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RÉSUMÉ

Il existe souvent, chez des sujets apparemment bien nourris, une déficience marquée, voire même totale, d'acide ascorbique dans les spécimens d'artères prélevés à l'autopsie. La vieillesse semble accentuer cette déficience. Ce manque d'acide ascorbique est probablement associé au stress de la dernière maladie plutôt qu'à une mauvaise nutrition. Certains segments d'artères sujets à tension mécanique et portés à l'athérome accusent une déficience localisée; des segments adjacents, mais où la tension mécanique est moindre, montrent un taux d'acide ascorbique plus élevé et rarement des signes d'athérome. L'importance de la carence en acide ascorbique réside dans le fait que le scorbut chez le cobaye donne rapidement naissance à l'athérosclérose. Il a de plus été rapporté que l'aorte peut synthétiser le cholestérol et que l'inclusion d'acétate radioactif dans le cholestérol des tissus est sensée être considérablement plus rapide dans les tissus pauvres en acide ascorbique que dans les tissus normaux. La déficience d'acide ascorbique dans les artères, résultant en la dépolymérisation du ciment inter-cellulaire, peut être la cause de la libération des glucoprotéines observées dans le sang des sujets affligés d'athérosclérose avancée. Des travaux d'approche semblent indiquer qu'il soit possible de relever la teneur des artères en acide ascorbique par l'administration de cette substance. M.R.D.

FAMILIAL ADRENAL PHAEOCHROMOCYTOMA WITH SUSTAINED HYPERTENSION

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A FUNCTIONING TUMOUR of chromaffin tissue (phaeochromocytoma), most commonly situated in the adrenal medulla, has been considered in the past to be a very rare condition. Graham[1] was able to collect reports of only 198 cases in the world literature up to the middle of 1949. To this number he added nine cases of his own, making a total of 207 which formed the basis of a comprehensive review. In discussing the incidence he points out that an increasing number of cases are being discovered at the time of lumbo-dorsal sympathectomy for essential hypertension, so that exploration of the adrenal areas, at least, is now almost imperative in this type of surgery. In addition, the tumour as a cause of hypertension is being recognized more frequently because of the wide use of relatively new diagnostic methods. He estimates that approximately 800 persons die annually in the United States from phaeochromocytoma, most of these being avoidable deaths. If this is so, the tumour is not as rare as formerly thought and is masquerading as essential hypertension in many instances.

Familial incidence of phaeochromocytoma is extremely rare. The primary purpose of this article is to report two cases occurring in a brother and sister, aged 15 and 12 years respectively, both of whom had a tumour of the left adrenal. One of these was treated successfully by surgery. Graham[1] encountered only one report of familial incidence in his broad survey. These cases were reported by Calkins and Howard[2] and were related as aunt and niece. Each had bilateral adrenal tumours which were surgically removed. Since Graham's review, Roth and coworkers[3] have reported on three additional cases, two sisters and a brother of the same family, who had bilateral adrenal phaeochromocytomas. In all these cases surgical removal of the tumours was successful. No other reports of familial incidence have been encountered by us.

A phaeochromocytoma may occur at any anatomical site where chromaffin tissue is found, but in approximately 80% of instances it is located in the right or left adrenal gland. In about 10%

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of cases bilateral adrenal tumours occur. Of all tumours, 8% are malignant.

The cause of the hypertension and most of the symptoms is an excessive secretion by the tumour of epinephrine (adrenaline) or the closely related norepinephrine (noradrenaline). The latter has a more pronounced pressor action than the former by virtue of its vasoconstrictor effect. The relative amounts of epinephrine and norepinephrine in phaeochromocytoma vary considerably. Either may be in excess. In persons with paroxysmal hypertension the attacks are attributable to an outpouring of excessive amounts of the secretions into the general circulation as a result of some stimulation, physical or emotional.

