HYPERTENSION and glycosuria are conditions which in the vast majority of cases are not accessible to causal therapy. Yet there is a small—but important—group of patients with high blood pressure, paroxysmal or persistent, and with glycosuria, transitory or even permanent, who can find curative treatment, if the correct diagnosis of their disease is made in time. These are the patients with pheochromocytoma. The pheochromocytoma is an endocrine tumor of adrenal medullary tissue and produces epinephrine. Its active cells are chromaffin and give a brownish stain when exposed to a solution of potassium bichromate; it is from this reaction, that the name pheochromocytoma (brown cell tumor) was derived.

The adrenal medulla originates from the sympathetic nerve system and the pheochromocyte is one of the final developmental forms of the sympathogonia, the stem cell of the sympathetic nerve system. It is therefore easily understandable that only those tumors of the adrenal medulla are hormone-producing in which the differentiation of the stem cells has progressed to the stage of the pheochromocyte. On the other hand, pheochromocytoma may develop outside of the adrenal medulla wherever sympathetic nerve cells are present, as for instance in the sympathetic glands along the aorta and the carotid body. Table 1 shows the pheochromocytoma in its relation to the other non-endocrine tumors of the sympathetic nerve system.

Like most endocrine tumors the pheochromocytoma manifests itself more by symptoms of hormonal overproduction than by invasive growth and metastases, which in fact are rather rare. Its “malignancy” is due mainly to the serious effects of the overflow of its incretory product upon the general metabolism and particularly the cardio-vascular system. But unlike the cortical tumors of the adrenals or the pancreatic islet cell tumors the symptoms of the pheochromocytoma are rather unspecific and may occur in numerous other conditions of functional or organic origin, from
neurocirculatory asthenia to malignant hypertension. Therefore its clinical diagnosis is rather difficult and is made more frequently where the physician is aware of its occurrence and considers the possibility of its presence in a given case, than when a correct diagnosis is expected to be the result of a series of objective laboratory tests. The pheochromocytoma is a rare disease, but the number of clinically diagnosed and surgically cured cases has been increasing rapidly since the first description of the syndrome, and this increase is certainly not due to an increased incidence of the disease, but only to the better diagnosis.

It was more than 25 years after the discovery of the medullary hormone of the adrenals (1895) that the clinical syndrome of the medullary tumor was described by Labbé, Tinel and Doumer in 1922 (9). Humphreys (8) was able to collect 103 cases from the literature up till 1939, but most of these were postmortem observations. In 1937 Howard and Barker (7) reported 18 clinically diagnosed cases, in 1941 Biskind and co-workers (1) analyzed 33 clinically diagnosed and operated cases from the world literature, out of which 26 had been cured surgically, and in 1944 Cahill (4) reported 9 cases of his own observation. In Billings Hospital 5 cases were seen in recent years, 3 of them reported by Brunschwig, Humphreys and co-workers (2). During the 2 years 1945–1946 at least 24 individual reports of successful removal of pheochromocytoma have appeared in the world literature.

It is gratifying to note the increasing frequency with which diagnosis is made or suggested by the practicing physician out in the field instead of being left to the rear echelon of the well equipped diagnostic hospital. The

| Table 1 |

**Sympathoadenoma**
- Highly malignant, metastasizing, not endocrine tumor consisting of immature lymphocyte-like cells, occurring in infancy and early childhood.

**Sympathoblastoma**
- Malignant, metastasizing, not endocrine tumor consisting of immature nerve cells and fibrils.

**Pheochromocytoma**
- Endocrine tumor of chromaffin cells, epinephrine producing, rarely metastasizing.

**Sym pathetic Ganglion Cell**
- Ganglieneuroma benign, usually asymptomatic tumor of sympathetic ganglion cells.
credit for the correct differential diagnosis of the case, here to be discussed, goes to the family physician who referred the patient to the hospital for further observation and treatment.

This patient's case is of special interest because among its presenting signs and symptoms were not only glycosuria but a typical diabetes. As far as we have been able to ascertain, this seems to be the second case of its kind to be reported, the first case being described by Duncan, Semans and Howard in 1944 (6).

