EXTERNAL OPHTHALMOPLEGIA, PIGMENTARY DEGENERATION OF THE RETINA, AND CARDIOMYOPATHY: A NEWLY RECOGNIZED SYNDROME

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IN 1958 SAYRE and I[1] reported on two patients under the title "Retinitis pigmentosa, external ophthalmoplegia, and complete heart block. . . ." Although chronic progressive external ophthalmoplegia has been associated with a multitude of other diseases, including retinitis pigmentosa, the triad of external ophthalmoplegia, retinitis pigmentosa, and heart block had not been previously reported. We believed then that this association, although seen in only two patients, represented a syndrome and was not merely a chance occurrence. Since that report, we have seen a number of similar cases. Although our better understanding of these cases and of the associated findings has produced some changes in our interpretation, we feel even more strongly that the association of these findings represents a syndrome not previously recognized.

The purpose of this paper is (1) to present the historical background of external ophthalmoplegia occurring alone or in association with pigmentary degeneration of the retina or cardiomyopathy and (2) to report a series of cases of a newly recognized syndrome consisting of the occurrence of external ophthalmoplegia in association with both pigmentary degeneration of the retina and cardiomyopathy.

HISTORY OF EXTERNAL OPHTHALMOPLEGIA

The disorder now most often called "chronic progressive external ophthalmoplegia" has been referred to by many names, indicating the undecided etiology of the condition. Since von Gräfe[2] first described the disorder in 1868, it has often been referred to as von Gräfe's

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TR. AM. OPHTH. SOC., vol. 63, 1965

disease. Möbius[3] named the condition "chronic progressive nuclear ophthalmoplegia," and this term, or variants implying its nuclear etiology, was the most frequently used until 1951, when Kiloh and Nevin[4] in their classic article showed that the disease is really a myopathy and suggested the term "ocular myopathy." Other terms used are "progressive paralysis of the extraocular muscles," "hereditary ophthalmoplegia," "symmetrical paralysis of the extraocular muscles," "familial ptosis with ophthalmoplegia," "hereditary congenital ophthalmoplegia," "infantile nuclear atrophy," "double ophthalmoplegia externa," and "abiotrophic ophthalmoplegia externa."

Since the disease is now generally recognized as being a disorder of the ocular muscles, it is being referred to as "ocular myopathy" or "ocular dystrophy." It would seem, however, that, for the sake of clarity, the preservation of the term "chronic progressive external ophthalmoplegia" would be wise, since it does not differ too greatly from the older terms.

The first description of chronic progressive external ophthalmoplegia in the English literature was by Hutchinson[5] in 1879. He proposed the term "ophthalmoplegia externa." He used this term in contradistinction to the term "ophthalmoplegia interna," which he had used to describe other conditions. He wrote:

> Drooping of the eyelids, so as to give to the face a half-asleep expression, is usually the first, and it is soon accompanied by weakness of all the muscles attached to the eyeball, so that the movements of the latter become much restricted, or even wholly lost. The condition is usually bilateral, though it is not always exactly the same in degree on the two sides. Its symmetry probably denotes that it is of central origin.

Hutchinson suggested that this disease is a close parallel to so-called bulbar paralysis. He also suggested that the initial lesion might be an inflammation of nuclei of the affected nerves. He further stated that although "this group of cases has not found any record in English medical literature, it has not escaped notice in Germany." He cited the patients described by von Gräfe and noted that the latter used the word "ophthalmoplegia" in referring to them.

Hutchinson then presented case histories of 17 patients and remarked that the first case was unusual in that he was able to produce a photograph of the patient. He injected a bit of humor in stating that the photographer complimented the patient on being "an unusually good sitter, for he never moved his eyes."

Syphilis was thought to be the cause in eight of Hutchinson's cases. Gowers[6] performed necropsy in one of Hutchinson's cases and said that the state of the nuclei of the ocular nerves was nearly the same as that of the gray matter of the spinal cord in progressive muscular atrophy. The roots of the ocular nerves outside and inside the brain were gray and small, and contained scarcely any normal fibers. In the nuclei a few nerve cells of normal size were seen, but these had mostly lost their processes, and a large number of the cells had been reduced to small angular bodies or had disappeared. This necropsy helped to perpetuate the idea that chronic progressive ophthalmoplegia was nuclear in origin. Gowers undoubtedly was correct in his observations, but the fault probably is that this case was not one of chronic progressive external ophthalmoplegia. Hutchinson remarked that although he had found no evidence of syphilis, this patient later had developed optic atrophy, and a daughter of this patient was seen later with notched teeth and a most characteristic syphilitic keratitis.

Following the report of Hutchinson, a number of reports concerning this disorder appeared in the English literature. Beevor[7] in 1887 reported a case and remarked that his patient did not know that the eyes were fixed until told so. This is true of many of these patients, and certainly their ocular complaints are not related to the lack of ocular rotation but to the drooping of the eyelids. Bristowe[8] reported on five patients in 1886; possibly one of his patients may have had a cardiac disorder similar to that of patients with the syndrome to be described in the present paper. This will be discussed later.

Birdsall,[9] in a paper written in 1884 but not published until 1887, described two cases of this disorder seen at the Manhattan Eye and Ear Hospital in New York City. He concluded on clinical grounds that "the nuclei of origin are the parts involved."

Mittendorf[10] in 1887, in addition to reporting another case, summarized the reported cases up until that time and was able to collect only 30 cases. He considered only three of Hutchinson's cases to be truly typical of the disorder, and he thought that only 21 of the 30 reported cases really represented pure chronic progressive external ophthalmoplegia, because others were complicated by paralytic affections of other muscles or by marked lesions of the nervous system. Mittendorf stated that the evidence pointed to a nuclear change as the cause for the ophthalmoplegia, but whether due to anemia or hyperemia or other causes could not be stated. He referred to four previous necropsies but thought that none of these cases represented

pure forms of the disorder since they were complicated with other brain or nervous symptoms. He said that lack of knowledge regarding the etiology was excusable since this entity had been described only recently and the cases were rare.

Davidson[11] in 1888 reported a case and speculated that the causative lesion was a central one. Lawford[12] also in 1888 reported four cases in one family and wondered whether the cause was not the absence or the abnormal insertion of extraocular muscles.

In 1889 Cheney[13] reported a case and also mentioned that the patient did not know that the ocular rotations were impaired. He also adhered to the "nuclear origin" theory.

To Fuchs[14] goes the credit for first stating, in 1890, that this disorder is due to disease of the muscle and not disease of the nerve nuclei. He reported five cases and did a biopsy of the levator in one. He found that the muscle fibers showed extensive degeneration. He interpreted this as a dystrophic change. However, this fact was soon forgotten and for many years the nuclear-origin theory was used to explain the disorder.

A considerable number of reports on chronic progressive external ophthalmoplegia appeared prior to 1900, and most authors[15–21] accepted the nuclear theory without question. Silex,[20] however, agreed with Fuchs and stated that the ptosis in his patients was due to primary muscle degeneration.

Jackson[16] in 1893 is the first to mention orbicularis weakness accompanying chronic progressive external ophthalmoplegia. Both of his patients had this feature. He used Mendel's hypothesis to reconcile the orbicularis weakness with a disorder thought to be due to a disease of the oculomotor cranial nerve nuclei; this hypothesis postulated that the fibers of the seventh nerve intended for the orbicularis palpebrum do not arise from the seventh nerve nuclei but from the nuclei of the third nerve. Beevor[17] in 1895 also described a patient with orbicularis weakness and used this same hypothesis as evidence that the etiology of the disorder was in the third nerve nuclei.

Norris and Oliver[22] in 1900 commented on this suggestion of Jackson. They stated that very occasionally there is partial paralysis of the orbicularis palpebrum so that "in washing the face, soap gets into the patient's eyes, and even with the greatest effort at closure, light is still seen between the eyelids and little resistance is offered to passive elevation of the upper lid." The probable explanation of this, they said, is that the oculofacial group of muscles (frontalis, corrugator supercilii, and orbicularis palpebrum) is innervated from

the third nerve nuclei by way of the posterior longitudinal bundles, the fibers passing there in the trunk of the facial nerve to supply the group in question.

Wilbrand and Saenger[23] in 1900 gave an excellent and often quoted description of this disorder.

> Bilateral, slowly progressive paralysis of the external muscles of the eyes develops without any other signs of disease. Years may elapse between the development of the first symptom and the development of complete ophthalmoplegia. The onset is gradual, usually beginning in childhood, seldom in adult life. The rate of progression is variable, but it generally ends in complete external ophthalmoplegia. Ptosis may be the first sign of the disease, and may, for a considerable period of time, be the only one. After the ocular muscles become affected diplopia may be complained of, but this symptom is infrequently noted because of the extremely slow progress of the paralysis, and because it is generally symmetrical. The health of the patient is not affected. It is a striking feature of the affection that no other signs or symptoms develop, indicating implication of other organs or other structures of the nervous system.
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> [Translated by Langdon and Cadwalader[24]]

They based their observations on 32 cases collected from the literature, and they regarded the disease as one of the ocular nuclei.

Numerous other case reports[25–34] soon appeared in the literature, none of which did more than add to the growing list of reported cases.

Friedenwald[35] presented a paper before the American Ophthalmological Society in 1922 on "ophthalmoplegia exterior." He described six cases, three of which were thought to represent chronic progressive external ophthalmoplegia. Collins[36] discussed this paper and suggested that the cause of the disorder was probably an "abiotrophy of the muscles of the eyeballs and the eyelids."

Li[37] in 1923 reported three cases and stressed the congenital nature of the disorder. Calhoun[38] in 1927 reported a case and gave the cause as a "lack of inherent vitality." He mentioned that this theory of endowed vitality of the nuclei of the third, fourth, and sixth cranial nerves was suggested first by McMullen and Hine. Calhoun thought that the endowed vitality of the nuclei in his patient had perhaps been impaired by a severe attack of dysentery at an early age. Ford[39] in 1927 also referred to McMullen's and Hine's theory that a congenital weakness of the nerve centers leads to premature decay.

Langdon and Cadwalader[24] in 1928 read a paper before the American Ophthalmological Society in which they presented the necropsy findings in a patient with chronic progressive external ophthalmoplegia

and said they believed theirs was the first reported necropsy in an authentic case of this disorder. They found that the cells of the ocular motor nerves of each side were slightly diminished in number while the cells of the Edinger-Westphal nucleus and Perlia's nucleus appeared normal. The fibers of the third nerve stained well in Weigert sections, but were much less conspicuous than in sections of normal tissue. They did not examine the extraocular muscles, but thought that they would have been severely atrophied. Their patient was 84 years old at the time of her death. Calhoun discussed this paper and again referred to the theory of McMullen and Hine. He stated that he accepted this theory and that the disorder was due to a "lack of inherent vitality, or in abiotrophy of the cells of the nerve nuclei involved and the time of the onset depending on the degree of vitality with which these cells were originally endowed."

Other articles[40,41] soon followed. De Schweinitz said he thought the ophthalmoplegia was due to the combined influence of nuclear aplasia and structural defects of the ocular muscles.

In 1936, Martin[42] described a case of progressive external ophthalmoplegia with wasting of the musculature of the face and neck, including the sternocleidomastoids. He thought that his case belonged to the group called "chronic progressive nuclear ophthalmoplegia," but other features of it suggested that the ophthalmoplegia was not nuclear but myopathic.

Other authors[43–46] accepted the nuclear theory. Elliott's[47] patient in 1939, in addition to having a type of chronic progressive external ophthalmoplegia, had weakness of the orbicularis and frontalis as well as some weakness of the shoulder girdle and upper extremities. Martin, commenting on this paper, said "a good case could be made out for some of the patients being considered as myopathic and not nervous," a statement that he had expressed in his 1936 article.

Wilson[48] in 1940 considered the disease to be a "progressive nuclear ophthalmoplegia," but stated that more than one process is capable of producing it. He pointed out that although theoretically no muscle groups except the ocular ones should be involved, sometimes the orbicularis muscles are weak. Although Wilson did not state this, it would seem that he too was dissatisfied with the nuclear theory. Other reports[49–54] adhered to the nuclear theory, however.

Sandifer[55] is sometimes cited as the first to point out, in 1946, the myopathic nature of the disease. He reported a typical case of chronic progressive ophthalmoplegia. The patient also had orbicularis weakness. Biopsy of the levator done at operation for ptosis revealed

myopathic degeneration rather than neuropathic atrophy. The patient had a bundle-branch block which the author suspected was due to cardiac myopathy. This patient did not have retinal degeneration. Despite Sandifer's article, other articles[56–60] continued to appear in support of a nuclear etiology.

In 1951, Kiloh and Nevin,[4] in their classic article, described five cases of chronic progressive external ophthalmoplegia which, on the basis of muscle biopsy, they thought represented forms of progressive muscular dystrophy with early and predominant affection of the extraocular muscles. They suggested that the term "ocular myopathy" be used. They found reports of 99 cases of this disease. They thought that no evidence was found to justify the view that the disease in any of these cases was due to a systematized degeneration of the ocular motor nuclei, and they said that all the cases appeared, in fact, to be examples of ocular myopathy. Their description of the disease, as they saw it, is given below.

> The condition may commence at any time from infancy to over 50 years of age. Some cases have been described in which slight ptosis was present at birth (Fuchs, 1890) but subsequently progressed. The majority commence before 30 years of age. . . . Males and females are about equally affected. A family history of ptosis or ophthalmoplegia is found in half of the recorded cases. Ptosis . . . is nearly always the first sign of the condition, though Jocqs (1893) and Hanke (1895) described patients in whom the ptosis was preceded by ophthalmoplegia.
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> The onset and the progress of the condition are both insidious. . . . Though slight fluctuation in the ptosis may occur in relation to fatigue, marked periodicity and remissions are not seen. The advance of the condition may be halted at any stage either temporarily or permanently. . . . Diplopia is sometimes an early symptom but is absent in the majority of cases. . . . Pupillary changes are not found. . . .
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> The facies . . . is characteristic. . . . The forehead is constantly wrinkled in an effort to elevate the lids, the head is tilted backwards and the drooping eyelids give the patient a remarkable sleepy expression. The eyebrows are elevated well above the supraorbital ridges, except in those cases in which the facial muscles are weak. In these, the forehead may be smooth and the eyebrows normal in position. The upper eyelids may become thin and wasted and sink underneath the bony margin of the orbit. In a quarter of the recorded cases various other muscles have been involved and with very few exceptions these have always included the orbiculares oculi. . . . The muscles of mastication are not infrequently affected. . . . Involvement of muscles supplied by spinal segments has been found in approximately 10 per cent of cases. All the neck muscles may be weak with considerable wasting of the sternomastoids. The upper trapezii are often affected and

the muscles of the shoulder girdle show varying degrees of weakness. . . . It is uncommon for the patient to complain of any disability affecting the trunk or limbs. . . . There is no evidence of any relationship between this group of cases and dystrophia myotonica.

Since this publication by Kiloh and Nevin in 1951, most articles on chronic progressive external ophthalmoplegia have accepted the view that the condition is a myopathy, but a few exceptions are found.[61-66]

Alfandary[67] in 1954 reported four cases and thought that they represented a special form of muscular dystrophy. Schwarz and Liu[68] in 1954 reported the histologic study of extraocular muscles and ocular motor nerves and concluded that chronic progressive external ophthalmoplegia is a form of muscular dystrophy. Thiel[69] in 1954 indicated that the disease is an ocular myopathy. His opinion was based on biopsy and electromyographic studies of non-ocular muscles.

Björk[70] in 1954, although he did not do electromyographic studies in a case of chronic progressive external ophthalmoplegia, thought that such studies would be a great aid in differentiating this disease from other conditions. Other reports[71-73] accepted the view that this disease is a myopathy.

The first report of electromyographic studies on chronic progressive external ophthalmoplegia is that of Papst[74] in 1959. He stressed the diagnostic importance of these studies and referred to the disease as chronic progressive ocular muscular dystrophy. Breinin[75] in 1958 showed that the electromyographic findings from ocular myopathic or dystrophic muscle were similar to those recorded from systemic myopathic or dystrophic muscles. He states that such muscle is characterized by loss of individual muscle fibers with retention of most of the motor units. This gives rise on effort to an abundant discharge of low-voltage units, some of which are polyphasic. Others[76-82] also reported electromyographic studies of ocular muscles of patients with external ophthalmoplegia.

A number of recent reports[83-88] state that histologic study of the ocular muscles has verified the myopathic nature of the disease. Mölbert and Doden[89] in 1959 reported the only case of chronic progressive external ophthalmoplegia in which the ocular muscles were studied by electron microscopy. They examined three patients and stated that the muscle cells, which appear normal by light microscopy, have a definitely affected appearance by electron microscopy. They found no changes in the nerve fibers and believed this further confirmed the myopathic nature of the disease.

A few additional reports[90-94] on the myopathic nature of the disease appeared.

The reports of this disorder that are considered significant by the present author are listed in Table 1.

TABLE 1. PREVIOUSLY REPORTED CASES OF CHRONIC PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA*

Author	*Date*	*Remarks*
von Gräfe[2]	1868	First description of this disorder
Hutchinson[5]	1879	First description in English literature, and disorder named "external ophthalmoplegia"
Gowers[6]	1879	Performed first necropsy (one of Hutchinson's cases): showed disappearance of nerve cells from cranial nerve nuclei
Mittendorf[10]	1887	Collected 30 cases from literature and further defined and clarified the disorder
Fuchs[14]	1890	First discovered that the disorder is a disease of muscle and is not "nuclear"
Jackson[16]	1893	Orbicularis weakness first noted to be associated with the disorder
Wilbrand and Saenger[23]	1900	Classic description of the disease given although considered to be of "nuclear" etiology
Collins[95]	1922	Suggested that the disorder might be a primary muscle degeneration
Langdon and Cadwalader[24]	1928	Reported what they thought to be the first necropsy in an authentic case, thought to be "nuclear"
Martin[42]	1936	Again it was suggested that the disorder was myopathic and not nuclear
Sandifer[55]	1946	Showed histologically that the disorder is "myopathic degeneration and not nuclear atrophy"
Kiloh and Nevin[4]	1951	Classic article proving histologically that the disorder is an ocular myopathy

*Only the reports the author considers significant.

HISTORY OF EXTERNAL OPHTHALMOPLEGIA ASSOCIATED WITH PIGMENTARY DEGENERATION OF THE RETINA

The association of chronic progressive external ophthalmoplegia and pigmentary degeneration of the retina has been reported fairly frequently, mostly in the last 20 years. It seems strange that no similar association was noted by the earlier writers on chronic progressive ophthalmoplegia.