A phaeochromocytoma produces either sustained hypertension simulating essential hypertension or paroxysmal hypertensive episodes. The latter is the more readily recognized, symptoms of severe headache, palpitation, dizziness, vomiting, profuse sweating, pallor and weakness being fairly common during the periodic attacks with sudden onset. However, the clinical picture may be obscured by complications of the hypertension such as cerebral-vascular hæmorrhage. Impaired glucose metabolism (with elevated blood sugar) and elevated basal metabolism frequently occur as an effect of the excessive secretions by the tumour.

Diagnostic measures of greatest value in the sustained type of hypertension involve the use of adrenergic drugs, including benzodioxane (Piperoxan, 933F) and phentolamine (Regitine, C-7337). When optimal amounts of these agents are injected intravenously in the presence of phaeochromocytoma, the blood pressure drops significantly. When the blood pressure is normal or only slightly elevated in the paroxysmal type, the injection of provocative agents, such as histamine, Etamon or Mecholyl, will produce a sharp elevation. Very recently considerable enthusiasm has resulted from the investigative work carried out on the quantitative estimation of epinephrine and norepinephrine in the urine. Cahill[4] gives a clear outline of the results obtained. In normotensive patients, about 20 to 50 micrograms of total pressor substances (10% as epinephrine and 90% as norepinephrine) occur in the 24-hour urine specimen. In persons with essential hypertension the amount was in the range of 75 to 100 micrograms. In subjects with phaeochromocytoma there was found to be a very marked elevation, particularly when a sustained hypertension existed, when the amount of excreted pressor substances varied from 600 to 2,700 micrograms. If these preliminary reports are confirmed, this procedure will probably become a most important diagnostic method. Intravenous pyelograms, retrograde pyelograms and perirenal air injection are valuable aids in diagnosis and localization of tumours.

In recent years surgical removal of a phaeochromocytoma has been rendered much less hazardous by the use of Dibenamine (or Regitine) and norepinephrine. The injection of Dibenamine several hours before operation has a prolonged antipressor effect and prevents a sharp and dangerous rise in blood pressure when the tumour is manipulated before removal. Norepinephrine, through its marked vasoconstrictor action, will prevent a severe hypotension when it is injected intravenously during the period immediately following removal of the tumour.

CASE REPORTS

CASE 1

D.M., a 15-year-old white male, was admitted to the Victoria General Hospital in Halifax on February 6, 1952, with complaints of severe temporal headaches, vomiting and weakness. He had been investigated at a pædiatric clinic in 1950 because of headaches. Nothing abnormal was found. In September 1951, headaches became much more severe and the family physician was consulted. Hypertension was discovered and, in addition, glycosuria. There was no previous personal history of diabetes or family history of diabetes or hypertension. Headaches became both more frequent and severe. They were often accompanied by dizziness, hot flashes, vomiting and marked weakness. Several nosebleeds occurred recently. A few days before admission he had a generalized convulsion.

The boy was pale and thin and greatly suffering from pain in his head. He appeared very weak. Skin was warm and moist. Temperature was elevated to 100° F., pulse 120, respirations 22. Pupils were equal and dilated. Both fundi showed papillœdema without hæmorrhages or exudates. The heart was not enlarged but the apex impulse was very forceful and diffuse. The sounds were loud and snapping, with a soft systolic murmur at the mitral area. The lungs were clear and there were no masses palpable in the abdomen. The blood pressure was 194/162 in the right arm and 210/166 in the right leg. There was 1+ albuminuria. Urine was negative for sugar on several examinations. Hæmoglobin value was 10.3 gm. %, packed cell volume 38%. White cell count was normal. Fasting blood sugar was 128 mgm. %. Non protein nitrogen, serum sodium, chloride, potassium and total protein values were all normal. Radiographs of the skull and chest were negative. The electroencephalogram was abnormal but nonspecific. It was interpreted as due to general cerebral depression. The electrocardiogram showed sinus tachycardia and abnormal P and T waves with prolonged Q-T interval, indicating myocardial impairment. On two attempts, intravenous pyelograms were unsatisfactory because of intestinal gas. A retrograde pyelogram under thiopentone anæsthesia disclosed the left kidney at the same level as the right and the pelvis slightly distorted. This suggested pressure on the left kidney from above.

