiperidyl) Methylbenzodioxane 1164 F		Adrenolytic, 1-2 mg/kg.

Bovet and Simon (32) have shown that with a constant dosage of 933 F the drop in blood pressure is greater with greater amounts of epinephrine. Thus, those pheochromocytomas producing less epinephrine produce less blood pressure depression with 933 F. By animal experiments Goldenberg (4) has shown that doses of 0.25 mg/kg. of 933 F have a purely adrenolytic action on the blood pressure. Vasomotor reflexes are effected and abolished when doses of 5-10 mg/kg. are given. Only 1/40 to 1/80 of the sympatholytic dose is required to produce a significant depression of hypertension due to epinephrine.

The recently proven existence of nor-epinephrine (23), a primary amine differing from epinephrine only by the absence of an N-methyl group, brought about further investigative work by Goldenberg (33) to determine the effects of the benzodioxans on the hypertension produced by tumors producing nor-epinephrine predominately.

Epinephrine within a physiologic range acts as an overall vasodilator and causes hypertension only by an increase in cardiac output (34). Nor-epinephrine acts as an overall vasoconstrictor with no change or slight decrease in cardiac output. The hyperglycemic effect of nor-epinephrine is much less marked than that ofepinephrine in a ratio of 1 to 8(16).

In previous tests Goldenberg (12) had shown by epinephrine infusion tests in man that blood pressure elevated by this method could be decreased approximately to the level maintained before infusion by the administration of benzodioxan 933 F. The same technique was employed using pure nor-epinephrine and it was shown the blocking action of 933 F was significant enough to be diagnositic. One case of pheochromocytoma with 97 per cent arterenol and 3 per cent epinephrine responded positvely to the test on two occasions prior to surgical removal of the tumor.

The effect of epinephrine on the heart rate is not abolished by 933 F. Rather the drug increases the tachycardia produced by epinephrine. This is attributed to the central nervous system stimulating effects of 933 F (9). In Goldenberg's work (4) cases of proven pheochromocytoma, known essential hypertension and purely normal persons were tested. Many cases of essential hypertension showed a purely pressor response following 933 F administration. In some a drop in blood pressure

of short duration, 30 seconds to 2 minutes and of small degree 5 to 26 mm., preceded the pressor response when an injection time of 30 seconds was used. This did not occur with a 2 minute injection time. In normal persons only a mild pressor effect both systolic and diastolic was noted. In 120 cases of hypertension reviewed by Calkins et al (31) all but two patients gave a negative response. Of these two cases one had a pheochromocytoma proven by surgery. The other had a large cell neuroblastoma and obtained relief of symptoms following removal of the tumor.

Certain facts seem well-established about 933 F although there has been much controversy concerning its properties. It is relatively non-toxic, rapidly destroyed and excreted, and its chief side effect is central nervous system excitement (3).

In a review of the literature Goldenberg et al (12) state that fifty-nine patients have shown positive benzodioxan tests, and were later operatively demonstrated to have pheochromocytomas. Taliaferro (30) reports one false positive test but at the time of the patient's death seven weeks later, no post-mortem was granted so his diagnosis of renal hypertension is in doubt. This is the only reported case of a false positive test in several thousand tests that have been performed. Only three cases of pheochromocytoma with persistent hypertension and negative benzodioxan tests are known to Goldenberg (12). Calkins and Dana (31) state that in certain patients with proven pheochromocytoma the results of the benzodioxan test may be equivocal or negative; the blood pressure may remain stable throughout

operation and return to normal only gradually thereafter. In these patients it is postulated that the pheochromocytoma may cause hypertension indirectly by stimulation of the pituitary and adrenal rather than directly by the effect of their secretions on the arteriolar bed or cardiac musculature.

No persistent damage from side actions has been recorded (12), although several alarming pressor reactions and one hypertensive encephalopathy have been reported (12) (35) (9). Goldenberg (12), using only a 30 second injection time on 59 hypertensive patients, found that most showed sinus tachycardia. Flushing, palpitation, nervousness, cold and clammy extremities, hyperpnea, mild headache, fright, sighing respiration and dizziness were the other side actions recorded in order of decreasing frequency. The disturbing side actions lasted as long as 3 minutes. By prolongation of the injection time from 30 seconds to 2 minutes the incidence of side actions was markedly decreased. Drill (9) reports that a slight increase in blood pressure is seen in normal persons and a greater rise is seen in persons with hypertension not due to pheochromocytoma following 933 F administration. Premature systoles with or without compensatory pauses were occasionally encountered by Calkins (31).