The first reported case that sounds like pigmentary degeneration of the retina associated with external ophthalmoplegia is the second of two cases reported by McMullen and Hine[34] in 1921 under the name "chronic progressive ophthalmoplegia externa." The patient, an 18-year-old girl, had ptosis and ophthalmoplegia typical of the condition under discussion. In addition, "both fundi show scattered, fine, pigmentary changes of old retinochoroiditis." The central vision could be corrected to only 6/18 in the right eye and 6/12 in the left. Perhaps this could have been retinochoroiditis, as the authors assumed, but it would seem more likely that this represented a degenerative retinal change and not an inflammatory one. As will be pointed out later, the retinal changes are frequently misinterpreted as post-inflammatory.

In 1944, Barnard and Scholz[96] reported four cases of "ophthalmoplegia and retinal degeneration." They remarked that although a number of diverse neurologic changes have been associated with forms of retinal degeneration, there were no previous reports of the association of ophthalmoplegia with retinal degeneration. Although Barnard and Scholz are usually credited with first noting this association, one may question whether all of their cases were true examples of the condition. Davidson[86] excluded these cases on the grounds that other factors might have been responsible for the external ophthalmoplegia. Barnard's and Scholz's first patient probably had Graves' disease since she had had a thyroidectomy, following which there was some question of proptosis. Later, when the ophthalmoplegia developed, the "lid fissures were abnormally wide and there was a lid lag." Their second patient had syphilis, with positive blood and spinal fluid reactions. The third patient also had syphilis. It would seem that the fourth patient was a true example of the association of chronic progressive external ophthalmoplegia and pigmentary degeneration of the retina; Walsh[97] recognized this case as such and reported three additional cases.

Chamlin and Billet[98] in 1950 reported three cases of ophthalmoplegia and pigmentary degeneration of the retina. They pointed out that the pigmentary changes may be scant and difficult to recognize. They thought it possible that some of the patients previously reported with chronic progressive external ophthalmoplegia may have had these retinal changes which were overlooked. They believed that the detection of these retinal changes was often a considerable aid in the diagnosis of degenerative disease and its differentiation from other causes.

Reinberg[99] in 1950 reported a case of progressive muscular dystrophy

associated with retinitis pigmentosa but the patient did not have ophthalmoplegia or ptosis. This was stated to be the first example of such a reported association.

In 1956, De Ruyter[100] reported a case of typical chronic progressive external ophthalmoplegia with pigmentary degeneration of the retina. He described the ocular fundi as having gray spots which covered almost the entire fundi but did not as yet affect the maculas.

Alfano and Berger[101] in 1957 reported a typical case of the association of ophthalmoplegia and pigmentary degeneration of the retina in a 37-year-old negro woman. Although they referred to the retinal changes as retinitis pigmentosa, they pointed out that the pigment spots in the macular area were similar to those seen in cases of cerebral macular degeneration. They concluded that the retinal changes should best be considered as "atypical retinitis pigmentosa."

Erdbrink[102] in 1957 added another case, under the name "ocular myopathy and retinitis pigmentosa," to the growing list of reported patients with this association. The family tree of the patient showed ptosis in five generations. Erdbrink was able to examine only two other members of this family. These, the 2- and 3-year-old sons of the patient, had early changes of retinitis pigmentosa. Although these two boys did not have ptosis or ophthalmoplegia, Erdbrink postulated that ocular myopathy might develop in these patients subsequently.

In 1958, Sayre and I[1] reported the two cases already referred to. These patients had retinal changes described as pigmentary degeneration of the retina, since, like the patient described by Alfano and Berger, the changes were not typical of retinitis pigmentosa.

Thorson and Bell[80] in 1959 reported one case in which the ophthalmoplegia was well documented by electromyography and biopsy of the lateral rectus muscle. The fundus changes consisted of wide areas of choroidal atrophy, merging with areas of choroidal sclerosis. There was diffuse pigmentation, especially in the peripheral areas of the retinas. The vessels were very attenuated and the optic disks were pale. The authors objected to calling this a syndrome and preferred to look upon this association as an example of multiple abiotrophies.

In 1960, Teasdall and Sears[81] reported on six patients with ocular myopathy. The second one, a 13-year-old girl, had a "fundus pattern suggestive of retinitis pigmentosa."

Under the name "abiotrophic ophthalmoplegia externa," Davidson[86] in 1960 added a case to the list of patients with ophthalmoplegia and pigmentary degeneration of the retina. In his patient, a 10-year-old boy with ptosis and ophthalmoplegia, both fundi showed a diffuse and

widespread, fine pigmentary disturbance which was most evident at the periphery and the macula. The disks were of normal color and the vessels were of normal caliber. The myopathic nature of the external ophthalmoplegia was demonstrated by electromyographic studies on the levator and confirmed by biopsy of the levator at the time of an operation for ptosis. Davidson concluded that this syndrome is a link between various abiotrophic disorders.

TABLE 2. PREVIOUSLY REPORTED CASES OF EXTERNAL OPHTHALMOPLEGIA ASSOCIATED WITH PIGMENTARY DEGENERATION OF THE RETINA

Author	*Date*	*Patients*	*Remarks*
McMullen and Hine[34]	1921	1	Thought at the time to represent old chorioretinitis
Barnard and Scholz[96]	1944	1	Four cases reported but only the fourth appears to be true chronic progressive external ophthalmoplegia
Walsh[97]	1947	3	Four cases reported but fourth is same as fourth by Barnard and Scholz
Chamlin and Billet[98]	1950	3	Perhaps should be considered the first report since they regarded this as a syndrome
De Ruyter[100]	1956	1	Recognized his case as typical of the association described by Barnard and Scholz
Alfano and Berger[101]	1957	1	Pointed out that retinal changes are not true retinitis pigmentosa
Erdbrink[102]	1957	1	First report of hereditary aspects of the association
Kearns and Sayre[1]	1958	2	First report of triad of external ophthalmoplegia, pigmentary degeneration of the retina, and cardiac abnormalities
Thorson and Bell[80]	1959	1	Patient also had a cardiac abnormality
Teasdall and Sears[81]	1960	1	Six patients reported with ocular myopathy but only second had pigmentary degeneration
Davidson[86]	1960	1	Syndrome of external ophthalmoplegia and pigmentary degeneration considered a link between various abiotrophic disorders
Jager *et al.*[103]	1960	1	Patient had triad of external ophthalmoplegia, pigmentary degeneration of the retina, and cardiac abnormality
Jampel *et al.*[104]	1961	8	All patients were negroes
TOTAL		25	

Jager and co-authors[103] in 1960 reported on a 13-year-old boy with ophthalmoplegia and retinal pigmentation. This boy also had heart block and will be referred to later.

Jampel and co-workers[104] in 1961 examined 20 individuals of a negro family and found ataxia, ophthalmoplegia, and retinal degeneration

in eight members (three generations). The fundi showed the same type of pigmentary change as that previously described by others. The authors stated that the "optic atrophy found frequently in this entity is secondary to the retinal degeneration." They overlooked the fact that optic atrophy does not occur in the retinal degeneration associated with retinitis pigmentosa and related atypical forms. Their diagnosis of optic atrophy was apparently based on clinical rather than pathologic study.

The previously reported cases of external ophthalmoplegia associated with pigmentary degeneration of the retina are listed in Table 2.

HISTORY OF EXTERNAL OPHTHALMOPLEGIA ASSOCIATED WITH CARDIOMYOPATHY

The first reported instance of chronic progressive ophthalmoplegia associated with cardiomyopathy is probably that of Bristowe[8] in 1886. Although it was not diagnosed as such, and is even now open to question, it would seem from the description that this was the cause of the patient's symptoms. Bristowe described four cases of chronic progressive external ophthalmoplegia, in the third of which there were some unusual attacks, described as follows:

> He was liable throughout his stay in the hospital to sudden attacks of extreme dyspnoea, which lasted from a second or two to 5 or 10 minutes at a time. The first of these was observed one day while he was at lunch. He suddenly became livid in the face, struggled violently for breath, and made loud snoring inspirations. The dyspnoea subsided after a few minutes. All his other attacks were the same in quality; but often, and more especially during the latter period of his stay in the hospital, they were of littel [*sic*] more than momentary duration. They came on quite irregularly, sometimes in the day, sometimes at night, and while he was asleep; and were often very alarming.

Although Bristowe did not understand the cause of these episodes, he remarked that at times the patient seemed in immediate danger of death.

The second reported instance of what appears to be a cardiomyopathy associated with chronic progressive external ophthalmoplegia is a case reported by de Schweinitz[41] in 1931. His patient, a 44-year-old woman, had what sounds like a straightforward example of chronic progressive external ophthalmoplegia. In addition, she had suffered from attacks of unconsciousness. One of these attacks occurred after she had eaten supper, when she suddenly fell into a deep sleep

and could not be aroused. It was thought that hysteria played a large part in her symptoms.

The first report of an unquestionable example of cardiomyopathy associated with chronic progressive external ophthalmoplegia is that of Sandifer[55] in 1946. Some authors (Bonduelle[90] in 1958) also credit Sandifer with the first recognition of chronic progressive external ophthalmoplegia as a myopathic degeneration rather than a neuropathic atrophy. Sandifer's patient, in addition to having ocular myopathy confirmed by histologic examination, also had bundle-branch block. The pulse rate varied between 20 and 66 per minute, on most occasions being about 32 per minute. The apex rate was usually about 50 per minute, extra beats being audible as premature systoles. An electrocardiogram showed very slow irregular rhythm without any normal waves. All QRS waves were wide, suggesting bundle-branch block.

Sandifer stated that the cardiovascular findings suggested that the heart muscle may have also been the site of myopathic degenerative changes. He referred to the monograph by Marinesco in 1910 on diseases of muscles, in which it is asserted that of all the muscles that offer extraordinary resistance to invasion by muscular dystrophy, the heart is most notable. Sandifer further stated that, although rare, cardiac myopathy has sometimes been described.[105,106]

Gartner and Billet[107] in 1949 reported a case of ptosis and ophthalmoplegia in a 25-year-old man with myocardial involvement. The electrocardiogram revealed right axis deviation with large R waves in leads CF1 and CF2, indicating probable myocardial hypertrophy of the right side of the heart. The authors interpreted these changes as indicating probable involvement of the myocardium. They also commented that defects of heart muscle have rarely been reported in cases of progressive muscular dystrophy but that they may well be less rare than is supposed.

Salleras and Ortiz de Zárate[108] in 1950 reported six cases of chronic progressive external ophthalmoplegia associated with myopia. Three of these patients were said to have "cardiac malfunction" but the exact nature of this was not elaborated. Dassen and colleagues[61] in 1951 described a 27-year-old man who had chronic progressive external ophthalmoplegia and complete atrioventricular block with Stokes-Adams syndrome. They refer to the ocular disease as nuclear ophthalmoplegia. Sayre and I[1] in 1958 described two cases of complete heart block associated with external ophthalmoplegia.

Thorson and Bell[80] in 1959 described a case of external ophthalmo-

plegia in which there was also an associated atrial fibrillation and an intraventricular conduction defect. Although they thought that the ophthalmoplegia was on a dystrophic basis, they said that the "cardiac conduction defect cannot be claimed to be associated with a primary myopathy from the data obtainable."

TABLE 3. PREVIOUSLY REPORTED CASES OF EXTERNAL OPHTHALMOPLEGIA ASSOCIATED WITH CARDIOMYOPATHY

Author	*Date*	*Patients*	*Remarks*
Bristowe[8]	1886	1	?diagnosis: patient had alarming attacks of dyspnea
de Schweinitz[41]	1931	1	?diagnosis: patient had attacks of unconsciousness from which he could not be aroused
Sandifer[55]	1946	1	First authentic association of external ophthalmoplegia and cardiomyopathy
Gartner and Billet[107]	1949	1	Interpreted by authors as dystrophy of cardiac musculature
Salleras and Ortiz de Zárate[108]	1950	3	? diagnosis, but all were said to have cardiac malfunction
Dassen, *et al.*[61]	1951	1	Case of von Gräfe's disease and cardiopathy (complete heart block)
Kearns and Sayre[1]	1958	2	Both had external ophthalmoplegia and complete heart block
Thorson and Bell[80]	1959	1	External ophthalmoplegia and intraventricular conduction defect
Jager, *et al.*[103]	1960	1	Findings almost identical with those in Case 2 by Kearns and Sayre[1]
TOTAL		12	
	(5 questionable, 7 definite)		

The patient described by Davidson[86] in 1960 did not have cardiac myopathy, but the author mentioned that this may occur. He pointed out that heart failure is common in Friedreich's ataxia and that this would seem to be due to progressive degeneration of the heart muscle.

Jager and co-authors[103] in 1960 reported the findings in a 13-year-old boy with retinal pigmentation, ophthalmoplegia, ataxia, deafness, and heart block. This case is of considerable interest since it represents exactly the syndrome under discussion. Apparently it is the only case representing perfectly the syndrome of external ophthalmoplegia, pigmentary degeneration of the retina, and cardiomyopathy that has been reported either before or after that reported by Sayre and me.[1]

The patient of Jager and his colleagues was normal until 10 years of age, when his parents noticed limitation of movement of the eyes.

Weakness of the muscles of the mouth soon developed, and drooping of the eyelids soon became apparent. Myasthenia gravis was suspected but treatment for this disease was ineffective. Physical examination at 13 years of age showed small stature (57 inches tall and 64 pounds in weight), small testes, ptosis, external ophthalmoplegia, pigment deposits in the peripheral part of the retina, weakness of the orbicularis oculi and orbicularis oris, and moderate bilateral nerve-type deafness. Spinal fluid examination revealed a protein content of 115 mg. per 100 ml. Two months later he was found to have atrioventricular conduction defects ranging from first degree to complete heart block. He died as a result of the cardiac conduction defects. On gross and microscopic examination of the heart at necropsy, no explanation of the cardiac abnormality could be found. The authors stated that the retinas appeared normal but apparently no flat retinal preparations were made and examined. The ocular muscles were said to have had "patchy atrophy." The authors discussed the similarity of the findings in their patient with those in patients with Refsum's syndrome. They were unaware that Sayre and I had reported our cases 2 years previously.

The previously reported cases of external ophthalmoplegia associated with cardiomyopathy are listed in Table 3.

REFSUM'S SYNDROME

In 1946, Refsum[109] described a previously unrecognized syndrome, which he referred to as "heredopathia atactica polyneuritiformis." He described five cases occurring in two unrelated Norwegian families. Although these patients did not have external ophthalmoplegia, they had other features related to the syndrome of external ophthalmoplegia, retinal degeneration, and cardiomyopathy. Refsum's syndrome consists of (1) atypical retinitis pigmentosa, (2) chronic polyneuritis, and (3) ataxia and other cerebellar phenomena. In addition to this triad, all five patients appeared to have cardiac abnormalities. Patients 1 and 2 suffered from sinus tachycardia, demonstrable by electrocardiogram in both patients. Patient 3 had prolonged atrioventricular conduction times, varying from 0.20 to 0.23 second. Patient 4 also had sinus tachycardia and definitely pathologic changes on the electrocardiogram. The fifth patient did not have an electrocardiogram but she fell dead suddenly outside the waiting room of the eye department. Refsum thought that her sudden death indicated a possibility that she also suffered from heart disease. Two of the other patients of this group

also died suddenly under conditions suggestive of respiratory paralysis. Refsum thought that nothing definite could be said about the pathogenesis of these electrocardiographic changes but considered it reasonable to interpret them as the outcome of disease of the bulbar vegetative centers.

Only three of the five patients had spinal fluid examinations but all three showed "a considerable increase of the protein content of the cerebro-spinal fluid without any corresponding increase of its cells,—an albumino-cytological dissociation."

Three of the five patients had abnormality of the pupils, usually consisting of miosis and sluggish reaction to light. Two patients suffered from neurogenic impairment of hearing. Two patients presented a radiologically demonstrable symmetric epiphyseal dysplasia in the elbow, shoulder, and knee joint. None of the patients had external ophthalmoplegia or ptosis. Refsum considered the syndrome to be hereditary and thought it probable that it followed a single recessive mode of transmission.

In 1949, Refsum and colleagues[110] described "heredopathia atactica polyneuritiformis in children." They reported on four children of three families (two children being twins). These children showed atypical retinitis pigmentosa, polyneuritis, ataxia and other cerebellar manifestations, deafness, ichthyosis-like skin changes, considerable increase in the protein content of the cerebro-spinal fluid, and electrocardiographic changes. The electrocardiographic changes included prolonged conduction times.

Other reports on Refsum's syndrome have appeared. Reese and Bareta[111] reported a case in 1950. Their patient had retinitis pigmentosa, deafness, and increased protein in the cerebro-spinal fluid, but the electrocardiogram was normal. Clark[112] in 1951 reported another case in an adult (thought to be the first such case described in Great Britain). This was identical to the cases described earlier, including an increase in the protein content of the cerebro-spinal fluid, but there were no electrocardiographic changes. Fleming[113] in 1957 reported on two patients, both with increased protein in the cerebro-spinal fluid and prolonged conduction times demonstrated on the electrocardiogram.

PRESENTATION OF CASES

Reports of nine cases follow. Cases 1 to 6 represent the syndrome of external ophthalmoplegia, pigmentary degeneration of the retina, and cardiomyopathy in its typical, or complete, form. Cases 7 to 9 are

reported as presumably representing the syndrome in an incomplete form. The features of these three cases are quite like those of the first six except that no cardiac abnormality has yet been demonstrated.

Cases of the Typical Form of the Syndrome

CASE 1

A 19-year-old white girl from Illinois was first seen in April, 1941, because of drooping of the eyelids for about 3 years. She had not had double vision or weakness of any other part of her body.

Her vision was 20/20 in the right eye and 20/25 in the left. The ptosis was graded +2 on the right and +3 on the left (on the basis of +1 to +4, grade +4 being most severe). All of the ocular rotations were limited, being graded −2 to −4 (on the basis of −1 to −4, grade−4 being most limited). This limitation of movement was most evident on upward gaze.