A benzodioxane test was performed on February 10, resulting in a fall in blood pressure from 230/174 to 150/120 in three minutes. This was interpreted as a positive (++) response (Fig. 1). On February 12, 175 mgm. of Dibenamine was administered by slow intravenous drip over a period of four hours. The blood pressure dropped from 240/170 to a low of 110/80 in four hours. After eight hours the blood pressure gradually rose and reached 190/150 in 18 hours (Fig. 2).

The diagnosis of phaeochromocytoma was now almost certain. Despite the fairly high incidence of bilateral and extra-adrenal types of tumour, in view of the retrograde pyelogram it was decided to approach extraperitoneally on the left. The operation was performed on the 8th hospital day. Twenty-four hours previously, Dibenamine (140 mgm.) was administered for the second time for the purpose of producing a depressor effect during the operative period. A lesser drop in blood pressure occurred on this occasion with the smaller amount of drug used, and at the time of operation it had risen to 230/190. A blood transfusion was given and adrenal cortical extract and cortisone were administered intramuscularly preoperatively. A slow intravenous infusion of saline with 25 c.c. of adrenal cortical extract added was maintained during the operative period. Norepinephrine in saline was at hand for immediate intravenous infusion when indicated.

A left loin incision was made and a bulging mass was exposed. The perirenal fat was brownish-yellow. Large, worm-like vessels were noted in the adrenal area. The adrenal tumour, size of a lemon, was mobilized. The vessels were clamped and ligated, and the tumour removed. There was only a slight rise in blood pressure while the tumour was being handled, but a sharp drop to 140/126 occurred immediately after removal. Norepinephrine was started at this point and administered at a rate sufficient to maintain the systolic blood pressure above 100. It was continued at a slow rate for two hours after the operation and during this time the blood pressure remained in the vicinity of 130/106 (Fig. 3).

The tumour was spherical in shape and measured 5 cm. in diameter. In sections it consisted of a fairly uniform yellowish tissue with a soft, degenerate centre. It had a well-defined capsule. Microscopically the picture was typical of phaeochromocytoma.

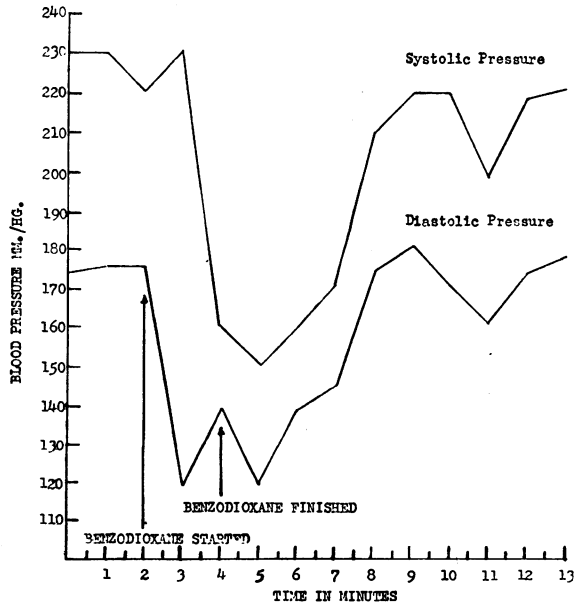

Fig. 1. — Benzodioxane response, preoperative. Note marked drop in blood pressure within two minutes of administration of benzodioxane.