Dibenamine hydrochloride test (dibenzyl-beta-chlorethylamino hydrochloride): Calkins, Dana, Seed and Howard (31) point out that dibenamine combines irreversibly with the epinephrine

specific receptor and once inhibition is established by this compound it cannot be overcome by an excess of pressor agent. Thus, when dibenamine is administered over a period of 1 hour in a dosage of 7.0 mg. per kilogram of body weight diluted in 300 cc. of 5 per cent glucose in physiologic saline solution to a patient with pheochromocytoma of the sustained hypertension type, the blood pressure drops to normal and is maintained at this level for 24 hours (24). In this case reported by Spear and Griswold (24) no symptoms appeared for 48 hours, nor could a positive histamine response be elicited.

SUMMARY:

It has been pointed out that it is now recognized that the classical syndrome of paroxysmal hypertension is not the only manifestation of pheochromocytoma. The clinical picture associated with pheochromocytoma has been shown to vary through the typical episodic hypertension, chronic progressive hypertensive, mildly symptomatic and asymptomatic states. It is known today that the majority of patients with pheochromocytoma are of the chronic hypertensive type.

Pheochromocytoma may arise from any of the widespread areas of the chromaffin system. Some have been demonstrated to secrete no known pressor substance. The incidence of pheochromocytoma as the etiologic factor for hypertension is probably over 0.5 per cent of all hypertensive patients. Of these more than

15 per cent are extra-adrenal and might thus escape detection by the use of pyelography or peri-renal air insufflation.

Normal adult adrenals contain as much as 8 mg. of pressor substance. One pheochromocytoma has been reported to contain as much as 2,300 mg. of pressor substance. Thus, the hypertensive crises of pheochromocytoma are due to the sudden release of massive quantities of pressor substance which may prove fatal.

Previous to 1945, diagnosis was made by palpation of the tumor, inducing a hypertensive crisis by mechanical means, and by pyelography and peri-renal air insufflation. An attempt at blood level determination of circulating epinephrine proved unsatisfactory because of the prodigious technical difficulties. Other blood values and the cold pressor test yield too variable responses to be of diagnositc value.

The first attempt to use a pharmacologic test was made in 1945. This was soon followed by others using different agents for their tests. Two distinctly different approaches were used. The first was to find a reliable method for the induction of a hypertensive crisis, and the second was to prove that the hypertension demonstrated in those patients with sustained hypertension was due to circulating pressor substance. For the latter the adrenolytic drugs were employed.

A review of the various pharmacologic tests is presented. Those tests which induce a pressor response are examined first.

The histamine test of Roth and Kvale produces a pressor response in patients with pheochromocytoma. It has been reported to have produced such an extreme elevation of blood pressure in one patient that the patient's life was endangered. On the other hand Roth and Kvale state that in a series of 250 cases no untoward effects were noted. It has been shown that some persons are hyper-reactors to histamine and thus may give an equivocal, if not false positive response. No true false positives have been reported.

The mecholyl test of Guarneri and Evans elicits a severe bypertension resembling the episodic attack of pheochromocytoma. All patients tested with this agent exhibited discomforting side reactions.

The tetraethylammonium bromide test of LaDue, Murison and Pack produces the same pressor response that histamine and mecholyl produce, but a much more prolonged hypertensive crisis than the two preceding tests. This test yields a large number of false negative and false positive responses.

The second diagnostic approach is by the use of the adrenolytic agents. Those with which this paper is concerned are the Benzodioxans and dibenamine hydrochloride. It is shown that the benzodioxans have a temporary effect, combine reversibly with the epinephrine specific receptor and produce a diagnostic depression of blood pressure if the hypertension is due to either cir-

culating epinephrine or nor-epinephrine. The blood pressure depression is in direct relation to the amount of circulating epinephrine in the blood stream. Of the benzodioxans the one receiving the most attention is piperidylmethyl benzodioxan or 933 F.

Cases of essential hypertension have been shown to have a slight drop of blood pressure preceding a mild pressor response or only a slight pressor response when 933 F is administered. Normal persons show only a slight pressor response.

Fifty-nine patients have shown positive benzodioxan responses and later been proven to have pheochromocytomas by surgery. Only three cases of pheochromocytoma with persistent hypertension and negative benzodioxan tests are known. Of the several thousand tests only one false positive test has been reported and this is questioned because post-mortem examination was not permitted.