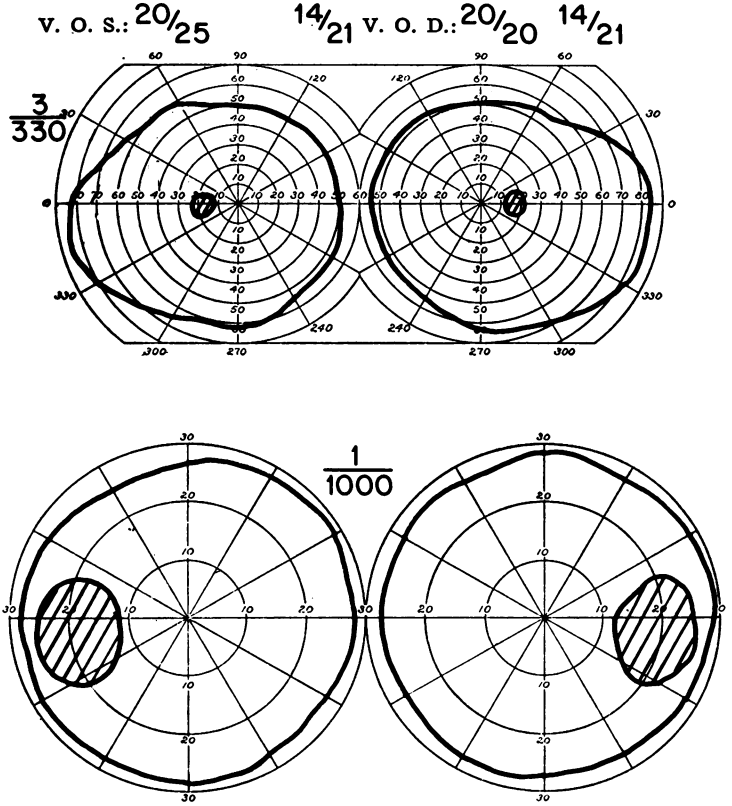

FIGURE 1. CASE 1.
Visual fields showing slight enlargment of the normal blind spots.

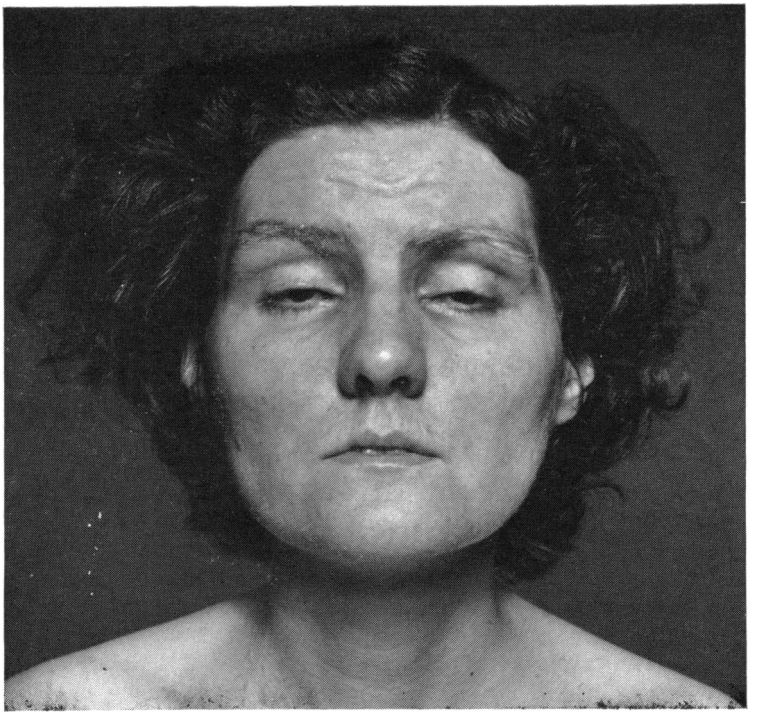

FIGURE 2. CASE 1.
White woman, aged 35, with external ophthalmoplegia, pigmentary degeneration of the retina, and cardiomyopathy.

The optic nerve heads had good color with pronounced choroidal rings. Ophthalmoscopic examination showed a moth-eaten appearance which was interpreted as representing "old choroiditis." There were some pigment changes in the macula; the retinal vessels were thought to be normal. The visual fields were normal except for slight enlargement of the normal blind spots (Figure 1). The consulting ophthalmologist remarked that the appearance of the fundus looked like that of healed chorioretinitis and that the movement disorder indicated a diffuse involvement of the midbrain. Syphilis was suspected, but the serologic reactions (Kline, Kahn, Hinton, and Wassermann) were all negative. General and neurologic examination revealed no other abnormalities. A neostigmine test was done with no beneficial effects. There was no other evidence of muscle weakness.

The patient was not seen again until January, 1958, at the age of 35 years (Figure 2). She returned because of fainting spells and rapid heartbeat of 2 weeks' duration. She also had had progressive weakness and difficulty swallowing for 2 to 3 years. A surgical attempt to correct the ptosis had

been made elsewhere in 1942. She had been almost completely incapacitated and had not been able to work for approximately one year. She was able to do only a limited amount of housework. She had been diagnosed by physicians elsewhere as having tachycardia and cardiac hypertrophy and was taking digitoxin.

General examination showed bradycardia with pulse rate varying from 46 to 52 beats per minute. Her heart was moderately enlarged and she had a grade 2 apical systolic murmur. An electrocardiogram showed a rate of 37 and nodal rhythm with an occasional sinus beat. The duration of the QRS complex was 0.10 second. The consulting cardiologist commented: "I believe this is probably the peculiar myocarditis which occurs in certain muscular dystrophies and which not uncommonly causes cardiac failure or sudden death due to rhythm disturbance."

Neurologic examination showed definite weakness of the neck flexors, she being unable to lift her head off the table. There was considerable weakness of all the muscles of the extremities but the neurologic findings were otherwise negative. Psychologic testing showed a low average mental level and it was thought that her condition had probably deteriorated since the initial examination in 1941, although no psychologic testing had been carried out on the initial examination. An electroencephalogram showed dysrhythmia, grade 1, which was generalized but maximal in the bisylvian areas. Electromyographic testing of a number of muscles showed motor-unit potentials of the type seen in myopathy. There was no evidence of a defect of neuromuscular conduction. A curare test (a fifth of a curarizing dose) gave negative results.

Biopsy of the left triceps brachii disclosed moderate variation in the size of the muscle fibers, some larger than normal, others quite small and with rare atrophic fibers and nuclear clumps. There was no active degeneration, regeneration, or inflammation. These findings were interpreted as being those of a myopathy.

Ophthalmic examination showed vision of 20/30 in the right eye and 20/40 in the left. There was marked narrowing of the lid fissures, the right measuring 4 mm., the left 3 mm. When the lids were closed there was still a 2-mm. exposure of each eye. The lower portions of both corneas stained slightly with fluorescein, and for this reason no further ptosis operation was recommended. The retinal findings were the same as in 1941, and again they were said to resemble those of old chorioretinitis. Nevertheless, it was now recognized that this patient represented the triad of pigmentary degeneration of the retina, ophthalmoplegia, and associated cardiac lesions. She had an almost complete external ophthalmoplegia, there being little if any movement of either eye in any direction.

CASE 2

A 34-year-old negro man from Illinois who had worked as a railroad dining car employee was first seen in November, 1948, complaining that he

had lost weight for about 5 years, had had fatigue and shortness of breath for about 2 years, and had lost sexual power for 3 to 4 months. He stated that in 1941 he weighed 165 pounds but was rejected by the Army because of a "spot" on his right lung. On later investigation his home physician thought that this so-called spot was of no great consequence. After this, the patient stated, he had lost 4 or 5 pounds a year. Although he had continued to work, for several years he had fatigued more easily than normal.

The man was slightly built (weight 128 pounds, height 5 feet 5½ inches). His radial pulse rate was 36 per minute. An electrocardiogram showed an auricular rate of 52 and a ventricular rate of 32, there being complete atrioventricular dissociation, with ventricular premature contractions. The electrocardiogram was also abnormal in that there was an abnormal degree of left axis deviation and a right bundle-branch-block type of configuration of the QRS complex (Figure 3). X-ray examination showed marked enlargement of the cardiac shadow, as well as a calcified mass, 4 by 3 cm. in area, in the right hilar region, which was thought to be a hamartoma by the radiologists. Although the patient did not have any visual complaints, he had ptosis of both upper eyelids and external ophthalmoplegia. He said he had had the ptosis for 15 years or more. The ptosis was graded +2 bilaterally, and the ocular rotations were graded −3 or −4 in all directions except downward; the downward gaze seemingly was normal. The patient was not seen by an ophthalmologist and no record of an ophthalmoscopic examination was made. The neurologist did not think that the ophthalmoplegia represented myasthenia gravis; a diagnostic dose of 1 ml. of neostigmine was given with negative results.

When seen again in April, 1949, the patient said he felt somewhat better. He looked better and his weight had increased about 5 pounds. He had not missed a day's work and he thought his exercise tolerance quite good. The electrocardiographic findings were essentially the same as before, as were the chest X-ray and other findings.

He returned in 1956 because of increasing symptoms of congestive heart failure. He was hospitalized immediately and treated for the congestive failure. The general physical findings were similar to those of the previous visit, including the atrioventricular heart block and the abnormal shadow on the roentgenogram of the chest. However, even greater cardiac enlargement was now evident on the roentgenogram (Figure 4). The electrocardiogram was unchanged except that it now showed atrial fibrillation. He said he had noticed an increase in eye symptoms, an increase in weakness, and marked dyspnea and ankle edema. He also said that for about 3 or 4 years, when he was drinking or eating, food or water would sometimes come out of his nose. He had noticed great difficulty in swallowing, and his gait had been unsteady for 4 or 5 years. He had no complaints regarding visual acuity, and vision was recorded as 20/30 and 14/21 in the right eye, and 20/40 and 14/21 in the left. Refraction was not carried out. The ptosis was graded +2 in both eyes and he was found to have almost complete external ophthalmo-

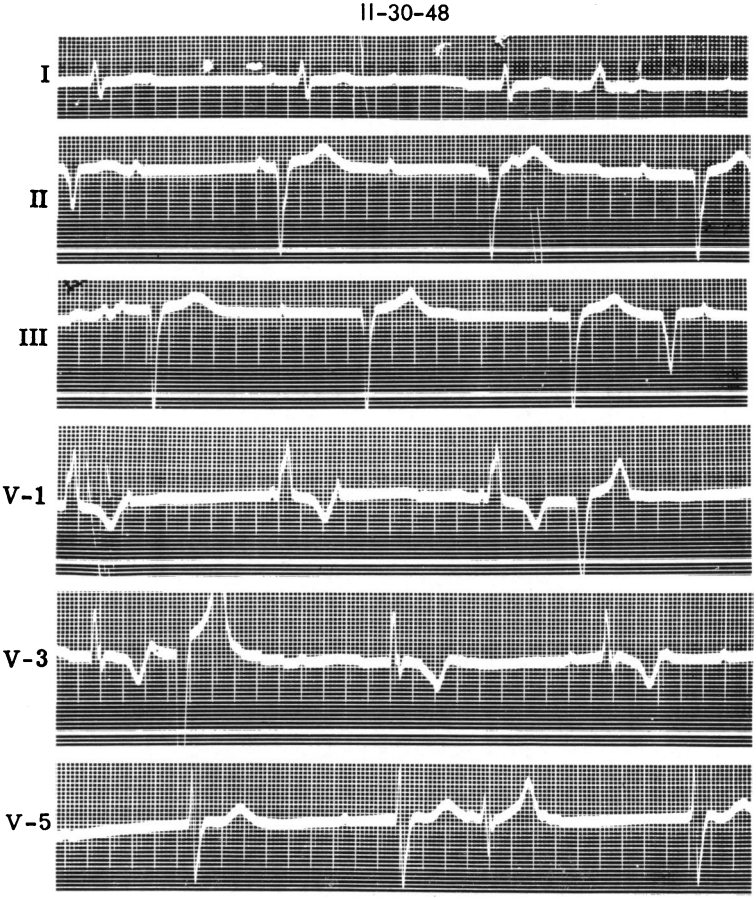

FIGURE 3. CASE 2.
Electrocardiogram showing complete atrioventricular block. The QRS complex shows a right bundle-branch-block type of configuration and there is an abnormal degree of left axis deviation.

plegia. The eyes were slightly divergent while the pupils were normal in all respects.

On ophthalmoscopic examination the optic disk had good color and the retinal vessels appeared normal. The pigment epithelium of the retina had a peculiar stippled appearance and a metallic sheen which was particularly evident around each optic disk. The choroidal vessels were markedly sclerotic in the areas around the optic nerve heads (Figure 5). No actual pigment clumping could be found even in the more peripheral portions of the retinas. Plotting of the visual fields showed huge enlargement of the blind spots

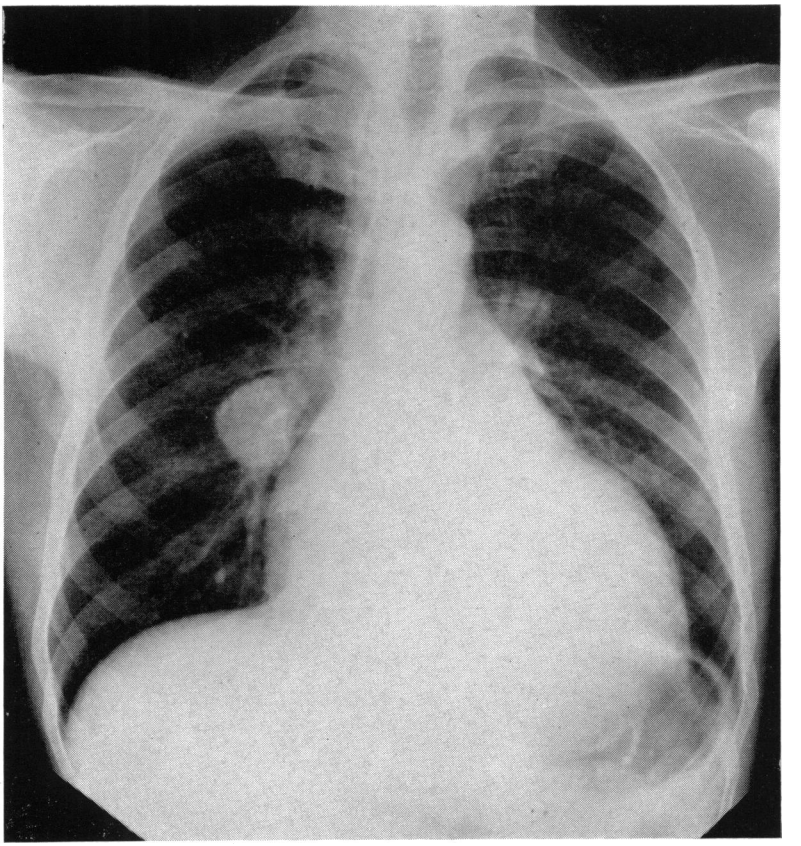

FIGURE 4. CASE 2.
Roentgenogram showing marked hypertrophy of the heart and a calcified mass in the right hilar region.

(Figure 6) which seemed to match the areas of most serious disturbance of the retina around the disk. The patient had had some trouble seeing in the dark; his wife always had to unlock the front door for him at night since he never did see well enough to find the lock.

Neurologic examination showed generalized depression of the muscle-stretch reflexes and slight weakness of the facial musculature. The orbicularis muscle of each eye was weak (grade −2). The palate moved well, as did the pharyngeal musculature. Electromyographic studies of the triceps brachii, the deltoid, the biceps brachii, the frontalis, and the orbicularis oculi muscles showed myopathic changes. A roentgenogram of the skull was normal. The serologic reaction for syphilis (Kline, Kahn, Hinton, and Kolmer tests) was negative. The value for hemoglobin was 14.3 gm. per 100 ml. of

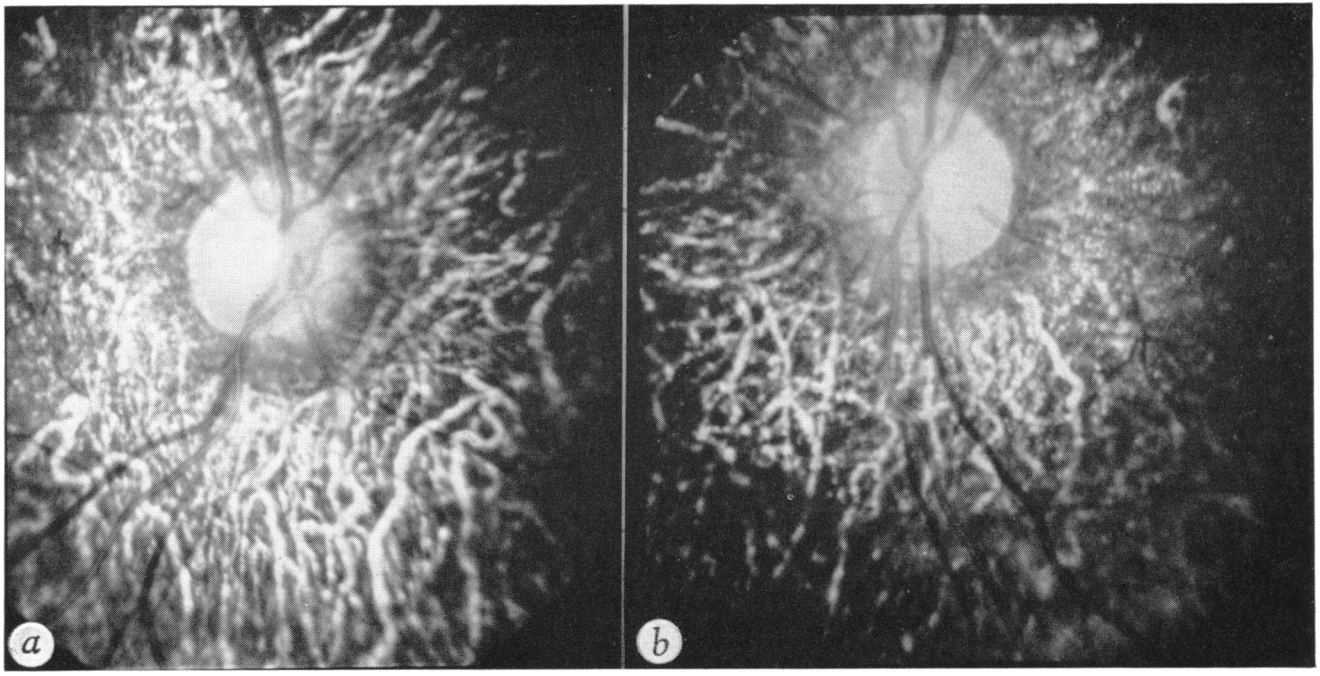

FIGURE 5. CASE 2.