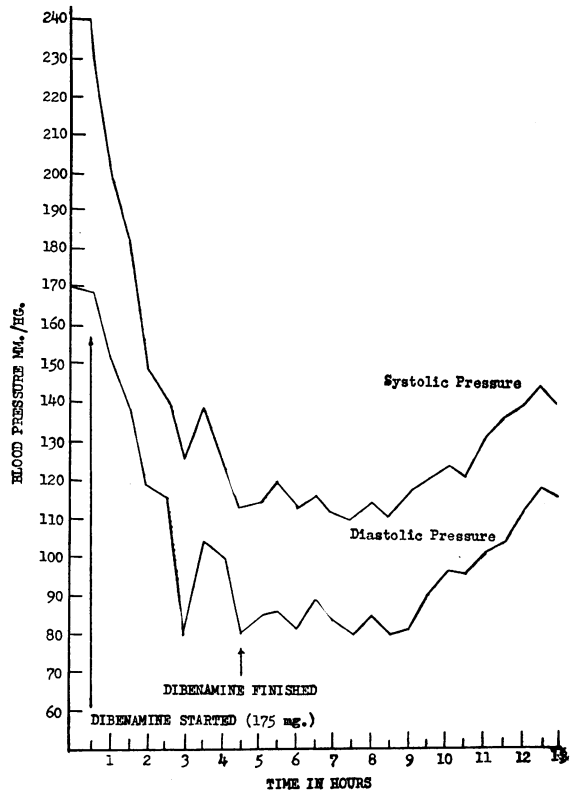

Fig. 2.—Dibenamine response, preoperative. Note marked and prolonged drop in blood pressure.

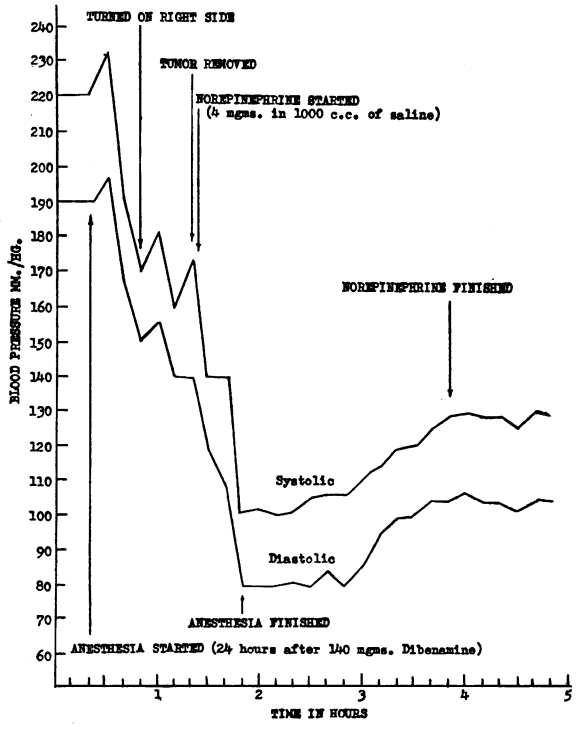

Fig. 3.—Note that blood pressure did not rise while tumour was being manipulated. Norepinephrine had a good pressor effect when blood pressure approached critical hypotensive level.

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The patient's postoperative course was uneventful. The blood pressure gradually rose to 164/130 by the seventh day. Although he was asymptomatic at this time, the possibility of a second tumour on the right adrenal or elsewhere was considered. Benzodioxane and Dibenamine tests were repeated. These were suggestively positive (Figs. 4 and 5). A Sodium Amytal test was

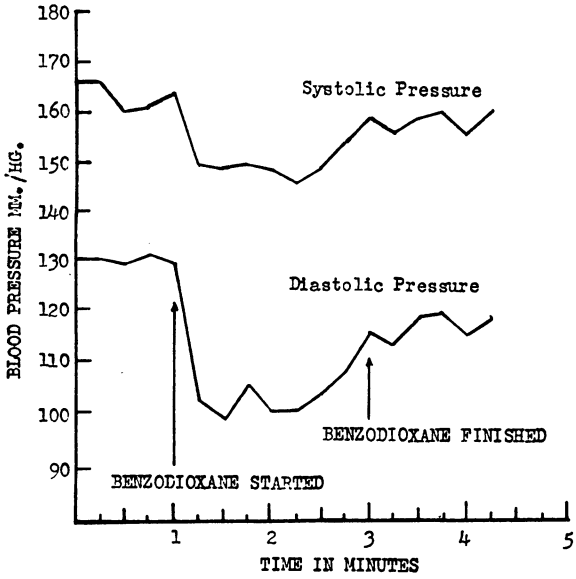

Fig. 4.—Benzodioxane response, postoperative. Note significant drop in blood pressure within one-half minute.

then performed which was also positive. In view of the latter and a negative histamine test it was thought unlikely that a second tumour remained. There was a marked improvement in the boy's appearance, he had no headache or other symptoms, and papilloedema had decreased. He was discharged on March 1, at which time the blood pressure was 170/120.

