MEDULLATED CORNEAL NERVES AND PLEXIFORM NEUROMA ASSOCIATED WITH PHEOCHROMOCYTOMA

BY *Alson E. Braley,* M.D.

BRUCE (1) reviewed the fundus findings in pheochromocytoma of the adrenal gland in 1947. He reviewed the cases in the literature and found that 108 had been reported. This review included one case reported by Van Epps and his co-workers. I was fortunate enough to see the patient in this case while he was being studied at the University Hospitals in Iowa City, Iowa. Koke (2) and I reported the external ocular findings in this patient in 1940. So far as I have been able to find this is the only case of extensive medullation of the corneal nerves reported. Since that time I have seen two patients with plexiform neuromas of the conjunctiva and medullated corneal nerves. Both of these patients were later shown to have pheochromocytoma of the adrenal. In none of these patients has there been any evidence of generalized neurofibromatosis. Bruce, in his review, stressed the ophthalmoscopic findings and concluded that they could not be differentiated from those in so-called "essential hypertension." Since the findings of medullated corneal nerves and plexiform neuroma of the conjunctiva have not been stressed, I believe the ophthalmologist should be aware of this association.

Bruce has reviewed the pathology and history of the disease. He stressed that there had been an increasing number of tumors reported in the last few years. The medical literature contains many reports of cases, but very little has been said in the ophthalmic literature since Bruce's report.

SYMPTOMS

The symptoms of pheochromocytoma are varied and complex. They may be associated with continuous hypertension, or hyper-

tension may come on in attacks. Some variation in blood pressure is an almost constant finding. The blood pressure may be normal between attacks or it may be moderately elevated. The attacks may last for only a few minutes or for several hours, and during the attacks the blood pressure may be very high. There is nervousness, palpitation, air hunger, and flushing or cyanosis.

In my experience glycosuria and hyperglycemia are frequent findings. In all three of the cases which I am presenting here, the fasting blood sugar was over 200 mg. %. (Case 1, 273 mg. %; Case 2, 240 mg. %; Case 3, 220 mg. %.) Two of the patients were treated as diabetics for several years before the diagnosis of pheochromocytoma was suspected. In addition to the symptoms of palpitation these patients had heat intolerance, excessive perspiration, and elevated basal metabolic rates. All three of these patients were considered to have thyrotoxicosis. The electrocardiographic findings will not be stressed in this report; however, it is of interest that there is a flattening of the T wave in all tracings.

The case reports will bring out additional symptoms.

CASE REPORTS

CASE 1. This white male was seen in September of 1938, when he was twenty-eight years of age. Koke and I reported the findings of medullated corneal nerves and plexiform neuromata in this case in 1940.

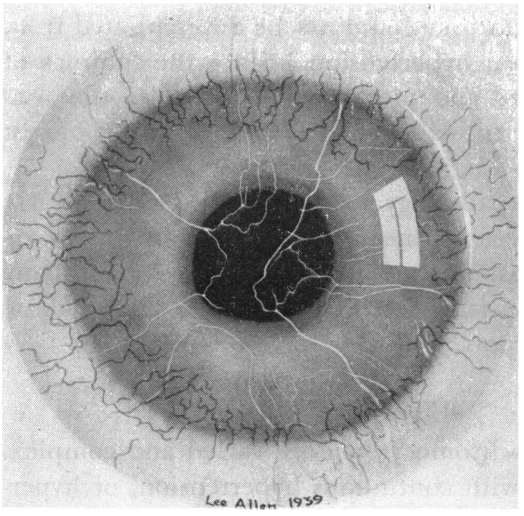

FIGURE 1. WHITE FIBERS IN THE CORNEA (MEDULLATED CORNEAL NERVES)

Figure 1 shows the extent of the white corneal nerves. The limbal vessels were also prominent, but they were entirely superficial and came from the conjunctival circulation. Biomicroscopic examination of the corneas under low power and with a broad beam of light revealed a network of fine grayish-white anastomotic and interlacing fibers situated in the stroma. Several of the main trunks, which were 5 or 6 mm. in length, could be seen without magnification. These whitish-gray structures were situated at the junction of the anterior two-thirds and the posterior third of the corneal lamellas, but as they extended toward the pupillary area they diminished in caliber and became more superficial. There were two sets of the whitish-gray structures, both of which branched dichotomously. The larger set sent branches into the pupillary area, while the smaller, more superficial set branched in the periphery. Some of the branches arched backward toward the limbus and anastomosed with similar branches, while others extended into the more superficial stroma and disappeared. At a few of the nerve forks there was a slight bulbar enlargement.