Photographs of fundus showing thinning of pigment epithelium and prominent sclerotic choroidal vessels. (a), right; (b), left.

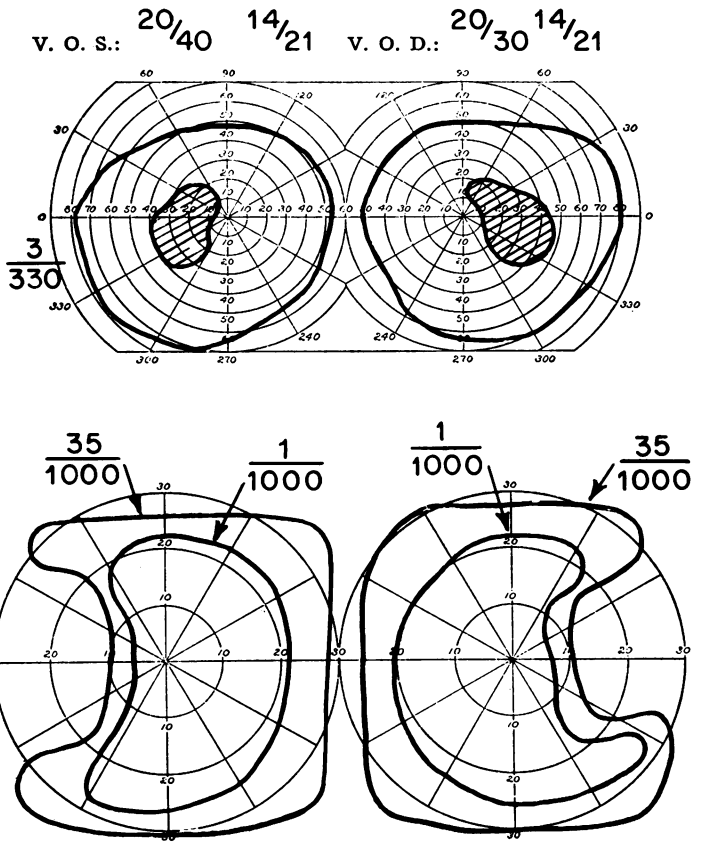

FIGURE 6. CASE 2.
Visual fields showing huge enlargement of normal blind spots.

blood, the leukocytes numbered 9700 per cubic millimeter, the sedimentation rate was 12 mm. in 1 hour (Westergren), and the urinary findings were not remarkable.

After relief of his cardiac decompensation, the patient was dismissed. He has not been seen here since, but he wrote in June, 1957, that although he had not lost any ground, he had been laid off from his job with the railroad because of the trouble with his eyes and his continuing loss of weight.

CASE 3

A 17-year-old white boy from Missouri, seen in September, 1955, was admitted directly to the hospital because of unconscious spells. His early development was considered normal. He weighed 9 pounds at birth, walked at 1 year, talked shortly after the first year, and weighed 35 pounds at that

time (he still weighed 35 pounds at 5 years of age). At 3 years of age, the parents noticed drooping of the eyelids. Shortly thereafter they noticed that his eyes were divergent. He was also thought to be smaller than other children of his age and did not seem to be growing normally. Progressive deafness began at about the age of 4 years and he started experiencing difficulty going downstairs because he seemed unsure of his footing. He had always been less active physically than other children and did not like games in which running or jumping was necessary. He had reached the level of the junior year in high school, having repeated the fourth grade because of poor work.

Two months before admission he began having spells of unconsciousness about every 2 to 10 days. These had become more frequent and on some days he had suffered as many as three. They were preceded by hazy vision for 10 to 15 seconds, followed by unconsciousness. He often fell and remained unconscious for periods of a few seconds to 15 minutes. These attacks had become so frequent that he was afraid to stand or walk alone and preferred to hold onto someone's hand while walking. He had suffered a number of minor injuries in these falls and often would strike his head.

On examination, his body proportions were thought to be normal, although he was quite small for his age. He had no beard and only scanty pubic and axillary hair. He had small but otherwise normal genitalia. The pulse rate was 42 per minute and the blood pressure was 105/40. The electrocardiogram was interpreted as showing complete heart block with an atrial rate of 95 and a ventricular rate of 37 beats per minute. In addition, the electrocardiogram showed an abnormal degree of left axis deviation and a right bundle-branch-block type of configuration of the QRS complex (Figure 7). He had marked bilateral loss of hearing but accurate study of this was not completed.

The central vision of each eye was slightly reduced, thought perhaps to be associated with the ophthalmoplegia. The right eye read 20/40, the left eye 20/60. The patient had grade +2 ptosis of each upper eyelid and his eyes diverged approximately 15 degrees. He compensated for his ptosis by holding his head back. The pupils reacted promptly to light and accommodation. Ocular rotations were markedly impaired, being graded −3 to −4 in all directions. On ophthalmoscopic examination the disks were found to have fairly good color. The arterioles were attenuated. There was mottling of the pigment epithelium, most evident around each optic disk. There was some clumping of pigment in the peripheral parts of the retinas, which was of the type seen in more typical retinitis pigmentosa. This patient showed the most advanced field defect of all the patients reported (Figure 8).

Two days after admission to the hospital he had one of his "spells." No pulse could be felt and no heart sounds could be heard for 30 to 60 seconds. Artificial respiration was carried out for 30 to 60 seconds and respiration and pulse became evident and his cyanosis cleared. The consulting cardiologist thought that the episodes of syncope were cardiogenic and represented

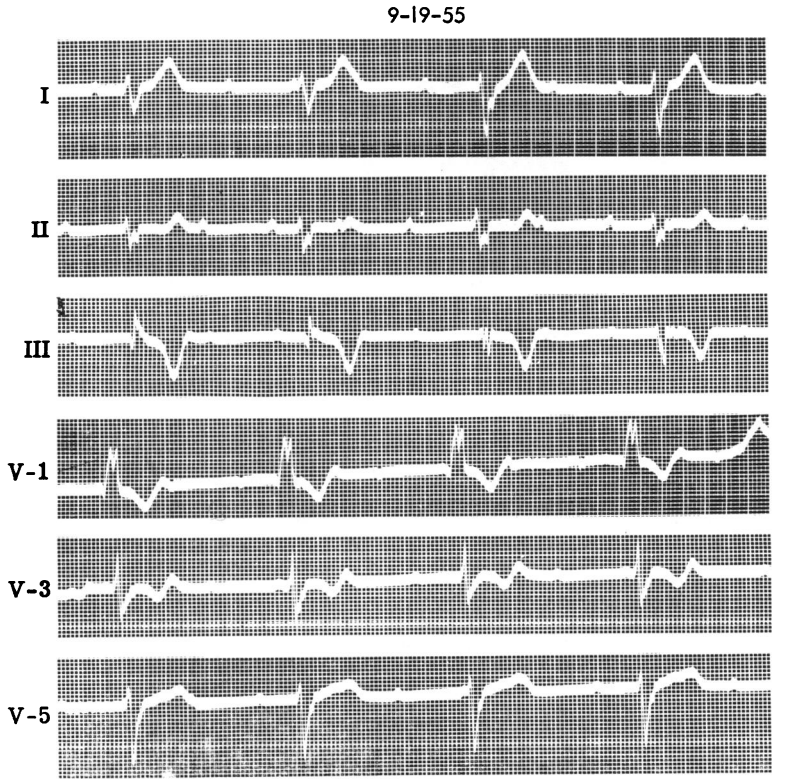

FIGURE 7. CASE 3.

Electrocardiogram showing complete heart block. The QRS complex shows a right bundle-branch-block type of contour and the degree of left axis deviation is abnormal.

Stokes-Adams attacks. However, no electrocardiogram was obtained during an attack.

Roentgenograms of the chest and skull were normal. The value for hemoglobin was 15 gm., the leukocyte count 5700, the findings on routine urinalysis normal, and the blood serologic reaction for syphilis negative. The spinal fluid was not examined. Three days after admission the patient had a prolonged episode of syncope, necessitating intravenous administration of epinephrine and artificial respiration. He recovered completely from this attack but the next morning he had a similar attack and died.

Necropsy Findings

The body was small for the stated age, measuring 58¼ inches in length and weighing 85 pounds. The pleurae and pericardium were normal. The

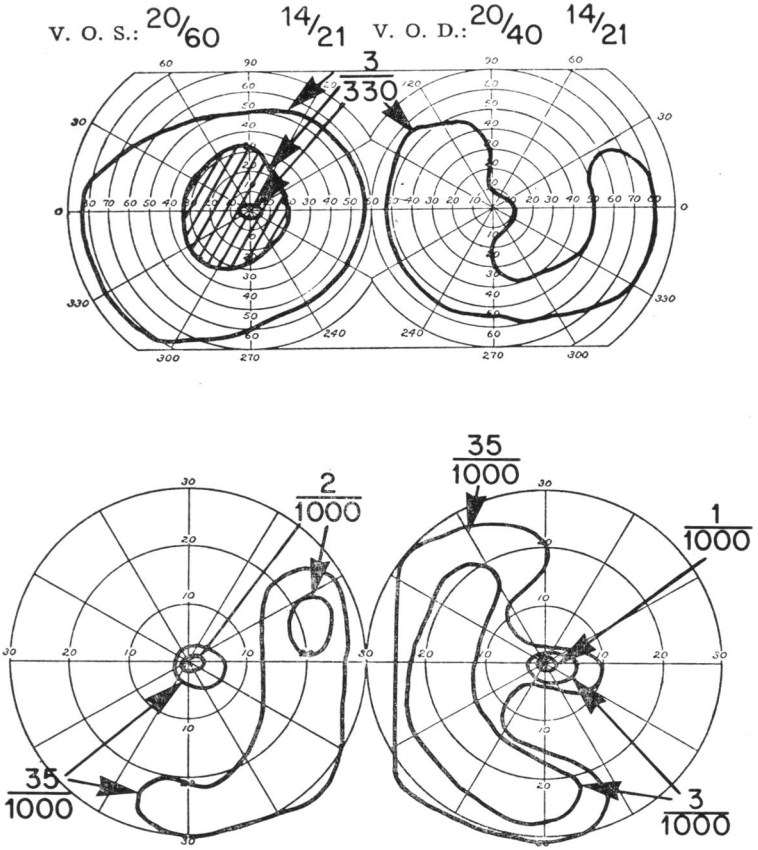

FIGURE 8. CASE 3.
Visual fields showing marked loss of field. Most advanced in any of the patients in the series.

heart weighed 250 gm. Genital hypoplasia and mild gynecomastia were evident. The thyroid, thymus, and testes were small. The brain, spinal cord, and muscles appeared grossly normal. The posterior segment of the left globe was removed along with several extraocular muscles for histologic study.

Histologic examination of the heart showed an occasional enlarged hyperchromatic muscle nucleus, focal subendothelial fibrosis, and a slightly thickened endocardium. These findings parallel the degree of cardiac hypertrophy present (Figure 9). Aside from immaturity of cellular development, the testes appeared normal. No abnormal changes were found in the thyroid. The thymus was of the prepubertal type. The other thoracoabdominal organs were essentially normal. Histologic examination of the cerebral hemispheres revealed marked siderosis of the globus pallidus, the

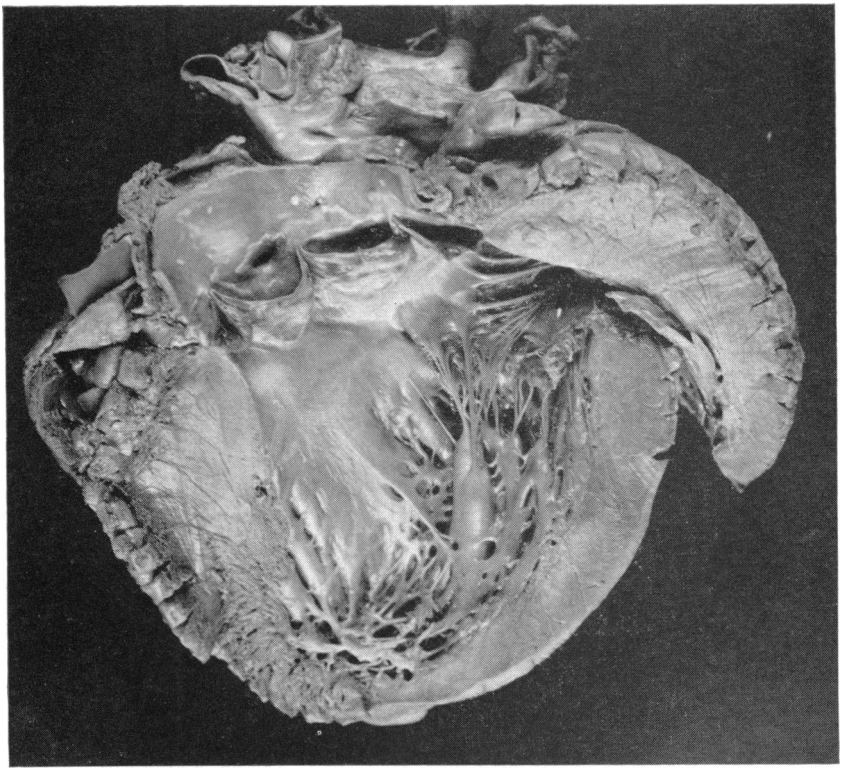

FIGURE 9. CASE 3.
Gross specimen of the heart showing hypertrophy of the left ventricle. (Weight, 250 gm.; normal for a patient of this size, 180 gm.)

iron being not only in the walls of the larger blood vessels but also in granules scattered profusely throughout the walls of small capillaries. There were occasional swollen astrocytes and, in addition, some microglial cells containing golden brown pigment.

The neurons of the third, fourth, and sixth cranial nerve nuclei and their fibers were normal. In the lateral portions of the substantia nigra there was a loss of neurons associated with an increase of astrocytes and deposition of iron granules similar to those found in the globus pallidus. There was a loss of neurons in the vestibular nuclei with similar siderosis, while the cochlear nuclei appeared intact.

The extraocular muscles showed a diffuse loss of muscle fibers with an increase in interstitial loose connective tissue. The muscle fibers varied considerably in size, with remaining normal fibers intermixed with degenerating fibers. These latter were sometimes swollen and sometimes atrophic. The usual degenerating fiber consisted of a normal-staining portion which

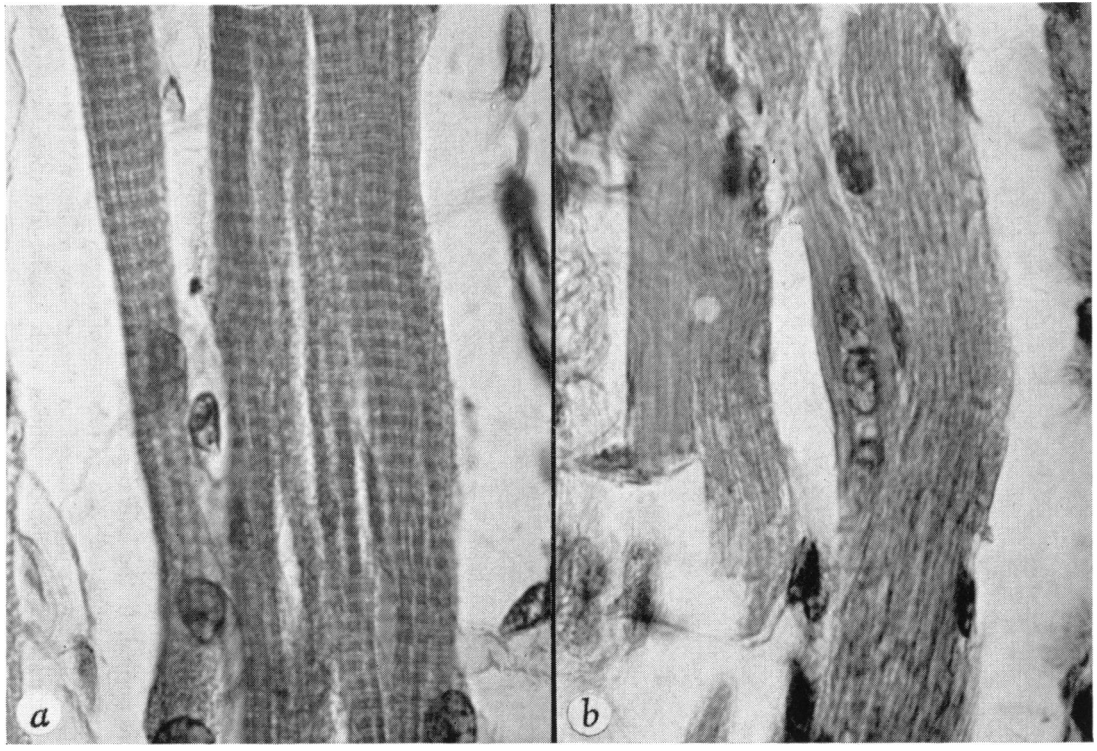

FIGURE 10. CASE 3.

Sections stained with hematoxylin and eosin (× 1000). (a) normal extraocular muscle; (b) myopathic extraocular muscle showing degenerating muscle fibers and loss of striations.

gradually became swollen, with separation of the fibrils followed by loss of cross-striations in the individual fibrils, leaving only a greater or lesser amount of granular material within the sarcolemmal sheaths (Figure 10). The nuclear changes were not marked, though some round nuclei with prominent nucleoli were centrally located within the cytoplasm. Clumps of distorted nuclei were rarely found in degenerating muscle cells. No evidence of regeneration, such as basophilia of the cytoplasm, was found. Careful observation of the interfascicular nerves after both routine and special neurohistologic staining revealed no evidence of degeneration. These findings were thought to be typical of a primary myopathy.

Numerous sections of the posterior segment of the globe, cross-sections of the optic nerve, and mounted flat retinal preparations were studied. The posterior segment looked fairly normal grossly. The central portion of the globe was prepared in the usual manner for paraffin sections. It was found that the remaining portions of the retina could be stripped from the underlying choroid with only a little, if any, more resistance than that met in stripping the retina from a normal posterior segment. The retina appeared to have numerous round atrophic areas on transillumination. These areas were scattered throughout the retina in an irregular manner. No pigment was visible grossly in the retina and there was no evidence that the pigment epithelium was adherent to any of the removed retina.