The patient returned on April 5, 1952, for reassessment. He was entirely asymptomatic and appeared in very good health. His strength and appetite had markedly increased, and he had gained 20 pounds. Blood pressure on admission was 140/90 and during four days under observation it fluctuated between 150/110 and 118/70, normal pressures being most frequently recorded. Physical examination was otherwise negative with the exception of a small amount of retinal exudate. Urinalysis, blood picture, and blood chemical findings were all normal. The electroencephalogram was now normal. Intravenous pyelography was done with no abnormality noted, the left kidney having resumed a higher position since operation. The electrocardiogram still revealed minimal evidence of myocardial impairment.

Last admission to hospital was on December 10, 1952. He remained for three days. General health was excellent; he was symptom-free and had gained further weight. The fundi and general physical examination were negative. Frequent blood-pressure determinations were consistently normal, with a mean of 120/74. The fasting blood sugar, glucose tolerance curve and intravenous pyelogram were normal.

In a communication on August 12, 1954, the family physician stated that the patient was in good health and doing any and all kinds of work and play. Blood pressure on that date was 132/100.

CASE 2

M.M., a 12-year-old white female, sister of the first patient, was admitted to the Victoria General Hospital, Halifax, on July 2, 1950. Complaints were severe headache, restlessness and weakness of two weeks' duration, present almost constantly and frequently accompanied by vomiting. A few hours before admission a generalized convulsion occurred.

At examination, the girl was in no apparent distress. Fundoscopic examination revealed distension of veins and a few hæmorrhages. The lungs were clear and the heart was not enlarged. There was sinus tachycardia with a rate of 110. The blood pressure in the right arm was 212/184, in the right leg 216/180. The abdomen was normal and the remainder of the physical examination negative.

Urinalysis disclosed 4+ albumin, no sugar, 10-12 white cells per high power field and a few hyaline casts. Red cell count was 5,500,000; hæmoglobin value 112%, white cell count 21,450 with 80% polymorphs, packed cell volume 54%. Fasting blood sugar was 146 mgm. %. Non protein nitrogen was 35 mgm. %. Kahn test was negative. The cerebrospinal fluid was clear, with a cell count of 1, protein 71, chlorides 700 and normal colloidal gold curve. The electrocardiogram was normal except for sinus tachycardia.

On the 3rd hospital day she had a convulsion with subsequent development of a left-sided hemiparesis and coma. At this time it was decided to do a benzodioxane test. A negative response was obtained; however, slightly less than the recommended amount of the agent was employed because of a very limited local experience with it. Great reliance was placed on the test, with the result

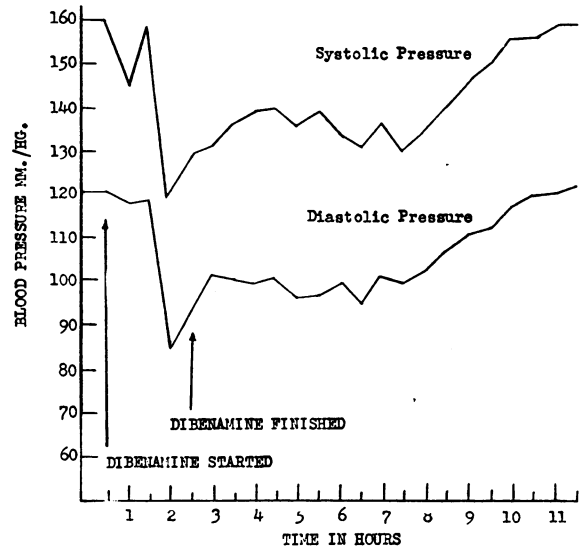

Fig. 5.—Dibenamine response, postoperative. Note marked and prolonged drop in blood pressure.

that the diagnosis of phaeochromocytoma was thought unlikely. A diagnosis of brain tumour was now considered seriously and ventriculography performed. This did not reveal any evidence of an expanding intracranial lesion. The patient remained comatose and died on July 5.