The patient, M.L.E. (§228050), was a 20 yr. old white female who was admitted to the Albert Merritt Billings Hospital of the University of Chicago on 7-11-44. She had been in excellent health until about 1942 when she first noticed periodically recurrent headaches, increasing nervousness, occasional attacks of mild dizziness and hyperhidrosis, nocturia and polyuria. It was not until two years later that she was seen by a physician whom she consulted not because of her symptoms but in order to obtain a health certificate. At that time glycosuria and hyperglycemia were found and the diagnosis of diabetes mellitus was made. Her diabetes proved to be hard to control, though she did not develop acidosis or coma. Even 85 units of insulin daily were insufficient to maintain normo-glycemia or to keep the urine free of sugar. Her blood pressure in the spring of 1944 was found to fluctuate between 110/70 and 150/120.

In May, 1944, patient was under observation of the Lilly Laboratory for Clinical Research, City Hospital, Indianapolis. There the fluctuating blood pressure was confirmed. Variations from 110/50 to 170/110 were noted in two daily readings over a period of 3 weeks. The retinal vessels showed a grade 1 constriction and questionable grade 1 sclerosis. Many small retinal hemorrhages were noted in either eye and an occasional white exudate was seen. Plethysmographic examinations of fingers and toes indicated no arteriosclerosis. Electrocardiogram and telerontgenogram of the chest were normal. Kidney function tests gave normal results. The diabetes showed again an unusually high insulin requirement and unusually wide fluctuations of the fasting blood sugar. On a diet of 200 C, 86 P, 100 F, the urine could be kept nearly sugar free but the fasting blood sugar ranged from 72 to 367 mg. per 100 cc.

On admission to Billings Hospital, the patient appeared apprehensive and complained about nervousness, headaches and excessive perspiration. Family history and history of previous illnesses were not contributory. Menstrual history was normal. The physical examination revealed a well developed female with a slight excess of dark hair on face, breast, abdomen and thighs. The patient was not certain whether or not her hair growth had increased recently. Her weight was 48.7 kg. (107 lb.), height 155 cm. (5 ft. 1 in.). The skin was moist and there was mild tremor manum and moderate hyperreflexia. The eye reflexes were normal. No exophthalmos or lid lag was noted. The thyroid was not enlarged. The chest was symmetrical and normal to auscultation and percussion. The heart appeared to be of normal size, rate and rhythm. There were no murmurs. The blood pressure was 170/120; the abdomen was soft, liver and spleen did not appear enlarged, no masses were palpated in the abdomen. The pelvic examination was normal. Fundoscopic examination (Dr. Spiro) revealed many hemorrhages of various sizes over both retinae, surrounded by irregular white exudates. The retinae appeared edematous, the veins were markedly engorged and tortuous, the arteries only slightly constricted. The crossing changes were marked.

The blood count was normal, the serology negative, the urinalysis negative for albumin but positive for sugar, the specific gravity 1.027, the sediment normal. X-ray
examinations of chest and skull were normal, intravenous and retrograde pyelograms showed no abnormalities in kidney shape or function; a small bony defect, in the right ilium near the sacro-iliac joint was observed. (This unidentified lesion was reexamined at intervals during the subsequent two years and has not changed in size.) The electrocardiogram was again normal.

Blood pressure readings were taken 4 times daily and again marked daily fluctuations were noted. Fig. 1 demonstrates the course of the blood pressure. Sodium amyatal and cold pressure tests gave normal responses. The kidney function was studied extensively with urea-, insulin- and diodrast-clearances, and was found to be normal.

The diabetes remained unstable, with fluctuations of the fasting blood sugar between 81 and 290 on a stable diet (200–50–100) and 85 units of insulin. The course of the blood sugar and the insulin dosage are demonstrated on Fig. 1. An insulin tolerance test showed an unusual response with a slight drop of the blood sugar during the first 15 minutes (from 225 to 190) and with a rapid return to a value higher than the fasting level (275) within 2 hours. Such a curve may be obtained if adrenaline is given together with or shortly after insulin. Because of the rather mild hirsutism the question of an adrenal cortical tumor was discussed. The 17-ketosteroid excretion was determined and found to be normal. The blood electrolytes were Cl 96 mEq./L, Na 136.8 mEq./L and K 4.5 mEq./L.