Histologic study of the posterior segment showed many areas of greatly disturbed retinal architecture (Figure 11). In these areas the retina was

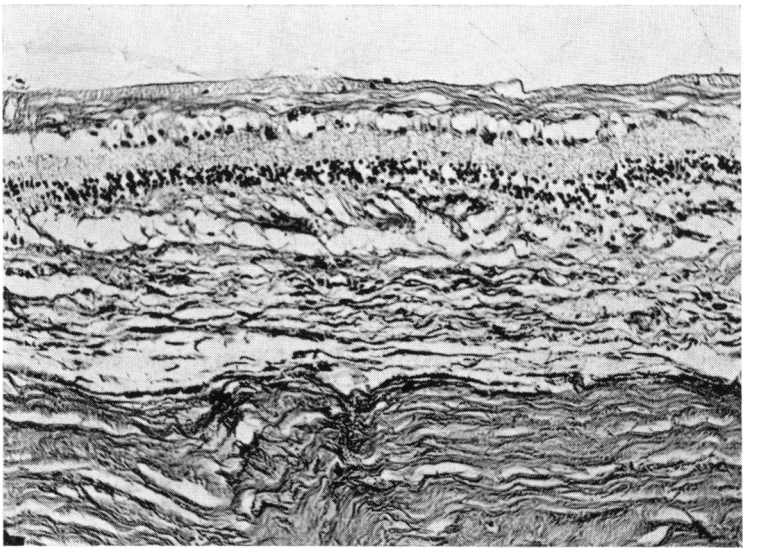

FIGURE 11. CASE 3.
Cross-section of retina showing areas of retinal degeneration (hematoxylin and eosin; × 125).

adherent to the underlying choroid. The choroid otherwise appeared normal. The pigment epithelium could be identified in only a few places and for the most part it was entirely absent. In the areas of retinal disturbance, the outer layers of the retina, the rods and cones, and the outer nuclear layers were affected. The bipolar-cell layer and the ganglion-cell layer were normal throughout the retina. In both longitudinal and cross-sections stained with the Bodian and Weigert stains the axis cylinders of the optic nerve and their myelin sheaths appeared normal, indicating the absence of optic atrophy (Figure 12).

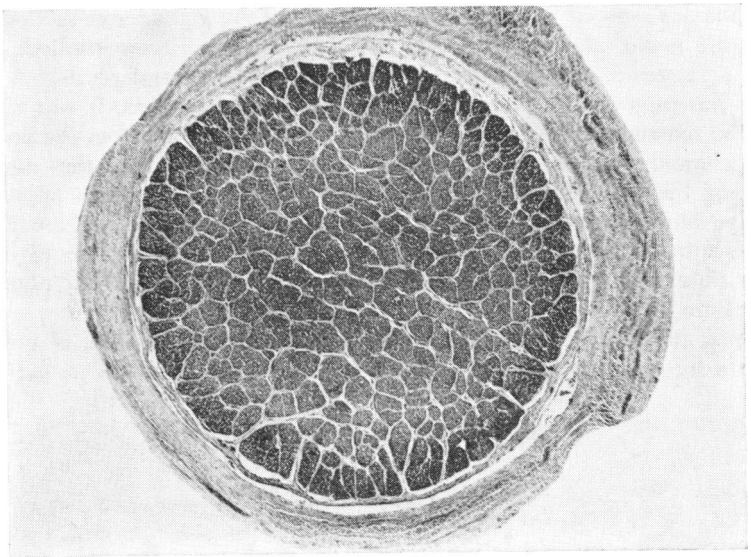

FIGURE 12. CASE 3.
Cross-section of optic nerve in patient with advanced pigmentary degeneration of the retina showing absence of optic atrophy (Weigert stain; × 27).

In portions of the retina placed flat on glass slides and stained with various agents, pigment clumping along the walls of the smaller retinal vessels could be seen (Figure 13A). In addition, there were circinate atrophic areas which seemed to be the horizontal counterpart of the retinal atrophy seen grossly. These areas appeared as giant "pseudorosettes" (Figure 13B). The center of the lesion was thinner than the surrounding normal retina, and the border of the lesion was surrounded by a palisade of cells. This border of cells appeared to consist of normal cells of one of the nuclear layers of the retina, probably the outer nuclear layer, that seemed to have changed their polarity and were running in a more horizontal plane. It appeared that these cells were being drawn by fibrosis

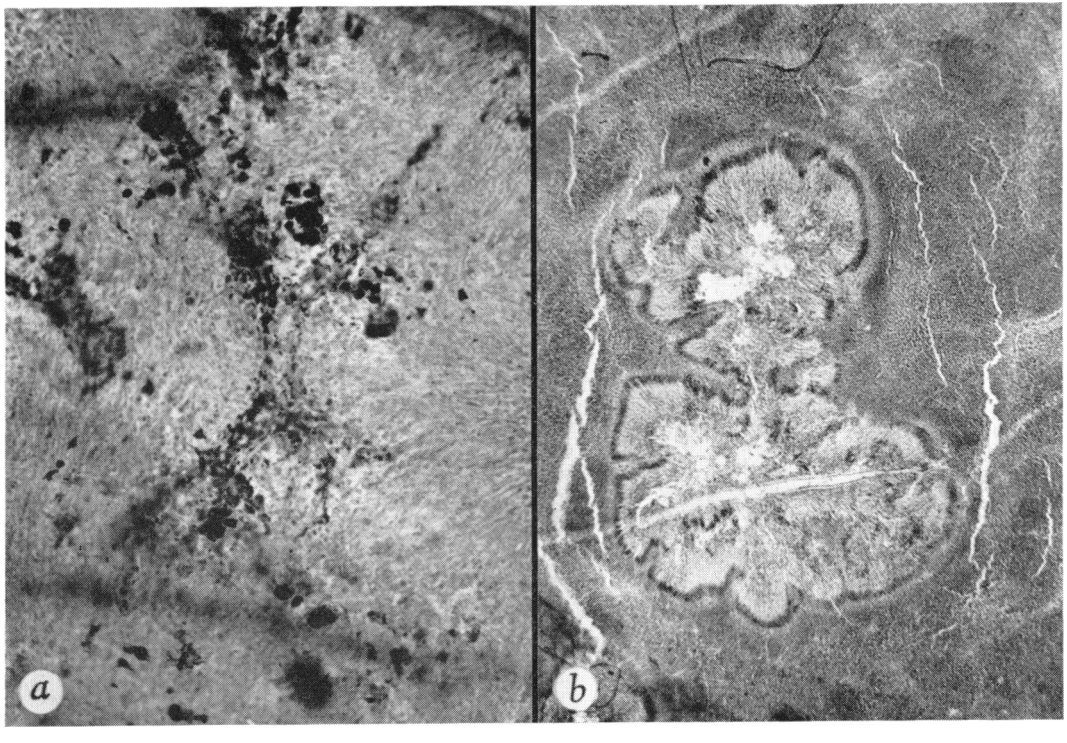

FIGURE 13. CASE 3.

(a), flat retinal preparation showing deposits of pigment along small retinal vessels; (b), giant pseudo-rosettes seen on flat retinal preparation (Giemsa stain; × 25).

toward the center of the lesion where this layer of cells was completely absent.

CASE 4

A 32-year-old white female bookkeeper from South Dakota who was first seen in September, 1959, said she had had very little, if any, eye trouble, but had been told 5 or 6 years previously that she had scars in both eyes. Several years previously her employer had noticed that she was turning her head instead of her eyes when she wished to look to either side. Neither the family nor she had been aware of this until it was pointed out. Her general health had been excellent and she considered herself well in all respects.

Her vision was 20/20 in the right eye and 20/25 in the left. She had minimal ptosis (Figure 14), but ocular rotations were very limited in all fields of gaze. This limitation of movement was graded −2 to −4. The media were clear. The disks had good color and the retinal arterioles were of normal caliber. The pigment epithelium appeared thin, allowing the choroidal vessels to be seen more easily than usual. This thinning of the pigment epithelium was more prominent in the peripapillary areas. There

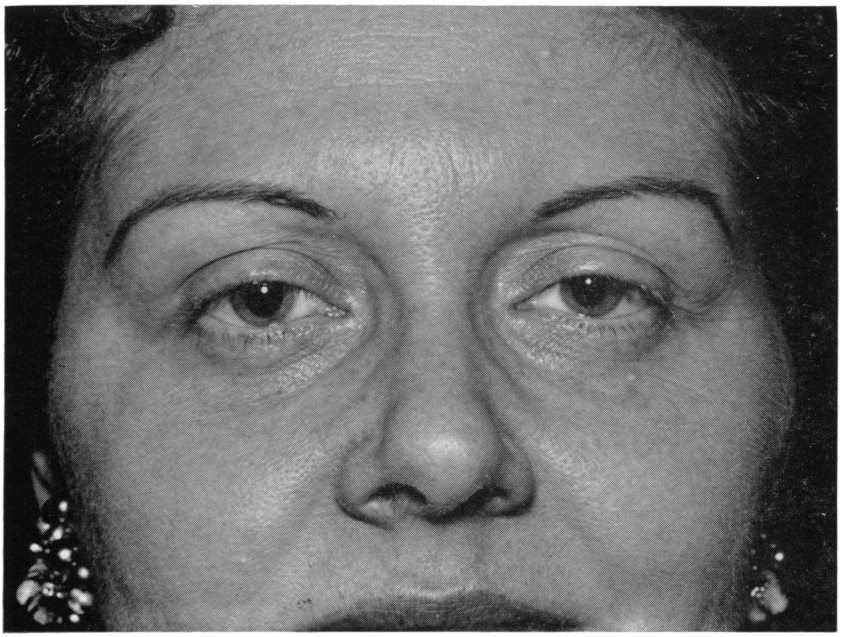

FIGURE 14. CASE 4.
White woman, aged 32, with external ophthalmoplegia, pigmentary degeneration of the retina, and cardiomyopathy.

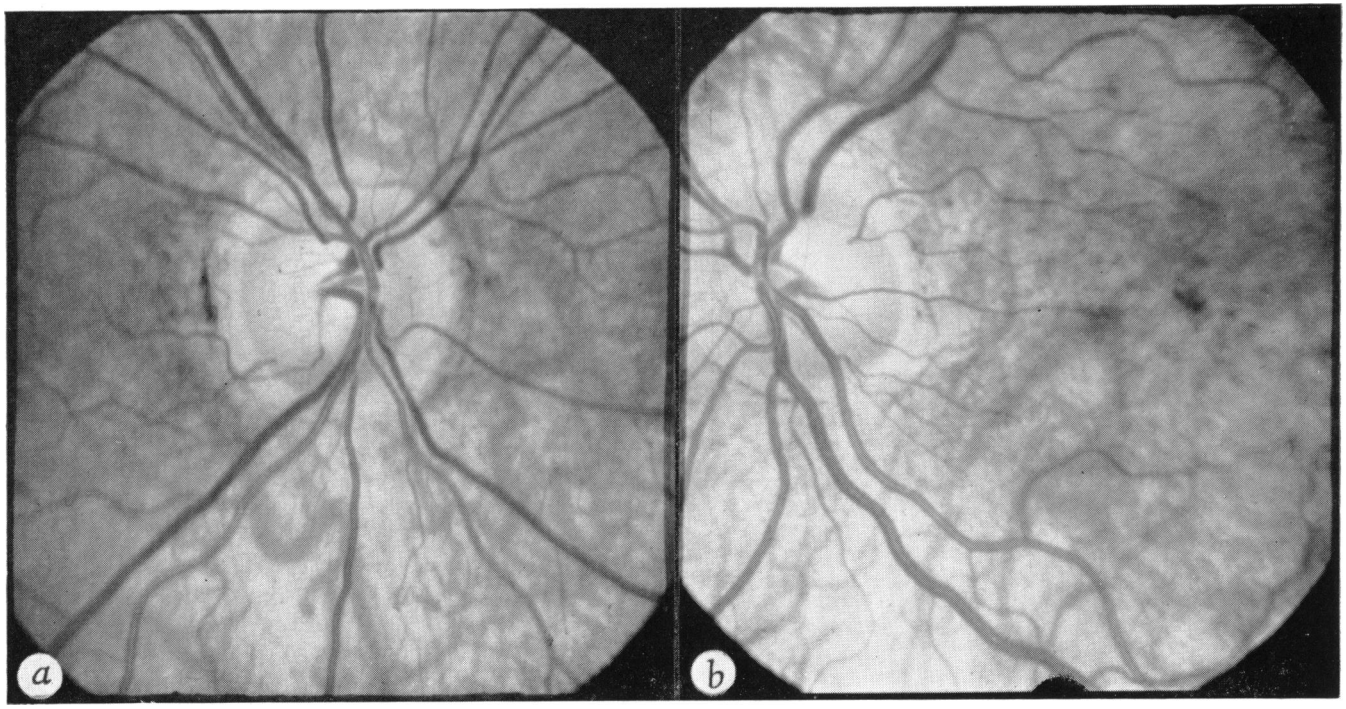

FIGURE 15. CASE 4.

Photographs of fundi showing thinning of pigment epithelium especially marked in peripapillary areas, and pigment stippling especially marked in left macula. (a), right eye; (b), left eye.

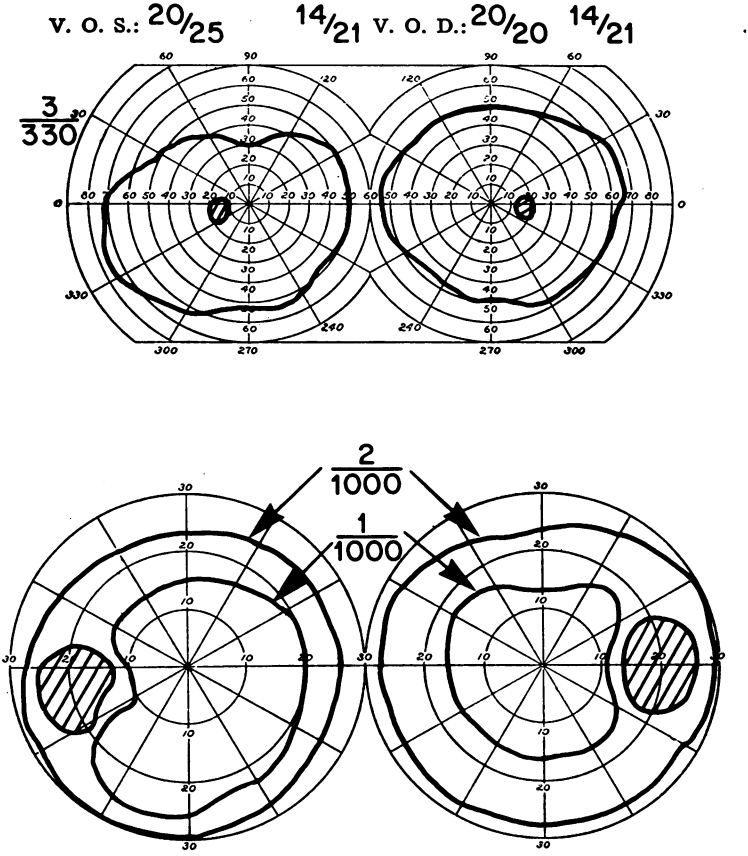

FIGURE 16. CASE 4.
Visual fields showing generalized depression and enlargement of normal blind spots.

was some pigment stippling in both retinas, this being more evident in the macular areas especially in the left eye (Figure 15). The visual fields showed slight depression for the 1/1000 isopter and an enlargement of the normal blind spot to the 2/1000 isopter (Figure 16).

The initial impression was that this woman had "old diffuse choroiditis" and myasthenia gravis. An edrophonium (Tensilon) test gave negative results. The next day another examiner recognized this as an example of external ophthalmoplegia and retinal degeneration. Because of previous observation of the association of cardiac lesions with these conditions, a consultation with a cardiologist was requested. He noted that she had had no cardiac symptoms and that there was nothing to suggest that she had

ever suffered any type of arrhythmia. Clinical examination of the heart gave normal results. The blood pressure was 130/80, the pulse rate 60 and regular. However, the electrocardiogram was abnormal, showing inverted T waves in the precordial leads.

The cardiac consultant recorded that, in view of previous experience with patients who have this combination of defects (external ophthalmoplegia and retinal degeneration), this might be of serious prognostic significance. The remainder of the findings on general examination, including X-ray examination of the chest and head, were normal. Neurologic and spinal fluid examinations were not done.

The patient was re-examined in October, 1960; again she had no complaints. She had had her first baby 4 months previously, after 12 years of marriage. She had had no difficulty with either pregnancy or delivery, and she continued to work half-time as a bookkeeper in addition to caring for the baby and her home. The vision and other ocular findings were unchanged although the ptsois seemed a little more apparent. The lid fissures measured 8 mm. on the right and 7 mm. on the left. The ocular fundi were unchanged. The electrocardiographic findings did not differ significantly from those seen in the 1959 tracing. Complete medical and ophthalmologic examinations were carried out again in December, 1961, and in November, 1962.

Ocular electromyography was performed with electrodes inserted into both the lateral and medial rectus muscles. Unfortunately, the recordings were not fully satisfactory, since the patient was very apprehensive and unable to co-operate, but the findings were thought to be consistent with myopathy.

CASE 5

A 39-year-old white housewife from California seen in April, 1960, wished to have an operation for droopy eyelids. At the age of 18 years she was first noted to have ptosis, greater on the left side. Shortly after this she was told that she was not using both eyes at the same time, indicating that there probably was some strabismus. At about the age of 21 it was noted that she had to turn her head to see objects to the side since she was unable to turn her eyes well. The ptosis increased over the next several years. She had had numerous examinations including several neostigmine tests and stated that she had been treated for a while as if she had myasthenia gravis although the physicians giving these treatments doubted this diagnosis.

Since the time the ptosis was first noted, at age 18, she had suffered from what she described as attacks of "rapid heart." These occurred once or twice a month and lasted only a few seconds. She usually could stop them by lying down and taking deep breaths.

Her blood pressure was 130/80. During physical examination she had a sudden onset of tachycardia; the rhythm was regular and the pulse rate

was 180. The rapid heartbeat subsided with pressure on the carotid sinus. It shortly recurred and was not affected by pressure on the eyeballs or a Valsalva maneuver. By lying down and taking several deep breaths she stopped the attack in 30 seconds. The remainder of the general examination, including X-ray examination of the chest, gave negative results. An electrocardiogram showed a rate of 75 beats per minute with sinus rhythm and an occasional ventricular premature contraction. Unfortunately, the episode of tachycardia had stopped before an electrocardiogram could be taken. Neurologic examination disclosed slight weakness of the facial muscles. Orbicularis oculi weakness was graded −1. The patient had no difficulty swallowing and the pharyngeal musculature was thought to be normal. There was some slight weakness of the sternocleidomastoids and the trapezii. The cerebrospinal fluid was not examined.