Side actions are non-existent in the majority of patients and mild in nearly all of the rest if a 2 minute injection time is faithfully observed. 933 F increases the tachycardia produced by epinephrine rather than abolishing it. This is thought to be due to the central nervous system stimulating effect attributed to the benzodioxans. One case of hypertensive encephalopathy has been reported following administration of 933 F, but no residual effect was noted. Premature systoles have been reported by one observer following the administration

of 933 F. No severe hypotensive reactions have been reported.

The dibenamine hydrochloride test of Calkins, Dana, Seed and Howard is the only other test employing an adrenolytic that has had significant investigation. Dibenamine combines irreversibly with the epinephrine specific receptor. This drug is administered over a 1 hour period. A blood pressure depression to normal levels results for a period of 24 hours and the patient remains asymptomatic for a period of 48 to 72 hours. Further research must be done to furnish more information concerning this drug.

CONCLUSIONS:

1. Patients with pheochromocytoma who present classical episodic hypertensive crises will not respond to the benzodioxan test during remissions. The only diagnostic pharmacologic test for these patients is one which will induce a hypertensive crisis.

2. All patients presenting complaints of chronic progressive hypertension of unknown etiology should be investigated for pheochromocytoma.

3. Tumors which produce chronic hypertensive states due to circulating epinephrine or allied pressor substance usually respond diagnostically to the blocking action of the benzodioxans.

4. The added strain of an induced hypertensive crisis on an already debilitated patient is undesirable. Therefore, the

use of those pharmacologics which produce pressor reactions should be avoided when possible.

5. Palpation and roentgenography are the only known methods of localization of the tumor prior to surgical exploration.

6. No test has been proposed that is diagnostic of those tumors which produce no pressor substance.

BIBLIOGRAPHY

1. Manasse, P.: Uber die hyperplastichen Tumoren der Nebennieren, Virchow's Arch. f. path. Anat. 133:391-404, 1893. Cited by Brines, O. A., and Jennings, E. R.: Paragangliomas - Review of Subject an Report of Five Original Cases, Am. J. Path. 24:1167-1197 (Nov.) 1948.

2. Kohn, A.: Das chromaffin Gewebe, Egebn. d. Anat. u. Entwcklngs. gesch. 12:253-348, 1902. Cited by Brines, O. A., and Jennings, E. R.: Paragangliomas - Review of Subject and Report of Five Original Cases, Am. J. Path. 24:1167-1197 (Nov.) 1948.

3. Labbe, M., Tinel, J., and Doumer: Crisis solaires et hypertension paroxystique en rapport avec une tumeur surrenale, Bull. et mem. Soc. med. d. hop. de Paris. 46:982-990, 1922. Cited from Brines, O. A., and Jennings, E. R.: Paraganglioma - Review of Subject and Report of Five Original Cases, Am. J. Path. 24:1167-1197 (Nov.) 1948.

4. Goldenberg, M., Snyder, C. H., and Aranow, H., Jr.: New Test for Hypertension Due to Circulating Epinephrine, J.A.M.A. 135:971, 1947.

5. Smithwick, R. H.; Personal communication to Goldenberg, M. (1946). Cited by Goldenberg, M., Snyder, C. H., and Aranow, H., Jr.: New Test for Hypertension Due to Circulating Epinephrine, J.A.M.A. 135:971, 1947.

6. Ganem, E. J., and Cahill, G.F.; Pheochromocytomas coexisting in adrenal gland and retroperitoneal space with sustained hypertension, New England J. Med. 238:692 (May 13), 1949.

7. Calkins, E., and Howard, J. E.: Bilateral Familial Pheochromocytoma with Paroxysmal Hypertension, Successful Surgical Removal of Tumors in Two Cases with Discussion of Certain Diagnostic Procedures (Including Histamine Test) and Physiologic Considerations, J. Clin. Endocrinol. 7:475-492 (July), 1947.

8. Roth, G. M., and Kvale, W. F.: Pharmacologic Tests as an Aid in Diagnosis of Pheochromocytoma, Canada M. A. J. 58:330-334 (April) 1948.

9. Drill, V. A.: Reactions from the Use of Benzodioxane (933 F) in the Diagnosis of Pheochromocytoma, New England

J. Med. 241:777, 1949.

10. Holland, C. W., and Strickland, S. C.: Medullary Pheochromocytoma, Canada M. A. J. 58:330-334 (April) 1948.

11. Green, D. M. : Pheochromocytoma and Chronic Hypertension, J. A. M. A. 131:1260-1265, 1946.

12. Goldenberg, M., and Aranow, H., Jr.: Diagnosis of Pheochromocytoma by the Adrenergic Blocking Action of Benzodioxan, J. A. M. A. 143:1139, 1950.