An egg-sized pheochromocytoma was removed from the right adrenal. Following this the blood pressure returned to 115/75 and the patient remained well. When he was last seen nearly all of the white fibers in the corneas had disappeared. For a complete case report one should read the reports by Van Epps, Hyndman, and Greene (3).

Case 2. A thirty-seven-year-old white woman, who was first seen on December 5, 1952. She gave a history of having been nervous and easily upset since being in high school. In October before admission she was found to have glycosuria and was treated with NPH insulin. On 26 units her urine was sugar free. A diagnosis of thyrotoxicosis was made and she was given propylthiouracil, 150 mg. daily, before admission. Physical examination yielded some suggestion of hyperthyroidism. The blood pressure was 165/90, but the heart was not enlarged. The electrocardiogram showed some flattening of the T waves. Her fasting blood sugar was 180 mg. per 100 c.c.; however, her glycosuria was stabilized on 10 units of regular insulin three times a day before each meal.

I first saw her on January 6, 1953, because of the peculiar limbal tumors (Fig. 2). One of these tumors had been previously removed, but the diagnosis had not been made. At previous times she had been examined by ophthalmologists and a tentative diagnosis of limbal vernal was suggested. Examination with the biomicroscope revealed white lines in the cornea in the middle layers of the stroma which suggested medullated corneal nerves. These white lines extended into the pupillary area and there were small bulbous enlargements at the bifurcations. There was no peripheral vascularization at the limbus. The tumors at the limbus looked like gelatinous masses with a sug-

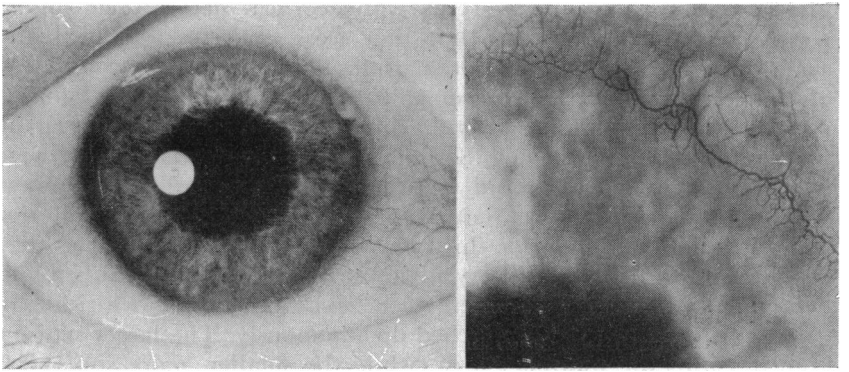

FIGURE 2. PLEXIFORM NEUROMA AT THE LIMBUS

gestion of coiled material. I suggested the diagnosis of pheochromocytoma because of my previous experience with medullated corneal nerves. There were two small neuromas on the upper tarsus, one of which had been removed for histologic study. (Fig. 3, the whole tumor; Fig. 4, Held stain.)

It was then possible to obtain the history that she had had attacks of palpitation since the age of thirteen. These attacks might occur many times a day, but many days were completely free of attacks. The attacks never lasted more than five minutes. They were associated with very rapid pounding of the heart, swelling of the neck, prominence of the eyes, dizziness, and rapid breathing. The attacks stopped as suddenly as they began without any residual. On a few occasions she had an attack during sleep and would be suddenly awakened. On January 23, the patient was observed during one of these attacks. Her pulse rate was 110 per minute, and the blood pressure was 240/140. The attack lasted about two minutes and her pressure returned to normal within one minute.

Two circular tumors were found above the left kidney after air unsufflation around the kidneys. On February 16, 1953, two masses were removed from the left adrenal, one 9 cm. in diameter and a smaller one of 3 cm.

Postoperative recovery was moderately stormy, her systolic blood pressure dropping to below 90 or rising to above 200. On April 13, 1953, she was re-examined and it was found that the medullated corneal nerves had not changed. Her fasting blood sugar was 268 mg. % and after 0.05 mg. of histamine intravenously the blood pressure rose above 200/160. Intravenous injection of 5 mg. of regitine was followed by a prompt fall of pressure to normal. She was readmitted to the hospital in August of 1953, stating that she had had almost daily episodes. During the attacks the blood pressure would rise to 204/120.