Ocular examination showed a vision of 20/20 in both eyes. The visual fields were grossly normal. Ocular rotations were markedly limited, being graded −3 or −4 in all directions. The ptosis was graded +3 in both eyes. Ophthalmoscopic examination showed that the disks and vessels were normal but that there was a salt-and-pepper type of pigment stippling over most of both retinas.

An operation for ptosis was not recommended for fear of progression of the orbicularis weakness. Changes of a myopathic type were recorded by electromyographic study of a number of muscles including the frontalis and the orbicularis oculi. No extraocular muscles were tested.

CASE 6

A 13-year-old Jewish refugee from Hungary was seen in August, 1961, because of progressive hearing loss, trouble with his eyes, and easy fatigability. His parents thought he was a normal child although he had not walked until he was 18 months old. At the age of 8 years he had an attack of fever, vomiting, and jaundice, and a diagnosis of hepatitis was made. During the Hungarian revolution in 1956 the boy was brought with his family from Hungary to Vienna, Austria, where he was hospitalized and was thought to have developed meningitis. One year later he came to the United States. In 1958 it was noticed that his eyelids were drooping and that his ocular movements were limited. The parents said that "he had to turn his head in order to see something to the side of him." They assumed that this was the result of meningitis. About a year after this was noticed, they first became aware of his hearing loss; several examinations revealed bilateral loss of hearing. He had been hospitalized elsewhere (New York City) and a diagnosis of probable myopathy of the eye muscles was made. Spinal fluid examination was said to have shown a protein content of 240 mg. on one occasion and 400 mg. on another. In 1961, an operation for bilateral ptosis was performed.

Examination showed a clumsy boy who was short and small for his stated age. He was 54¾ inches tall and weighed 72½ pounds. However, his mother

was only 62 inches tall, and the father was only 60 inches tall. His blood pressure was 82/42. Neurologic examination showed marked weakness of the upper extremities, the weakness of the biceps, the triceps, and the brachioradialis being graded −3 to −4. There were no clear cerebellar signs. The alternate motion rate was slow. Swallowing was thought to be normal. Spinal fluid examination was refused. An audiogram showed a 25-decibel loss on the right and a 60-decibel loss on the left. An electroencephalogram showed a dysrhythmia, grade 2, in the anterior head region which was maximal on the left side. Psychologic testing with the Wechsler test for children showed an I.Q. of 80.

Vision was 20/50 in the right eye and 20/30 in the left. Grossly the visual fields were normal. There was extensive clumping of pigment in the fundus in both eyes. There was nearly complete (grade 3) external ophthalmoplegia and there was considerable ptosis, although a ptosis operation had previously been performed. There was some irritation of the eyes due to exposure of the corneas, and the patient was using artificial tears.

A cardiologist found no evidence of cardiac dysfunction clinically. There were no murmurs. The heart was thought to be slightly enlarged and had a globular appearance on the roentgenogram. An electrocardiogram showed an abnormal degree of left axis deviation and a slight delay in intraventricular conduction (0.10 second). Atrioventricular conduction was normal. The consulting cardiologist thought that the abnormal radiographic and electrocardiographic findings were the result of a myocardiopathy.

Cases of the Presumably Incomplete Form of the Syndrome

CASE 7

A 13-year-old white boy from California was first seen in February, 1960. The parents had noticed drooping of his eyelids at the age of 8 years. They thought him normal otherwise except that he had never eaten well.

His vision was 20/40 in the right eye and 20/30 in the left. Ophthalmoscopic examination showed a stippled appearance of both fundi and a grayish halo around each optic nerve head. The pigment epithelium appeared thin and atrophic, and the choroidal vessels could be visualized although they did not appear to be sclerotic (Figure 17). The visual fields showed a huge enlargement of the blind spots (Figure 18). There was marked bilateral ptosis. The lid fissures measured 3.5 mm. each. There was almost complete external ophthalmoplegia. The pupils were normal in all respects.

Pediatric examination showed a height of 58 inches, a weight of 74½ pounds, and a blood pressure of 98/62. The pulse rate was 84 and regular. No history could be elicited of any cardiac attacks although his father recalled an episode when the patient was about 10 or 12 months old in which he had suddenly "thrown back his head and rolled up his eyes."

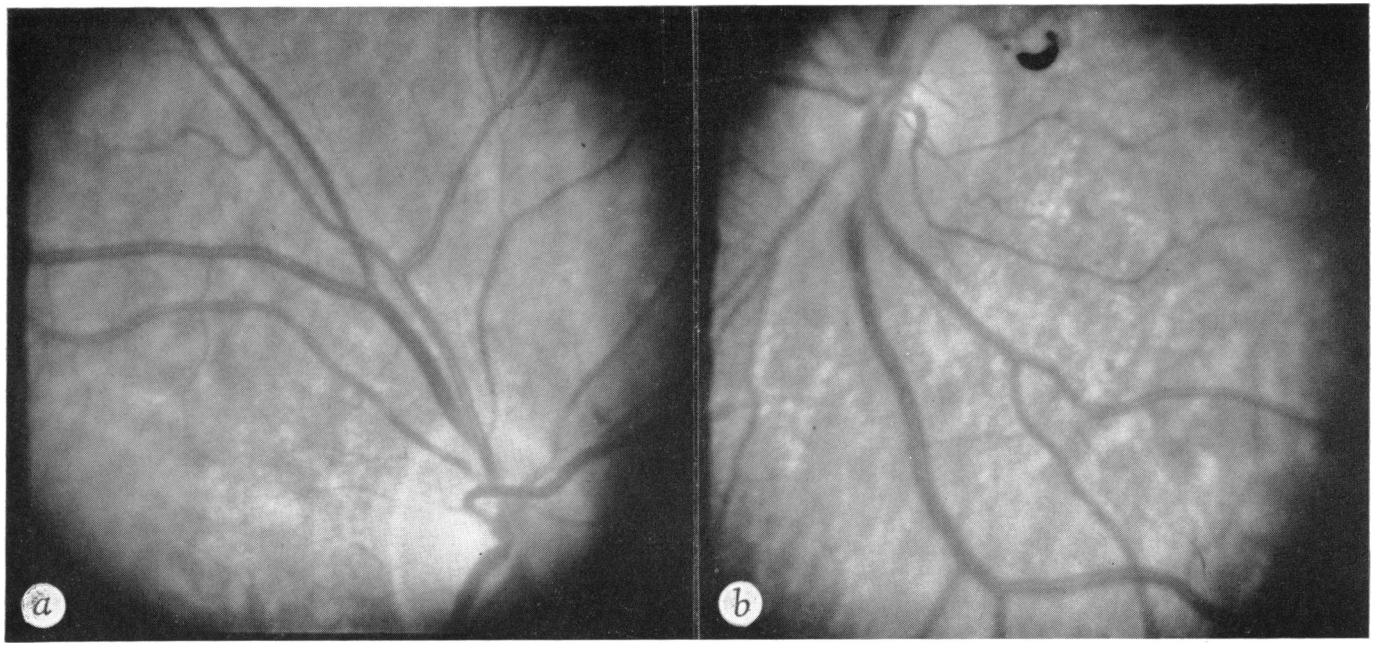

FIGURE 17. CASE 7.

Photographs of fundi showing thinning of pigment epithelium. There is a band of grayish discoloration around each optic nerve head that is not well produced in black and white photographs. (a), right eye; (b), left eye.

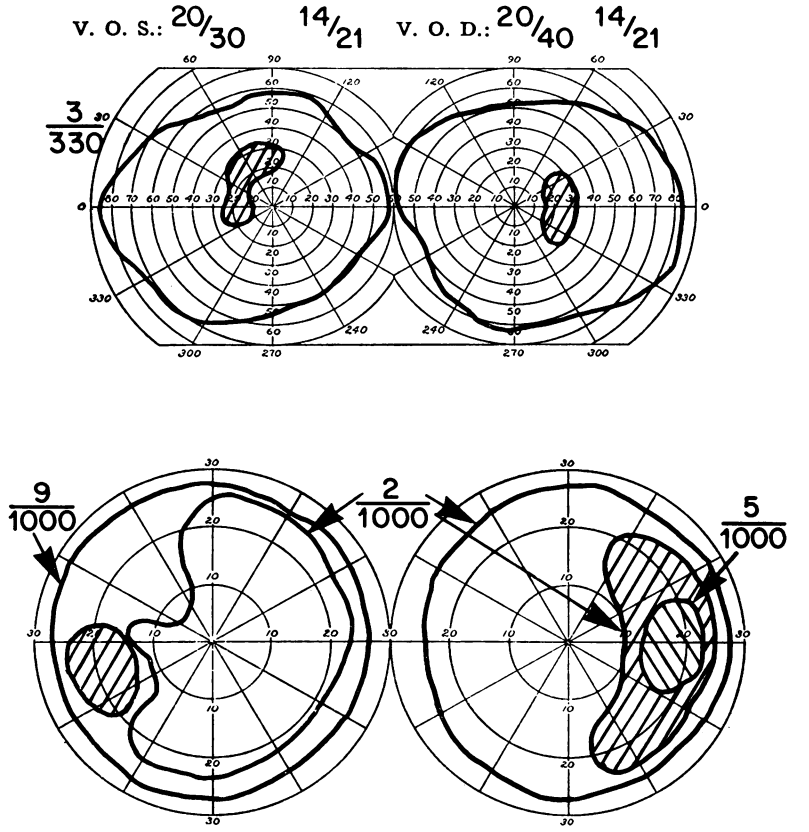

FIGURE 18. CASE 7.
Visual fields showing marked enlargement of normal blind spots.

His Wechsler I.Q. was 83 (dull normal). He had no pubic or axillary hair, and the testicles were infantile. Neurologic examination showed weakness of the neck muscles (grade —2 or —3). The mouth, the frontalis, and the orbicularis muscles were all weak (grade —2 or —3). His co-ordination and alternate motion rate were poor. Cerebro-spinal fluid examination showed a protein content of 300 mg. per 100 ml. Electromyographic studies of the right orbicularis oris and the right deltoid revealed no abnormalities. An electroencephalogram showed a generalized grade 1 dysrhythmia.

Unfortunately, electrocardiograms were not made. He was dismissed. Then, only a few minutes after departure of his plane, he became numb all over and almost stopped breathing. A physician aboard the plane administered oxygen. At the first stop of the airplane he was transferred to a local hospital. The attending physician wrote that no definite diagnosis had been made and that no electrocardiographic examination had been done.

CASE 8

A 13-year-old white girl from Minnesota was referred in November, 1955, for examination because of bilateral ptosis, smallness of stature, anorexia, halitosis, and non-resistance to infection. Because the dye test for *Toxoplasma* had given a positive reaction in a dilution of 1:64 and because of complement fixation in a dilution of 1:8, she had been given a course of sulfadiazine and pyrimethamine (Daraprim). Testing with neostigmine had given severe chest pains and abdominal cramps but did not affect the ptosis. Her parents had first noticed drooping of the eyelids in 1953, and by 1954 the drooping had become much more severe. She had had no muscle weakness or difficulty swallowing.

Examination showed a small, well-developed, thin, pleasant, and cooperative child. She was 57¼ inches tall and weighed 60½ pounds. Her blood pressure was 100/36 and her pulse rate 80 and regular. Neurologic examination revealed that her muscles seemed even smaller than her size warranted. The interossi, the triceps, and the quadriceps were weak. Also the muscles of the forehead and the orbicularis oculi were weak (grade about −2). Spinal fluid examination showed a protein content of 100 mg. per 100 ml. Electromyography of the triceps and biceps brachii showed typical myopathic changes. Vision was 20/20 in each eye.

The disk and retinal vessels were normal, but there was thinning of the pigment epithelium around each optic disk, giving a halo appearance. There was also widespread pigment stippling, which was most pronounced in the macular areas (Figure 19).

The patient was examined again in 1956 and 1958. On the latter examination the visual fields and the fundi were the same but the extraocular muscles were now weak (grade −2 to −3 in all directions). The ptosis was slightly worse (Figure 20). A diagnosis of chronic external ophthalmoplegia was made. Electrocardiographic findings were normal. On several subsequent visits the question of an operation for ptosis was raised, but in view of the orbicularis weakness this was not thought advisable. She had passed the college entrance examination, ranking in the lower third, but had been turned down for work as a practical nurse. Her only occupation had been occasional baby-sitting. By this time the ophthalmoplegia was almost complete and the ptosis was increased, the lid fissures measuring only 2 to 3 mm. each. The facial muscles were weak (grade −2). An electroencephalogram showed a dysrhythmia, grade 2, in the posterior regions of the head.

The fundi had the same appearance as before, but the pigment disturbance seemed to be a little more pronounced (Figure 21). The visual fields were normal as far as the peripheral fields were concerned, although the blind spots were enlarged (Figure 22). The central vision was 20/40 in the right eye and 20/30 in the left. This slight reduction in vision was thought due to the external ophthalmoplegia and the difficulty fixing on the letters rather than to a central scotoma.

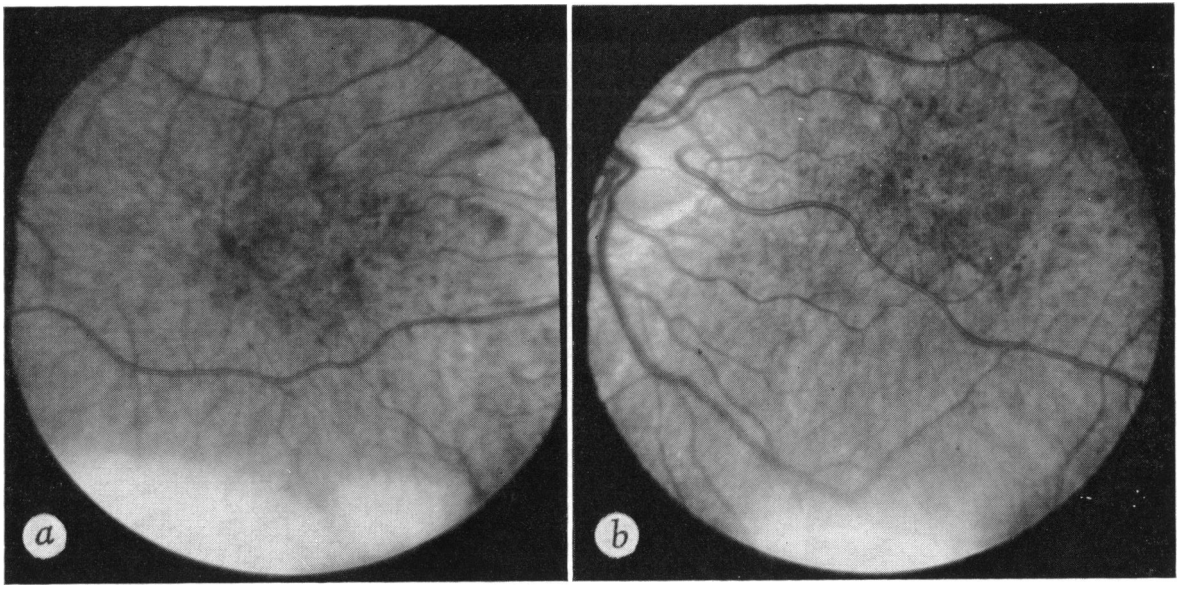

FIGURE 19. CASE 8.

Fundus photographs showing thinning of pigment epithelium most pronounced around optic nerve heads, and pigment stippling most marked in maculas. (a), right eye; (b), left eye.

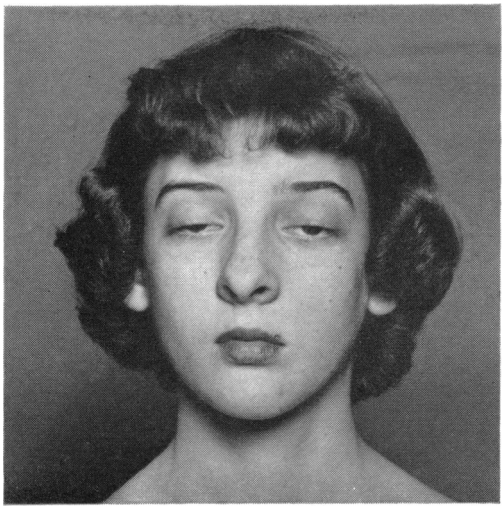

FIGURE 20. CASE 8.
Patient with external ophthalmoplegia and pigmentary degeneration of retina showing marked ptosis.

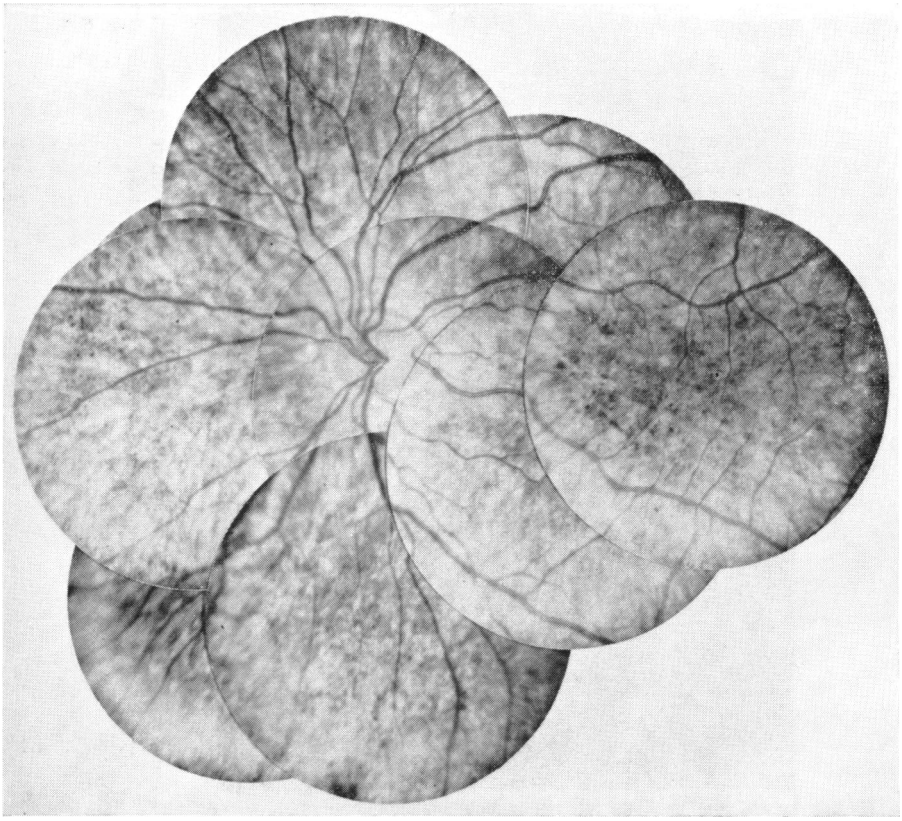

FIGURE 21. CASE 8.
More recent photograph of left fundus showing marked macular and peripheral deposition of pigment.