13. Bartels, E. C., and Wall, N. M.: Pheochromocytoma - Clinical problem, S. Clin. North America 27:605, 1947.

14. Smith, C. A.: Paragangliomas, J. Urol. 60:697-701, 1948.

15. Phillips, B.: Intrathoracic Pheochromocytoma, Arch. Path. 30:916 (Oct.) 1940.

16. Ganem, E. J., and Cahill, G. F.: Pheochromocytoma Coexisting in Adrenal Gland and Retroperitoneal Space with Sustained Hypertension. Case with Surgical Care, New England J. Med., 238:692, 1948.

17. Roth, G. M., and Kvale, W. F.: Tentative Test for Pheochromocytoma, Am. J. M. Sc. 210:653, 1945.

18. Brines, O. A., and Jennings, E. R.: Paragangliomas. Review of Subject and Report of Five Original Cases, Am. J. Path. 24:1167-1197, (Nov) 1948.

19. Brunschwig, A., and Humphries, E.: Excision of Pheochromocytoma Following Near Fatal Attack of Paroxysmal Hypertension, J. A. M. A. 115:355, 1940.

20. McKieth, R.: Adrenal Sympathetic Syndrome; Chromaffin Tissue Tumor with Paroxysmal Hypertension, Brit. Heart J. 6:1-12, 1944.

21. Burrage, W. C., and Halsted, J. A.: Medullary Tumor (Pheochromocytoma); Case Report with Successful Operation, Ann. Int. Med. 28:838-849, (April) 1948.

22. Tullar, B. F.: The Separation of Arterenol from Natural U. S. P. Epinephrine, Science 109:536, (May 27) 1949.

23. Auerbach, M. E., and Angell, E.: The Determination of Arterenol in Epinephrine, Science 109:536, (May 27) 1949.

24. Spear, H. C., and Griswold, D.: The Use of Dibenamine in Pheochromocytoma, New England J. Med. 239:736, 1948.

25. Guarneri, V., and Evans, J. A.: Pheochromocytoma; Report of a Case with New Diagnostic Test. (Especially Hypertensive Response to Methacholine.), Am. J. Med. 4:806, 1948.

26. LaDue, J. S., Murison, P. J., and Pack, G. T.: Use of Tetraethylammonium Bromide as a Diagnostic Test for Pheochromocytoma, Proc. Am. Federation Clin. Research 3:67, 1947.

27. Hecht, H. H., and Anderson, R. B.: Influence of Dibenamine (n,n-dibenzyl-beta-chlorethylamine) on Certain Functions of the Central Nervous System in Man, Am. J. Med. 3:3-17, 1947.

28. Best, C. H. and Taylor, N. B.: The Physiologic Basis for Medical Practice, ed.4, Baltimore, Williams and Wilkins, 1945, p. 688.

29. Roth, G. M., and Kvale, W. F.: Histamine Test for Pheochromocytoma; Further Studies, J. Lab. and Clin. Med. 32:1510 (Dec) 1947.

30. Taliaferro, I., Adams, R. A., and Haag, H. B.: Benzodioxan Test, J. A. M. A. 140:1271, 1949.

31. Calkins, E., Dana, G. W., Seed, J. C., and Howard, J. E.: On Piperidylmethyl Benzodioxane (933 F), Hypertension, and Pheochromocytoma, J. Clin. Endocrinol. 10:1, 1950.

32. Bovet, D., and Simon, A.: Recherches sur l'activite sympatholytique de derives de l'aminomethylbenzodioxane, Arch. Internat. de pharmacdyn. et de Therap. 55:15, 1937. Cited by Goldenberg, M., Snyder, C. H., and Aranow, H., Jr.: New Test for Hypertension Due to Circulating Epinephrine. J. A. M. A. 135:971, 1947.

33. Goldenberg, M., Faber, M., Alston, E. J., and Chargaff, E. C.: Evidence of the Occurence of Nor-epinephrine in the Adrenal Medulla, Science 109:534-535 (May 27) 1949.

34. Goldenberg, M., Pines, K.L., Baldwin, E. deF., Greene, D. G., and Roh, C. E.: The Hemodynamic Response of Man to Nor-Epinephrine and Epinephrine and Its Relation to the Problem of Hypertension, Am. J. Med. 5:792, 1948.

35. Green, D. M., and Peterson, E. M.: Hypertensive Encephalopathy After Administration of Benzodioxan, J. A. M. A. 142: 408, 1950.