At autopsy a round, well-encapsulated tumour was found, arising from the lower pole of the left adrenal. It measured 3.9 cm. in diameter. Histologically it had the typical characteristics of a phaeochromocytoma.

DISCUSSION

Goldenberg, Snyder and Aranow[5] reported on the use of benzodioxane intravenously as a test for hypertension due to the circulating epinephrine. Since that time the agent has been used

extensively as a diagnostic aid in differentiation of persistent hypertension due to phaeochromocytoma and essential hypertension.

In phaeochromocytoma with hypertension the benzodioxane has a marked adrenergic effect, resulting in a striking drop in blood pressure within one or two minutes. In essential hypertension the pressure is not lowered and sometimes elevated. Goldenberg and Aranow[6] clearly demonstrated that hypertension produced by either epinephrine or norepinephrine was markedly diminished by administration of optimal amounts of benzodioxane. The positive response with benzodioxane occurred both in persons who had a secreting tumour and in normal subjects who were infused with epinephrine and norepinephrine separately.

A false negative test has been reported on a few occasions in cases later proved to have a phaeochromocytoma. Goldenberg and Aranow[6] encountered only three reported false negative tests before surgical removal of the tumour. They feel that these negative tests may be due to absence of circulating epinephrine and norepinephrine in the blood stream at the time of the administration of the benzodioxane. They offer good evidence to support this view, and they postulate further that the persisting hypertension in the absence of epinephrine and norepinephrine is due to a secondary mechanism. This mechanism, they believe, is initiated by the presence of these compounds in excess in the circulation for considerable periods of time. The false negative test in our Case 2 may be explained on this basis but may have been due to the use of a slightly sub-optimal amount of benzodioxane. More recently others[7, 8] have noted false negative responses.

False positive tests with benzodioxane are extremely rare according to Goldenberg and Aranow.[6] They contend that in the few cases reported the diagnosis is open to considerable doubt.

The false positive test following removal of a phaeochromocytoma in our Case 1 is somewhat puzzling to us. Goldenberg and Aranow[6] apparently do not believe that this can occur unless there is a second tumour remaining. We are reasonably certain that our patient has no other phaeochromocytoma. The explanation may be that a certain amount of epinephrine and norepinephrine still remained in the circulation at the time of the test, seven days postoperatively.

We had no experience with phentolamine (Regitine) at the time our cases were treated. This agent has very recently established itself as an extremely valuable diagnostic agent. Grimson and co-workers[9] first reported on its use. An extensive study on 259 patients, all but 20 with hypertension, was carried out by Gifford and colleagues[10] in order to evaluate the new drug. Their findings led them to conclude that phentolamine is a more reliable drug than benzodioxane, provided it is used intravenously in the dose of 5 mgm. for adults. It is safe to use, has minimal unpleasant side-reactions and is easy to administer. It has been stressed, however, that no one drug is infallible and a positive or equivocal phentolamine test should be confirmed if possible by testing with benzodioxane as well. A positive response is indicated by a prompt drop in blood pressure of more than 35 mm. systolic and 25 mm. diastolic. False negative responses have not been reported and false positives have been few. The latter can be kept to a minimum by adhering to the criteria outlined and taking the precaution of giving the patient no sedative or antihypertensive drug for at least 24 hours preceding the test. It is unreliable in hypertension associated with uræmia.

The use of Dibenamine as a diagnostic agent is not recommended because of its unreliability.[11] It regularly exerts a depressor effect in phaeochromocytoma hypertension but sometimes does so in essential hypertension as well. In addition there is some danger involved in its use. A positive response was obtained by us in Case 1, and served to some degree as a confirmation of the benzodioxane positive test. In view of its non-specificity the false positive response obtained postoperatively was not considered of much significance.