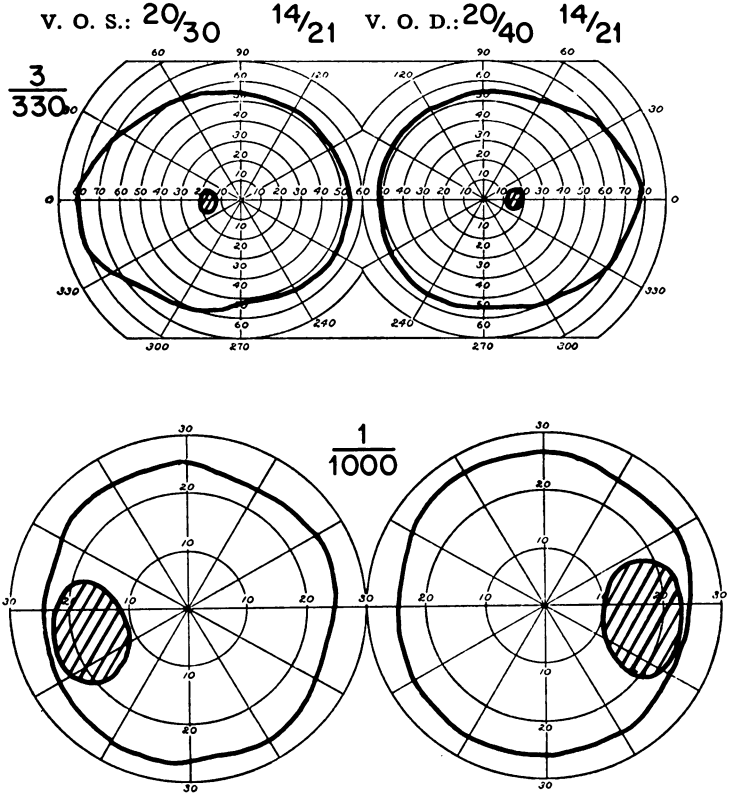

FIGURE 22. CASE 8.
Visual fields showing enlargement of blind spots. Reduction in visual acuity appeared to be due to inability to fix on letters as a result of ocular myopathy.

When the patient was last seen in 1964, the findings were essentially unchanged. Dark-adaptation studies gave nearly normal findings (Figure 23). Electroretinography revealed a wave form of fairly normal appearance, but of greatly reduced amplitude. The electro-oculogram was also abnormal (Figure 24). A description of the technic and an evaluation of the findings will be given in the discussion.

CASE 9

An Indiana boy, 12 years old, was seen in August, 1962, because of hearing loss and bilateral drooping of the eyelids. The parents thought his difficulty had started at the age of 7 years when he fell at school, striking his head on concrete. Three or 4 months later, it was noticed that he was

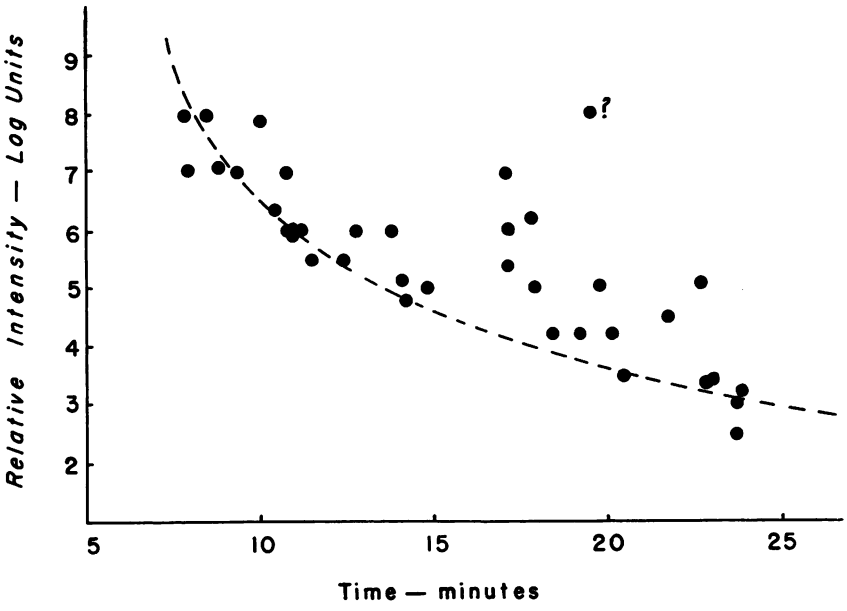

FIGURE 23. CASE 8.
Dark-adaptation study. See discussion in text for description.

becoming hard of hearing. Shortly after this, ptosis had developed. He had been taking pills for myasthenia gravis, although the parents did not think that this lessened the drooping of his eyelids (Figure 25).

Pediatric examination showed a height of 50½ inches and a weight of 57½ pounds. The blood pressure was 100/55, the pulse rate was 88 and regular, and the patient was wearing a hearing aid. An audiogram showed a 35- to 40-decibel loss in both ears; an I.Q. of 92 was obtained on the Wechsler scale. An electrocardiogram showed a normal sinus rhythm. An electroencephalogram showed a dysrhythmia, grade 2, generalized but maximal in the bisylvian areas. The cardiac consultant found the heart of normal size and contour (roentgenograms). There was no apparent heart disease. Vision was 20/50 in each eye. The ptosis was graded +2 in each eye, and ocular rotations were limited in all directions (grade −3). Ophthalmoscopic examination showed slight mottling of the pigment in both eyes. The optic nerve heads and the retinal vessels were normal. The choroidal vessels were prominent and appeared sclerotic in an area around each optic nerve head (Figure 26). This appearance resembled that seen in case 2 (Figure 5) except the changes were not as striking as they were in the negroid fundus. The visual fields could not be accurately plotted because of lack of co-operation.

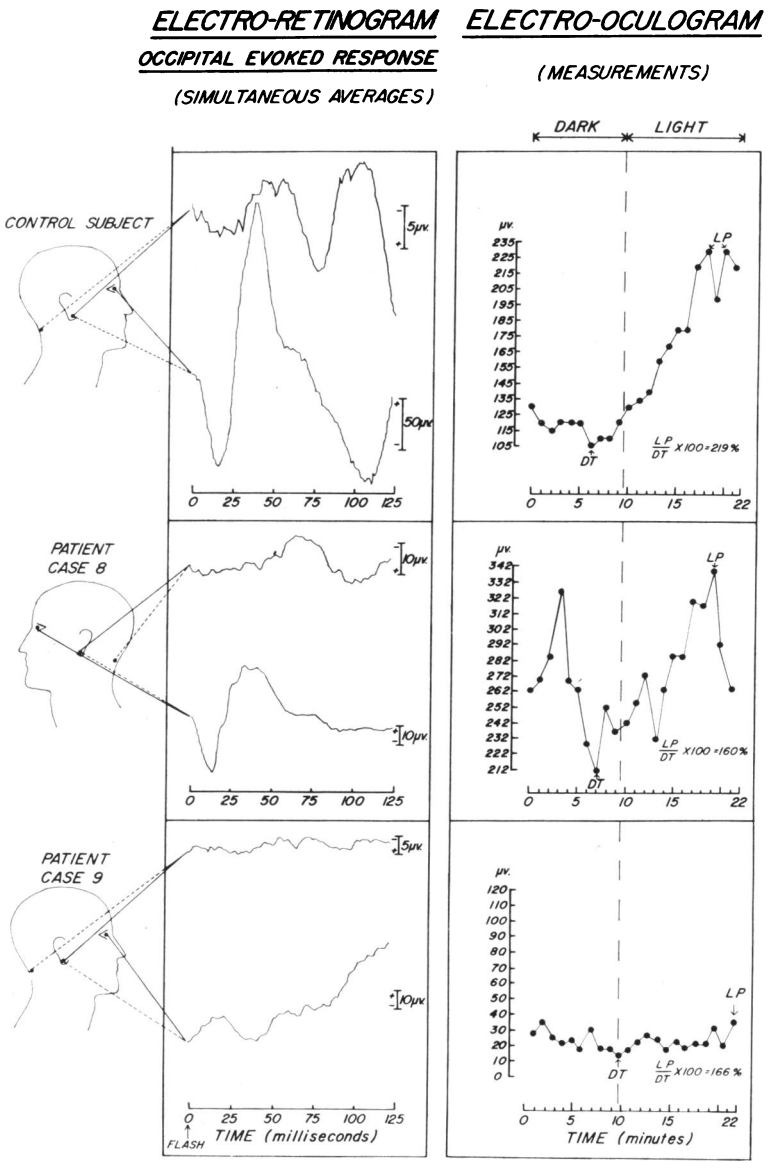

FIGURE 24

Electrophysiologic studies of control patient, patient 8, and patient 9. See discussion in text.

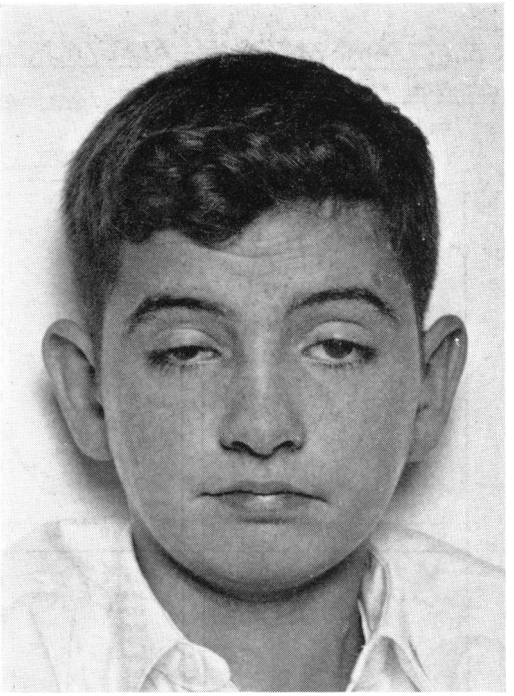

FIGURE 25. CASE 9.
Twelve-year-old boy with chronic progressive external ophthalmoplegia and pigmentary degeneration of the retina.

Electroretinography showed a response so reduced and abnormal that it could not be measured or evaluated (Figure 24). The slow rise of the base line in the illustration is probably an artifact. The electro-oculogram showed a ratio of light peak to dark trough of 166 per cent, which is well below the 185 per cent usually considered as the lower limits of normal. A complete description of the electrophysiologic testing will be given in the discussion.

DISCUSSION

DESCRIPTION OF SYNDROME

The triad of external ophthalmoplegia, pigmentary degeneration of the retina, and cardiomyopathy, although represented in a few previous sporadic reports, has not been generally recognized. The association of the first two members of the triad has been recognized and a number of cases have been reported. The third member, cardio-

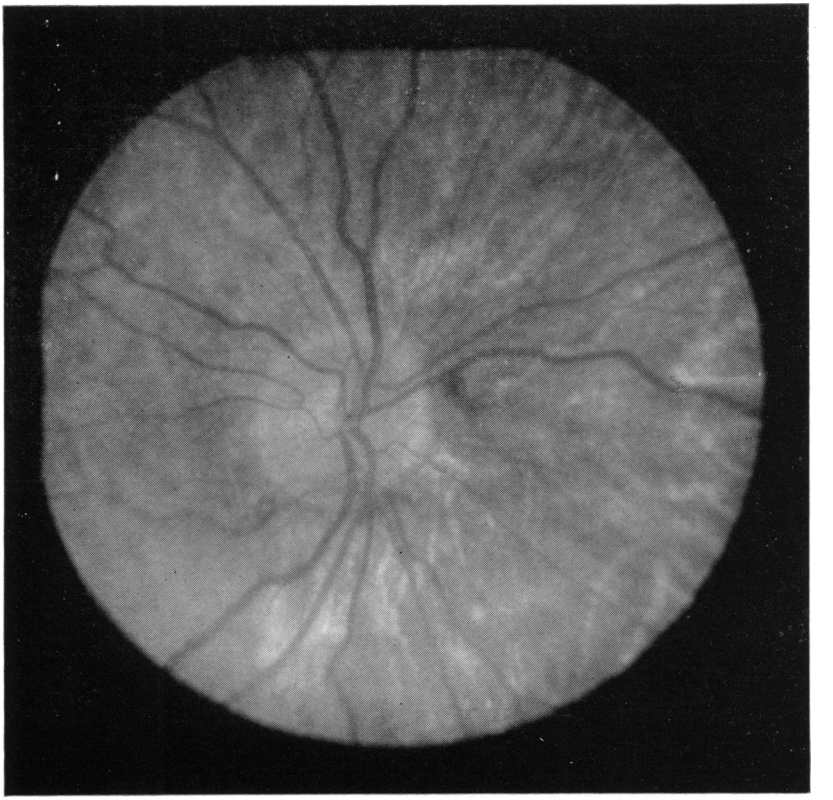

FIGURE 26. CASE 9.
Photograph of fundus of right eye showing thinning of pigment epithelium and prominent sclerotic choroidal vessels in peripapillary areas.

myopathy, is the most important in that it may lead to great disability and at times to a fatal termination.

Frequently associated with the triad in this group of patients were weakness of the orbicularis, facial, and peripheral muscles, deafness, small stature, abnormal electroencephalographic findings, and increased protein content of the cerebrospinal fluid. The facial weakness is easily explained as a part of the myopathy and is seen frequently with uncomplicated external ophthalmoplegia. The deafness and the small stature are not unusual as associated findings in patients with true retinitis pigmentosa; however, the electroencephalographic findings and the increase of protein in the spinal fluid seem unique and are difficult to explain. In patients with Refsum's syndrome, spinal fluid

TABLE 4. SYNDROME OF EXTERNAL OPHTHALMOPLEGIA, RETINAL DEGENERATION, AND CARDIOMYOPATHY WITH ASSOCIATED FINDINGS*

	Form of syndrome								
	Typical						*Incomplete*		
	Case						*Case*		
	1	2	3	4	5	6	7	8	9
Age at onset, years	16	19	3	25	18	9	8	11	7
Sex	F	M	M	F	F	M	M	F	M
Ophthalmoplegia	+	+	+	+	+	+	+	+	+
Ptosis	+	+	+	+	+	+	+	+	+
Retinal changes	+	+	+	+	+	+	+	+	+
Cardiomyopathy	+	+	+	+	†	+	?	0	0
Non-ocular muscle weakness	+	+	+	+	+	+	+	+	+
Deafness	0	0	+	0	0	+	0	0	+
Small stature	0	0	+	0	0	+	+	+	+
Spinal fluid protein increased	−	−	−	−	−	+	+	+	−
Abnormal electroencephalogram	+	−	−	−	−	+	+	+	+

*Key: + = present; 0 = absent; − = no data.
†Cardiac arrhythmia. See text.

protein is increased, but these patients are thought to have interstitial polyneuritis of the peripheral nerves and not myopathy. Although patients with Refsum's syndrome do have atrioventricular conduction defects and retinal degeneration, they do not have external ophthalmoplegia.

Features of the nine cases reported herein are summarized briefly in Table 4 and discussed in ensuing pages.

AGE AT ONSET

The age at onset of the ocular myopathy in this group of patients varied from 3 years (Case 3) to 25 years (Case 4). This seems to agree with the age at onset of most reported cases of uncomplicated chronic progressive external ophthalmoplegia.

Kiloh and Nevin[4] found that usually the disease commences before 30 years of age. The insidiousness of the symptoms makes dating of onset difficult, and it is likely that the ophthalmoplegia appears even before the ptosis but goes undetected by both the patient and the parents.

The patient with the earliest onset, age 3 years (Case 3), had all of the findings of the syndrome, and the cardiac conduction defect terminated fatally. On the other hand, the patient with the latest onset, age 25 (Case 4), had minimal symptoms. Her ptosis was minimal and the diagnosis was established, not because of her

complaints, but because of curiosity and interest on the part of the physicians.

SEX OF PATIENT

Five of the nine patients were male and four were female. Of six patients with cardiomyopathy, three were male and three were female.

This also seems to parallel the 50 : 50 sex incidence usually seen with uncomplicated chronic progressive external ophthalmoplegia. Kiloh and Nevin, in reviewing all of the reported cases of chronic progressive external ophthalmoplegia up to 1948, found an even sex distribution. It is further noted that the two patients with a fatal outcome resulting from this syndrome were young males: Patient 3 of the presently reported group died at age 17 and the one reported on by Jager died at age 13 years.

HEREDITARY ASPECTS

Kiloh and Nevin[4] found that there was a history of ptosis or ophthalmoplegia in about half the recorded patients with chronic progressive external ophthalmoplegia. Furthermore, there are numerous reports[18, 19,21,30,45,63,64,72,73,108,114,115] of uncomplicated external ophthalmoplegia appearing in several generations of the same family. François[116] states that external ophthalmoplegia is hereditary and is generally dominant but that transmission is sometimes recessive.

It seems strange that none of the nine patients of the present report had any family history of ptosis or ophthalmoplegia. Whether this means a lack of hereditary factors or is merely a statistical quirk is debatable. The similarity of the ophthalmoplegia in the present group to the ophthalmoplegia of uncomplicated external ophthalmoplegia would suggest that hereditary factors should play a part.

It should be pointed out that Erdbrink's patient, although he did not have a cardiopathy, did have ophthalmoplegia and retinal degeneration and a history of ptosis in five generations. Furthermore, the only other patient in the literature with the exact syndrome under discussion (Jager's case) did not have a family history of ptosis or ophthalmoplegia, and four siblings were normal.

Refsum's syndrome is hereditary (heredopathia atactica polyneuritiformis). It is thought to be recessive, and a history of consanguinity is usually obtained when more than one sibling is affected.

Thus, in its hereditary aspects, the syndrome of external ophthalmoplegia, pigmentary degeneration of the retina, and cardiomyopathy apparently differs entirely from Refsum's syndrome as well as other related disorders.

OPHTHALMOPLEGIA

All nine patients had the typical ophthalmoplegia of chronic progressive external ophthalmoplegia. The onset was gradual, usually in childhood, which accords with what Wilbrand and Saenger[23] observed in their work. The rate of progression was variable, but in the more advanced cases there was complete external ophthalmoplegia.