It was felt that pheochromocytoma was the most likely possibility in the differential diagnosis and surgical exploration was recommended. This was performed by Dr. William E. Adams on 7-24. The abdominal approach was used. Exploration of the region of the right adrenal gland revealed a mass approximately 5×3 cm. in size which was medial and superior to the kidney and in the medial aspect of the adrenal gland. The left adrenal appeared normal. The tumor mass was freed from the surrounding tissue, the blood vessels of the tumor were clamped, and the tumor was then removed. During this procedure the blood pressure rose to 240/120 and then fell to a shock level of 60/40; under ephedrine the blood pressure returned to normal levels within a short period of time.

Morphological-pathologic examination of the tumor by Dr. E. Humphreys revealed the following: The tumor, 3×5 cm. in diameter, consisted of rather homogenous tissue.
and had a fibrous capsule. Two pieces of the tumor were immersed in 3 per cent bichromate solution and developed the brownish color typical of pheochromocytoma. Microscopically the tumor was composed of cells arranged in nests and cords separated by small blood vessels. In many regions, the appearance was identical with that of the normal adrenal medulla.

Post-operative course: The patient had an uneventful recovery from her operation. The blood pressure remained within normal limits throughout and was 120/90 on 5-6-46, about two years after the operation (Fig. 1). Headaches, dizziness, nervousness and hyperhidrosis have disappeared completely and permanently.

Reexamination of the fundi showed gradual disappearance of the bilateral retinopathy. By May 1946 the vessels of the fundi had returned to normal appearance; neither hemorrhages, nor exudates or retinal edema were visualized.

The diabetes showed the most spectacular change. Immediately after the operation the fasting blood sugar level began to drop, in spite of the fact that the daily insulin dose had been decreased. Within 10 days the blood sugar had returned to normal and the urine remained sugar free. Only 10 units insulin daily were given during that period. The patient then was permitted a free diet and insulin was discontinued. Her fasting blood sugar remained normal and her urine sugar-free. To check this apparent cure of her diabetes an oral glucose tolerance test was performed the day prior to her discharge from the hospital. This test showed a typical diabetic curve and thus revealed that though the diabetes had improved markedly, it had not been cured (Table 2). After discharge from the hospital the fasting blood sugar was found to be normal at various examinations and the urine to be sugar-free at all times. Annual glucose tolerance tests however showed the persistence of a mild diabetic state.

**COMMENT**

Almost all of the typical features of a pheochromocytoma are illustrated by this patient's history: The fluctuant hypertension, the palpitations, dizziness and headaches are classical symptoms of epinephrine overactivity. Hyperhidrosis, nervousness and tremor manum are encountered frequently as associated symptoms. These, if very marked and accompanied by an elevated basal metabolic rate, may occasionally mislead to the differential diagnosis of hyperthyroidism. It should be remembered

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that epinephrine itself may cause hypermetabolism. The age of the patient and the location of the tumor illustrate the fact that pheochromocytomata occur most commonly in young or middle aged persons and are more frequently found in the right than in the left side of the abdomen. The occurrence of the relatively minor fluctuations of the blood pressure during the operation reminds of the sometimes very serious complications of surgery. Manipulation of the tumor may express large amounts of adrenaline into the circulation which may suddenly precipitate an extremely high rise of blood pressure, peripheral vasoconstriction, lung edema and death. Ligation of all blood supply prior to removal of the tumor, as was done in this case, prevents this hazard. On the other hand, circulatory shock threatens after extirpation of the tumor and substitution therapy with epinephrine and cortical extract is frequently necessary for a short period postoperatively. Because of the occasional multiplicity of pheochromocytomata and the importance of examining both adrenals prior to extirpation of the diseased one, the abdominal approach, as used here, has been accepted generally as superior to the retroperitoneal dorsal method, which permits only unilateral inspection. The return of the blood pressure to a normal level and the practically complete disappearance of the retinal changes are the gratifying and common results of surgery if done in time.