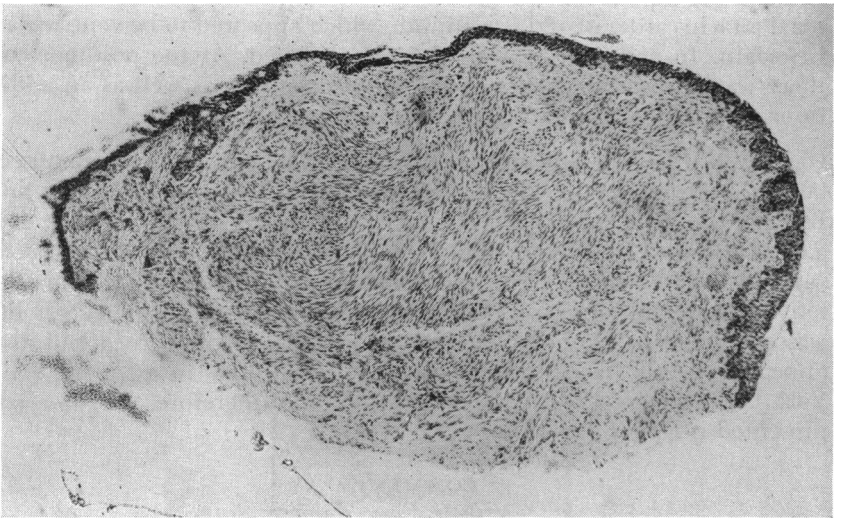

FIGURE 3. HISTOLOGY OF THE PLEXIFORM NEUROMA

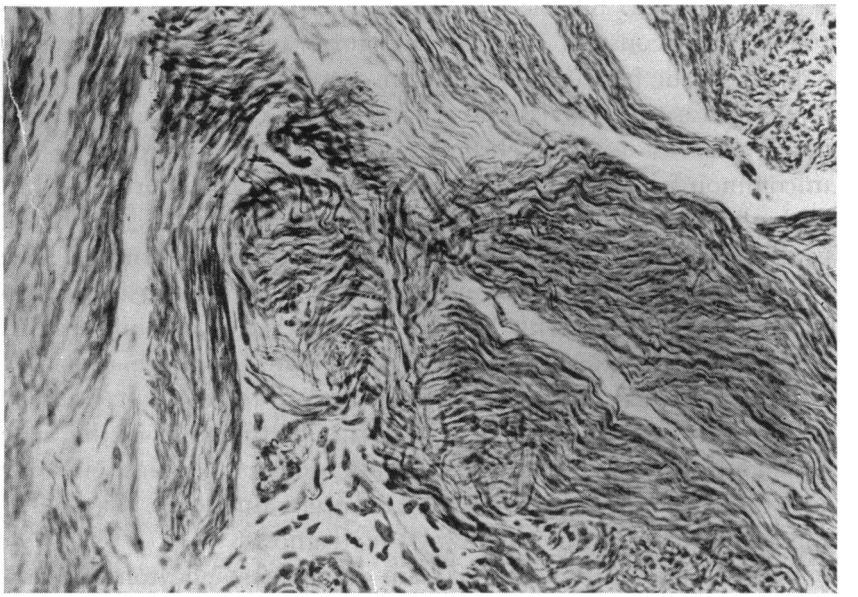

FIGURE 4. SILVER STAINS OF THE PLEXIFORM NEUROMA

She was transferred to Urology for surgery. During preparation for surgery, an exploration of the left kidney region, she suddenly developed a tachycardia of 180 per minute, which appeared to be ventricular in origin. In spite of vigorous therapy she died. At the post-mortem there was residual tumor in the right adrenal area as well as an additional tumor in the left adrenal area.

CASE 3. A thirty-six-year-old male was seen in 1949. He was examined because of nodules on the palpebral conjunctiva of the upper lid. Biomicroscopic examination showed white fibers in the cornea. He gave a history of recurrent attacks of hypertension. His fasting blood sugar was 220 mg. %. A pheochromocytoma was removed from the left adrenal and the postoperative course was uneventful. When he was examined in May of 1950, the white fibers in the cornea had disappeared. (This history is that of a patient I saw in 1949 in New York, and whose record is not available to me; therefore, the material presented is from memory.)

COMMENT

Pheochromocytoma of the adrenal gland may produce either a constant hypertension or an intermittent hypertension. The constant hypertension, secondary to the tumor, may be seen at any age, but is most common in children. The blood pressure is constantly elevated, but may be further elevated by insults to the tumor. The constant type is invariably associated with vascular changes in the fundus. The vascular changes vary with the severity of the disease, and are predominately those which occur in essential hypertension. The chronic form is more bizarre. It is not uncommon for these patients to have a normal blood pressure, but with a history of attacks of syncope. During these attacks the blood pressure will rise sharply, with rapid recovery to normal. The attacks usually last a few minutes. Glycosuria or elevated metabolic rate may be present. Medullated corneal nerves which extend to the center of the cornea, particularly when they are associated with the so-called "amputation neuromas" of the conjunctiva, may be found in the chronic form. The clinical diagnosis of this type of pheochromocytoma is very difficult because the symptomology and the findings are so varied. The ophthalmologist may be of considerable assistance in making the diagnosis.