Dibenamine, as a therapeutic adjunct, was first used by Spear and Griswold.[12] Their enthusiasm was supported by Cahill and Aranow[13] and later by Cahill and Monteith.[14] Others have been equally enthusiastic. Our experience with the drug in the operative management of our Case 1 was quite satisfactory. The amount recommended, 5 to 7 mgm. per kg. of body weight in 300 to 500 c.c. of saline, is administered over a period of 1 to 2 hours. A period of 22 hours had elapsed between the time of administration of the agent and removal of the tumour. Although the blood pressure had become elevated again almost to pre-existing level, there was no

further significant rise as the tumour was being manipulated before removal. Following removal of the tumour the blood pressure began to drop to a normal level, and a hypotensive crisis was prevented by infusing norepinephrine in adequate amounts. There is a potential major risk in the use of Dibenamine relating to this period following removal of the tumour. If the depressor effect of Dibenamine is great during the operative period, norepinephrine is ineffective in reversing the hypotension and death may result. Since the maximal effect of Dibenamine may last for 18 to 20 hours, it would seem essential to allow this interval of time to elapse after its administration before proceeding with surgery. Certainly, it is extremely important to have a good time adjustment in order to insure the desired effect from the drug, without jeopardizing the patient with its inherent dangers. Cahill[4] feels that Regitine is a safer and equally effective drug and should replace Dibenamine for the purpose of lowering the pressure preoperatively and preventing sharp elevation during manipulation of the tumour. Regitine, differing from Dibenamine, will not suppress the effect of norepinephrine and accordingly will not interfere with the sustaining effect of the pressor agent.

The use of norepinephrine during the operation and immediate postoperative period has contributed greatly to the safety of the surgical removal of phaeochromocytoma. Holton[15] in 1949 demonstrated that this compound, along with epinephrine, existed in significant but varying amounts in phaeochromocytomas. It is secreted into the systemic circulation from the tumour during life. The rate of secretion varies and is influenced by different factors, including stress, abdominal palpation of the tumour and position of the body. The presence or absence of hypertension and the degree of the latter are dependent largely on the rate of secretion of epinephrine and norepinephrine and the amount of these compounds in the circulation at any given time.

The actions of epinephrine and norepinephrine in man are quite different, although chemically they are very similar. This has been well demonstrated by Goldenberg and colleagues[16] in 1948. Epinephrine exerts its pressor effect by increasing the cardiac output, an effect which exceeds its other action of decreasing the peripheral resistance by vasodilatation. On the other hand, norepinephrine influences the cardiac output very little and exerts its pressor effect by increasing the peripheral resistance through vasoconstriction.

When a phaeochromocytoma is removed surgically in the presence of hypertension there is usually a sudden and marked drop in the blood pressure, which may reach a critical hypotensive level. This occurrence has contributed considerably to the high operative mortality in the past. The proper use of norepinephrine intravenously during the critical period following removal of the tumour has been responsible for a decided lessening of the mortality rate. Four mgm. of the agent is mixed in 1,000 c.c. of saline and the rate of infusion is gauged by the level of the blood pressure at any given time. Cahill and Monteith[14] believe that norepinephrine should be administered for 24 hours after operation. In our case it was considered necessary to maintain the infusion for only two and a half hours.

The operative approach may be transabdominal or postero-lateral. If the tumour has been definitely located on one or other side, the postero-lateral is considered to be preferable. If it has not been located, both renal areas may be explored postero-laterally, if necessary, at the same operation. The surgeons who operated on our case prefer this type of approach. The lateral decubitus usually used may precipitate a hypertensive crisis; this danger is stressed by Conley and co-workers.[17] Such a crisis is most likely to occur in the paroxysmal type and they recommend the prone operative position for all such cases. The transabdominal approach involves more operative risk, but its advocates consider the advantage of a much better exploration of the possible sites of extra-adrenal tumours very important.