It is noteworthy that, except for the diabetes, the symptoms in our patient were rather mild. None of them alone would have been indicative of a pheochromocytoma, yet the combination of all was very suggestive of the diagnosis which proved to be correct at surgery. This supports Howard's dictum that "when diabetes mellitus, hypertension and hypermetabolism are encountered, the possibility of pheochromocytoma should be considered," to which we may add that this consideration is warranted especially if the patient is of middle age or younger and if no evidence of arteriosclerosis or primary kidney disease is found. Occasionally palpation, more frequently a pyelogram or radiography, in combination with perirenal air insufflation will establish the diagnosis, but not infrequently the tumor is so small that nothing short of exploratory laparotomy will prove the presence or absence of a pheochromocytoma. This, of course, should be done only if the symptoms are suggestive, but then it is indicated, indeed. In many instances exploratory laparotomy may mean the difference between a chance for complete cure on one hand and the poor prognosis of progressive hypertension and arteriosclerosis on the other hand, with the added danger of sudden death in a hypertensive crisis.

The course and the significance of the diabetes in our patient deserves a special discussion. There are a few case reports in the literature where a typical diabetic syndrome, persistent hyperglycemia and glycosuria, was associated with pheochromocytoma, but with the exception of the case of
Duncan, Semans and Howard (6), either the diagnosis of pheochromocytoma was made only postmortem or the patient died soon after operation so that no observations about the later course of the diabetes could be made nor could any conclusion be drawn as to the relationship of the diseases. In the only case similar to ours, an insulin resistant diabetes of more than three years' duration improved to such a degree that it could be considered cured for all practical purposes. The patient did not require insulin any longer and was sugar free and normoglycemic on a daily intake of 300 Gm. carbohydrate. Here too, however, decreased glucose tolerance tests were obtained months after removal of the tumor, but the authors were inclined to minimize the significance of this "slight residual defect in the mechanism of carbohydrate disposal." In this as well as in our case the marked, rapid and persistent post-operative improvement of the disturbed carbohydrate metabolism argued strongly against the possibility that the diabetes was a coincidental and independent disease. The relatively high insulin requirement in both instances points in the direction that extra pancreatic factors were at least contributory to the occurrence of hyperglycemia and glycosuria. Overactivity of epinephrine, causing increased glycogenolysis in the liver, was most likely the initial step in this mechanism. As long as the hormone secreting tumor was present the hyperglycemia persisted. After the operation a return to normal, a restitutio ad integrum, seemed to have occurred, but a persistent though latent disturbance of the carbohydrate metabolism became evident under the stress of the glucose tolerance test. It seems to us that this remaining decreased carbohydrate tolerance deserves the same emphasis as is given to the marked clinical improvement. It has long been argued that prolonged hyperglycemia of non-pancreatic origin may lead to irreversible pancreatic islet cell damage and diabetes. The present stand on this problem and the evidence in favor of this hypothesis has been summarized ably by Ricketts (10), and only recently Dohan and Lukens (5) have demonstrated islet cell degeneration in cats, the blood sugar of which had been elevated for prolonged periods of time by glucose injection. The assumption, therefore, seems permissible that the prolonged hyperglycemia which was produced by the pheochromocytoma had exerted irreversible damage upon the blood sugar regulatory mechanism so that a decreased carbohydrate tolerance persisted after removal of the tumor. Unfortunately no biopsies from the pancreas were obtained in our patient. Further clinical observations will have to prove whether such damage is manifested by histological changes in the pancreas.

**SUMMARY**

A new case of pheochromocytoma with diabetes is reported and the symptomatology of this syndrome is discussed. The persistence of a de-
creased carbohydrate tolerance after successful removal of the tumor seems to give support to the theory that hyperglycemia of extrapancreatic origin may cause irreversible pancreatic islet cell damage and diabetes.

ACKNOWLEDGMENT

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REFERENCES

8. Humphreys, E. Personal communication (see ref. 3).