In some cases of the chronic form of pheochromocytoma medullated corneal nerves are present, while in others there are none.

The mechanism of their development is unknown. Vogt (10), Berliner (11), and many others have described medullated corneal nerves observed with the biomicroscope in some normal people. These white lines rarely extend beyond the limbus for more than a millimeter. The embryological explanation for their occurrence may be similar to the explanation of the medullated nerve fibers seen in the fundus.

The important differentiation must be made between the diagnosis of neurofibromatosis and pheochromocytoma. Cases were reported in which there were thickened or medullated corneal nerves associated with neurofibromatosis by Snell (4), Collins and Batten (5), Sutherland and Mayou (6), Loos (7), and Hine and Wyatt (8). All these cases had wide involvement of the face, lids, or other areas. Several had extensive elephantiasis of the lids and face (Duke-Elder [9], Vol. 5, p. 5104).

The three cases reported here all showed a type of plexiform neuroma of the conjunctiva. These tumors are similar to amputation neuromas and consist of coils of medullated nerve fibers. Neurofibromas are composed chiefly of fiber-like tissue arranged in palisades, and contain a nerve that runs through, or is adjacent to, the tumor. Neurofibromas are common, and few patients with neurofibromatosis show medullated corneal nerves. It is not beyond the realm of possibility that the patient reported with medullated corneal nerves may also have had a pheochromocytoma. In the past year four patients have been seen with clinical diagnoses of pheochromocytoma. All of these had a continuously elevated blood pressure with paroxysms in which the blood pressure would rise much higher. I feel, therefore, that there are two types of pheochromocytoma, the acute and the chronic.

The acute form is most common in children. It is associated with almost constant hypertension and hypertensive vascular changes in the fundus. There is no evidence that this type will develop medullated corneal nerves or plexiform neuroma of the conjunctiva.

The chronic form is slow in developing and the attacks of hypertension are irregular and of short duration. They last only a few minutes and the blood pressure is normal between the attacks. As the attacks increase in frequency glycosuria may de-

velop. If the attacks are infrequent the diagnosis of pheochromocytoma may not be made for twenty or more years.

SUMMARY

Three cases of medullated corneal nerves and plexiform neuroma of the conjunctiva occurring in patients with the chronic form of pheochromocytoma of the adrenal are reported. This occurrence seems to be more than incidental since in two cases the tumors disappeared and the white fibers in the cornea disappeared after complete removal of the tumor. The ophthalmologist should be acquainted with the clinical syndrome.

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DISCUSSION

DR. CECIL W. LEPARD. Dr. Braley's most interesting report of three cases of plexiform neuroma of the conjunctiva and medullated nerve fibers of the cornea associated with pheochromocytoma seems to be entirely original.

Since a review of 210 cases of paraganglioma or pheochromocytoma in 1947 by Brines and Jennings, they estimate the present total to be almost double that number. It would seem then that the number showing associated ocular findings would be larger than the absence of reports would indicate.

One must keep in mind the great variety of manifestations of pheochromocytoma. It has been reported in an infant one year old and in a man of seventy. Also there is a form of pheochromocytoma reported in which there is no elevation of blood pressure and no symptoms or signs of the disease. It would seem, then, that one might classify pheo-

chromocytoma as benign or malignant, rather than as acute or chronic.

Although the records at the Children's and Receiving Hospital of Detroit failed to show the associated conjunctival and corneal changes which Dr. Braley described, the fundus findings in a series of 10 cases (9 adults and 1 child) closely parallel those reported by Doctors Braley and Bruce. One of the cases, a ten-year-old Negro boy, came to the Receiving Hospital complaining of impaired vision. Many superficial retinal hemorrhages, edema of the disc, and advanced hypertensive changes were noted in the retinal arteries and veins. Following the removal of an adrenal tumor the retinal changes receded, while a previously constantly elevated blood pressure returned to normal, as Dr. Braley suggests happens in children.

The reason for the loss of myelin sheaths following the removal of a pheochromocytoma is very intriguing and a subject of much speculation. It is known that pheochromocytomas contain a vasopressor substance which can be fairly accurately measured. One can speculate, and it is of course pure speculation, that this tumor also may give rise to substances in some cases which are related to the medullation of corneal nerves and conjunctival plexiform neuromas.

With the increasing reports by pathologists and internists, Dr. Braley's paper should stimulate ophthalmologists to further clinical and pathologic investigation.

DR. ALSON E. BRALEY. I would like to thank Dr. Lepard for his discussion. I was hoping that some other members of the Society might have seen some of these cases, and I hope in the future that you will all look at patients with pheochromocytoma with the slit-lamp microscope.