We are of the opinion that close team-work among the surgeons, internists and anæsthesiologists in the preoperative and operative phases of management of these rare cases is essential.

The persisting hypertension for several weeks postoperatively, as in our Case 1, has been reported previously. Goldenberg and Aranow[6] encountered the phenomenon in 7 of their 12 surgically treated cases. They were satisfied that the hypertension was not due to circulating epinephrine or norepinephrine. Rather, they attribute it to a secondary mechanism initiated by the action of the pressor agents over a considerable period of time before removal of the

tumour. Calkins and others[18] have expressed a similar view.

The nature of this secondary mechanism has not been adequately explained. The fact that it is apparently not operative in the paroxysmal hypertensive type of case causes more confusion. Further, a fair percentage of cases of phaeochromocytoma have consistently normal blood pressures after surgical removal of the tumour. It appears to follow that the secondary mechanism is set in action only in certain persons with phaeochromocytoma. This chance or possibly selective action may depend on one or more factors. The amount of either epinephrine or norepinephrine in the circulation, their ratio, the duration of their effect or individual susceptibility may be responsible. Possibly the important deciding factor is some undiscovered agent or agents.

Whatever the cause or nature of the secondary mechanism, it is evident that it is reversible. There is generally a slow but steady decline in the postoperative elevated blood pressure. The time interval varies considerably. Normotensive levels are attained in the great majority of persons, if not all, who have the entire phaeochromocytomatous tissue removed.

SUMMARY

1. Two cases of adrenal phaeochromocytoma occurring in a brother and sister are reported, one of which was successfully treated by surgical removal of the tumour.

2. The use of Dibenamine and norepinephrine in the management of the surgical case is discussed.

3. A false positive benzodioxane response postoperatively is commented upon.

4. A gradually declining hypertension persisted for several weeks postoperatively. The causative mechanism is not clearly understood.

5. The literature is briefly reviewed in regard to the nature, incidence, clinical picture, diagnostic methods and surgical management of this tumour.

The authors wish to express their appreciation to Dr. M. M. Hoffman, former Research Professor of Medicine at Dalhousie University, for invaluable help in management of Case 1 and in preparing this review; to Drs. C. L. Gosse and F. Gordon Mack of the Urological Department for close diagnostic and surgical assistance; and to Dr. C. W. Holland, Chief of the Medical Service at the Victoria General Hospital, for permission to publish these cases.

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ACTH AND CORTISONE

"Experience acquired in the course of their investigations also enabled the [M.R.C.] Committee to make a clearer assessment of the dangers of ACTH and cortisone therapy than was possible at the outset of their trials. These dangers are far from negligible. Above a certain dosage side-effects such as coarsening of appearance, increase in weight, hairiness and so on may appear. Unfortunately, increasing experience tends to show that the minimum doses required to maintain freedom from joint symptoms are commonly at or above the level which produces such side-effects. By themselves this group of side-effects could not be regarded as a general contraindication to the use of the drugs; but they need to be weighed carefully against the expected benefits. There are also more serious dangers: high blood pressure, heart failure, diabetes mellitus, activation of latent tuberculosis, perforation of peptic ulcers, and mental disturbances have all been reported as occasional complications. To some extent these can be avoided by excluding from the treatment patients who show even the slightest evidence of any of these conditions. In some patients, however, such evidence is not forthcoming; and, in these, dangerous complications may appear with unexpected, and perhaps uncontrollable, rapidity. Thus, therapy with ACTH and cortisone should never be undertaken lightly and ought not to be used save when the patient can be kept under constant medical supervision and when all necessary facilities for controlling treatment are available.

"It is as yet too early to determine the precise part that cortisone and other hormones will ultimately come to play in the treatment of rheumatoid arthritis; but there can be no doubt that the carefully planned and controlled investigations of the Joint Committee are adding substantially to knowledge of the natural history of the disease under various therapeutic measures. It is from such observations that it should in time become possible to decide whether the new hormones are in the long run more beneficial than other forms of treatment."—*Rep. Med. Res. Council*, 1952-53.