Diplopia or a history of diplopia was lacking in all nine patients even though there was often a gross strabismus in addition to the impaired ocular rotations. This feature along with the lack of variability and the lack of remissions and exacerbations helps differentiate the syndrome from myasthenia gravis. Not only did the patients not complain of diplopia but they were usually unaware of the defect in ocular rotation until it was called to their attention by family or physician. This lack of diplopia and of awareness of the limitation of the ocular rotations in uncomplicated chronic progressive ophthalmoplegia has been noted and commented on by numerous authors.[7,23,42,98]

The histologic changes in the ocular muscles of the patient that came to necropsy were those of a myopathy. No changes of a neuronal nature were found in either the motor endplates or in the oculomotor cranial nerves themselves. This is identical to the reported findings in patients so examined that had uncomplicated chronic progressive ophthalmoplegia. This would seem to be of importance in demonstrating that the present syndrome is more closely related to chronic progressive external ophthalmoplegia than to Refsum's syndrome, which had been shown to be a chronic polyneuritis. Electromyographic study of the ocular muscles was possible in only one patient (Case 4). The recording, though not entirely satisfactory, was thought to be consistent with ocular myopathy.

On clinical grounds the ophthalmoplegia of the nine patients is identical to that seen in patients with ordinary chronic progressive external ophthalmoplegia. The frequent association of ocular myopathy in the nine patients with myopathy of the facial and laryngeal musculature suggests that it is identical to the ordinary form of chronic progressive external ophthalmoplegia. Numerous authors mention this frequent association in describing cases of chronic progressive external ophthalmoplegia.

PTOSIS

All nine patients had ptosis. Like the ophthalmoplegia, it varied from very mild (Case 4) to very severe (Case 3). The degree of ptosis seemed to parallel the degree of ophthalmoplegia. If a discrepancy

existed, it was usually that the ptosis was less evident or that it developed more slowly than the ophthalmoplegia. On the other hand, the ptosis was generally noticed by the patient or parents before the ophthalmoplegia. The ptosis in all cases was bilateral and was fairly symmetrical.

The facies of the patients was rather characteristic. The droopy lid, the facial muscle weakness, and the infrequent blinking are identical to the facies of some patients with myasthenia gravis. If the ptosis was severe, the patient held his head back with the chin up to compensate for the drooping of the eyelids.

Surgical treatment of the ptosis was not advised for any of the patients. One patient (Case 5) sought consultation primarily in the hope that such treatment would relieve the droopiness of her eyelids. Another patient (Case 6) had had bilateral operations for ptosis previously. Although the ptosis had been lessened for a while, he had constant irritation of his eyes from exposure and from inability to close the lids completely. He was using artificial tears to protect his eyes, but in spite of this there was considerable punctate staining of the lower parts of both corneas.

The potential danger to the corneas of these patients is great if the ptosis is treated surgically. The orbicularis oculi is weak and lagophthalmos may exist even without such an operation. The orbicularis muscle generally becomes weaker as time passes, and even if no exposure symptoms occur initially after operation, they are likely to appear later. This contraindication to operation in this group of patients is the same as in ordinary chronic progressive external ophthalmoplegia. Many authors have commented on this problem in the latter group of patients, and there are a number of reports[69,117,118] of serious ulceration of the corneas following operations for ptosis.

Despite the obvious dangers in the surgical treatment of ptosis in patients with chronic progressive external ophthalmoplegia, only one author[68] writing on this subject mentions that he thinks such treatment contraindicated.

RETINAL CHANGES

The retinal changes observed in the nine patients varied in severity, but none of the patients complained of their vision and none was seriously handicapped by this feature.

The retinal changes were similar to but not characteristic of retinitis pigmentosa. Although there was occasional clumping of pigment in the peripheral retinas, this was never present in the degree usually

seen in typical retinitis pigmentosa. The pigment epithelium of this group of patients appeared thin and atrophic and there was a diffuse mottling of the pigment epithelium. These retinal changes were usually greatest in the peripapillary zone. This zone was usually about one disk diameter wide and was described as a halo around the disk. This halo had the appearance of a band of grayish discoloration. In the patients with the most advanced retinal changes (Cases 2 and 9) there was an area of sclerotic appearing choroidal vessels in this zone around each disk.

In addition to a diffuse stippling of pigment over the retinas, most of the patients had a heavier pigmentation in the maculas. Despite this macular pigmentation, there was no significant impairment of central vision in any of the nine patients. Patient 8 showed the most macular pigmentation.

The histologic changes in the retina in the one patient that came to necropsy (Case 3) were similar to those of retinitis pigmentosa. The retinal disturbance was mainly in the rod and cone layers and the outer nuclear layer. The bipolar and ganglion cell layer was normal. There was no optic atrophy; nevertheless, it is impossible to make a diagnosis of retinitis pigmentosa on histologic study alone.

The rosettes seen in the flat retinal preparation are unique and yet do not clarify the problem in any way. Wolter[119] has described rosettes in retinitis pigmentosa. The rosettes in the retina of this patient were considerably larger than those described by Wolter. It was thought that the areas of rosettes represented the patchy areas of retinal atrophy seen in the cross-section of the fixed retinas. After considering all of these factors, one is left with the conclusion that this is a non-hereditary, idiopathic, retinal degeneration. It is not true retinitis pigmentosa. The visual symptoms are not severe and the rate of progression is not as rapid.

VISUAL FIELDS

Visual fields were plotted in all except Cases 5, 6 and 9, and in these three the visual fields were thought to be grossly normal although co-operation was not good in the two younger patients (Cases 6 and 9).

Patients 1 and 8 showed essentially normal visual fields except for enlargement of the blind spot. It was thought that this enlargement represented the earliest field change in this type of pigmentary degeneration of the retina. As mentioned previously, the peripapillary area of the retina usually shows the most pronounced retinal changes.

Patients 4 and 7 showed even greater depression of the visual fields in an area surrounding the normal blind spots and yet the peripheral fields were normal. (Patients 2 and 3 showed further progression of the defects in that the blind spots are tremendously enlarged. In Case 3 a blind area surrounded fixation and this scotoma has broken through superiorly in the right eye.)

It would appear that the visual field defects start as an enlargement of the normal blind spot and then progress to form pericentral scotomas. Such a progression was not actually observed in any of these nine patients but it is surmised on the basis of the type of visual fields found in the individual patients and their relation to the pronounced retinal changes surrounding the optic nerve heads.

Since the retinal changes and the visual field changes were not typical of retinitis pigmentosa and there was no history of hereditary retinitis pigmentosa in any of the nine patients, it would seem that this is not true retinitis pigmentosa. It is true that inflammatory retinal disease may sometimes leave a residual, indistinguishable from retinitis pigmentosa, but none of these nine patients showed any evidence of inflammatory eye disease, past or present. More recently, toxic factors, especially the antimalarial group of drugs such as chloroquin, plasmoquin, and camoquin, has been found to produce retinal changes. Retinal lesions from these drugs produce visual field defects of a pericentral nature similar to the field defect found in Case 3; nevertheless, none of these nine patients had been exposed to any such drugs and most of the patients were not receiving medication of any type.

ELECTROPHYSIOLOGY

Electro-oculography was performed on two patients (Cases 8 and 9). The technic used is that described by Arden and associates.[120,121] Electrodes were placed on the skin near the lateral canthus of each eye and on the bridge of the nose. Thus the standing potential of each eye could be recorded on the electroencephalograph (Grass Model 6). The patient fixed on a small red point of light straight ahead and on command shifted fixation to a second light placed horizontally to the first. The separation of the two lights is unimportant since it is the comparison of the potential change in the light as compared to that in the dark that is measured. Therefore in these cases the lights were placed at a distance of 1 meter and separated by a distance of 20 cm. This relatively short separation ensured that the patient was able to shift fixation easily from one to the other despite the limitation of ocular rotations imposed by the ocular myopathy. The changes in the

standing potential of the eyes caused by changes in retinal illumination are shown in Figure 24. In these patients both eyes were tested and the results, being quite similar, were combined and expressed as one figure. Our normal patients have had values of light peak to dark trough in the neighborhood of the 252 per cent given by Arden and associates as normal.

As can be seen, Patients 8 and 9 both had abnormal electro-oculographic responses. Patient 8 had a ratio of light peak to dark trough of 160 per cent while patient 9 had a ratio of 166 per cent. These ratios are below the lower limits of normal (185 per cent) given by Arden and co-workers.

Electroretinography was performed on the same two patients. The pupils were dilated with 10 per cent neosynephrine and a standard Burian-Allen contact-lens electrode was used. The stimulus was obtained by using a Grass photostimulator at intensity no. 16 placed 1 meter from the patient. The evoked retinal responses, as well as the evoked cortical responses, measured from a scalp electrode with the ipsilateral ear lobe as reference, were monitored on an electroencephalograph (Grass Model 6). These evoked responses were then fed into a Mnemotron computer of average transits (cat computer), and the average responses were written out with an X-Y plotter.

The results, as recorded in Figure 24, represent the average of 200 samples using the described stimulus spaced at 1-second intervals. The light-adapted electroretinogram of Patient 8 had a fairly normal wave form. The ratio of *b*-potential to *a*-potential is approximately 2 to 1, but the over-all amplitude is much reduced. The light-adapted *b*-wave potential was 63 microvolts. After 10 minutes of dark adaptation (not illustrated), the *b*-wave potential was 180 microvolts. Computer averaging was also used to record the dark-adapted electroretinogram. The technic was identical except that the stimulus was spaced at 60-second intervals and only 10 samples were averaged.

Patient 9 gave no measurable electroretinographic response, either light- or dark-adapted.

One further point might be noted concerning the electroretinogram of Patient 8. There was no delay in the *a*-wave latency described by Ruedemann and Noell[122] as occurring in the preserved electroretinograms of patients with retinitis pigmentosa.

In our normal patients the latency to the first evoked cortical response is in the neighborhood of 25 milliseconds, as in our control subject represented in Figure 24. The subsequent components with negative peaks at approximately 40 to 50 and 90 to 110 milliseconds

are also normal. In contrast, Patients 8 and 9 give abnormal results. Neither shows discernible initial positive components, and the later components are of low amplitude. Since both had abnormal electroretinographic responses, these abnormal evoked cortical responses could be associated with defective retinal transmission.

Dark-adaptation testing was done only on Patient 8. The results are shown in Figure 23. These data were taken with the right eye, the test patch being a circular area about 1 arc degree in diameter at 20 degrees in the nasal field. The light-adapting field was about 300 millilamberts. The dark-adaptation curve did not begin until 7 minutes after the light-adapting field was extinguished. This delay is approximately normal for the rod system, but suggests a defect in the cone system.

Because of the ptosis the lid tended to lower over the pupillary area in spite of the patient's trying to keep the lid raised with fingers, and this caused an increase in light threshold; accordingly, the curve to describe the course of the adaptation was drawn to favor the lower thresholds.

Because of patient fatigue the test was not continued beyond 25 minutes, so that the lowest threshold could not be determined. Despite the variation in the data it is believed that the lowest threshold was not a great deal higher than normal.

CARDIOMYOPATHY

The cardiomyopathy, the unique part of this syndrome, is most important in that it may produce incapacitating symptoms (Cases 1, 2, and 3). Furthermore, the prognosis of patients with such a cardiac lesion is ominous: sudden death may occur at any time.

There was evidence of cardiac disease on physical examination or by electrocardiogram in six of the nine patients. There was no evidence of rheumatic, coronary, or hypertensive heart disease, and the abnormalities found are believed to be the result of a cardiomyopathy. Histologic examination of the cardiac muscle in the patient who came to necropsy (Case 3) showed significant lesions: hyperchromatic muscle nuclei, focal subendothelial fibrosis, and slight thickening of the endocardium. These changes were apparently responsible for the complete atrioventricular block, the abnormal degree of left axis deviation, and the right bundle-branch-block type of contour in the electrocardiogram.

Histologic evidence of cardiomyopathy was not obtained in the other patients. However, there were significant electrocardiographic

abnormalities also in Patients 1, 2, 4 and 6. In three of these (Cases 1, 2 and 6) there was an abnormal degree of left axis deviation which is considered to be a significant electrocardiographic abnormality, indicative of myocardial damage.[123] In addition, in Patient 4 there were T-wave abnormalities of non-specific nature, but the consulting cardiologist thought that these were significant. In Patient 5 the only cardiac abnormality detected was the arrhythmia, which in itself is not evidence for cardiomyopathy but is evidence of increased myocardial irritability.

The most serious heart lesion present in these patients was the complete heart block present in Patients 2 and 3, which was responsible for the death of Patient 3. The cardiologists now believe that an abnormal degree of left axis deviation is also of serious prognostic significance; such deviation was present in Patients 1, 2, 3, and 6.

It seems significant that the cardiac abnormalities were found in all of these patients before the age of 35 years, and in no case was a history suggestive of ischemic heart disease obtained. The cardiologists who saw Patients 1, 2, 3, 4, and 6 concluded that the electrocardiographic abnormalities were the result of a cardiomyopathy of undetermined etiology.

In view of the known ocular and systemic myopathy in these patients, it seemed reasonable to conclude that a similar myopathy affected the cardiac musculature.

MUSCLE WEAKNESS AND ELECTROMYOGRAPHY

Although all nine patients had some degree of facial weakness, this was not a serious problem except in connection with ptosis operation as mentioned previously. Facial weakness, especially orbicularis oculi weakness, is expected in patients with chronic progressive external ophthalmoplegia.

Pharyngeal weakness with difficulty swallowing, present in some patients, was a major feature in only two (Cases 1 and 2). Such weakness is also at times encountered in patients with uncomplicated, chronic progressive external ophthalmoplegia. Although weakness of the limbs and the trunk musculature was not a major feature, it was present in a greater proportion of patients (Cases 1, 2, 5, 6, 7, and 8) than would be expected in patients with ordinary uncomplicated chronic progressive external ophthalmoplegia.

Electromyographic examination of non-ocular muscles was carried out in five patients (Cases 1, 2, 5, 7, and 8). All five had two or more muscles studied by classic needle-electrode electromyography. Only one patient (Case 7) was considered to be normal. Patient 8 was

studied on three different occasions over a number of years and became increasingly abnormal with the passage of time.

The abnormal electromyograms were all of the same sort, although variable in degree of abnormality from one to another and variable in different muscles in the same patient; also, as noted, involvement increased with time in Patient 8. The changes were of the myopathic (as opposed to neurogenic) type. They consisted of an increase over the normal proportions of potentials that were polyphasic, a decrease in the mean duration and amplitude of motor-unit action potentials, and an increase in number of units firing in proportion to the strength of effective contraction. Evidence of denervation characterized by fibrillation potentials was not seen in any muscle in any patient. Resting muscles were electrically silent.

Routine stimulation studies were done in four patients (Patient 7 was excluded). These included determination of motor conduction velocity, distal motor latency, and amplitude and duration of evoked motor action potentials in appropriate muscles after stimulating two or more nerves; the results were all normal. Repetitive stimulation at 2 or 3 per second was done in nerves of three patients (Cases 1, 2, and 8) and showed no decline in potential suggestive of defective neuromuscular transmission. A provocative test done with curare in Patient 1 gave negative results. A peripheral muscle biopsy done in one patient (Case 1) revealed myopathic changes.

DEAFNESS

Deafness is one of the most frequent associated findings in patients with retinitis pigmentosa. Although these patients did not seem to have true retinitis pigmentosa, three of them had a nerve-type deafness (Cases 3, 6, and 9). All three were young boys and all three had severe deafness. One patient used a hearing aid.

SMALL STATURE

Smallness of stature is not unusual as an associated finding in patients with retinitis pigmentosa. Five patients of this group had an abnormally small stature (Cases 3, 6, 7, 8, and 9). In two patients (Cases 3 and 8), this was considered by the parents to be of major concern.

INCREASE IN SPINAL FLUID PROTEIN

The spinal fluid was examined in only three of the nine patients, but in all three (Cases 6, 7, and 8) the protein content was increased, varying from 100 to 400 mg. per 100 ml.

Increase of spinal fluid protein in ordinary chronic progressive external ophthalmoplegia has been noted by other authors.[49,56,100] Of the patients cited in these three reports, only one had retinal degeneration.[100] The only other reported patient with what would seem to be findings identical to those of the present group also had a spinal fluid protein content of 115 mg. per 100 ml.[103]

Of Refsum's five original patients, three had examination of the spinal fluid and in all three the protein was increased.

Since an increase in spinal fluid protein is not generally a part of any ordinary myopathy, this finding would suggest that these patients may have involvement of the central nervous system or of the spinal and cranial nerve roots within the subarachnoid space, in addition to the myopathy.

ELECTROENCEPHALOGRAPHIC FINDINGS

Electroencephalographic examination, done in five of the nine patients, showed a minimal dysrhythmia (grade 1) in two patients (Cases 1 and 7) and a moderate dysrhythmia (grade 2) in three (Cases 6, 8, and 9).

Such dysrhythmias are not always indicative of disease of the central nervous system, but it should be noted that a grade 1 dysrhythmia occurs in only about 10 per cent of normal persons and a grade 2 dysrhythmia in only 2 to 3 per cent. It would seem, then, that these five patients with this electroencephalographic abnormality may have some cerebral malfunction. Such abnormalities, like the increase of protein in the cerebrospinal fluid, although non-specific, do suggest involvement of the central nervous system.

COMPARISON WITH OTHER DISEASE ENTITIES AND SYNDROMES

In many respects, the ocular myopathy of these nine patients is identical with chronic progressive external ophthalmoplegia. Certainly the clinical appearance, the insidious onset, and the slow progressive nature are identical. The associated facial and pharyngeal weakness was also similar.

The main difference would seem to be the more widespread involvement by the myopathy in these nine patients. It is extremely unusual for patients with chronic progressive external ophthalmoplegia to have peripheral (limb and trunk) myopathic changes.[4] Some authors[10,23] even deny that such occur. It would seem that the present myopathy, while probably clinically identical with ordinary chronic progressive external ophthalmoplegia, is different in that it is only the focal or

ocular component of a systemic myopathy in which the ocular involvement is the most serious feature.

The retinal changes are not typical of retinitis pigmentosa: the changes in the retina are not as great, the visual field changes are not as severe, and the greatest disturbance in the retina is in the peripapillary areas. Although the association of hearing loss and small stature suggests that this is ordinary retinitis pigmentosa, the other factors suggest that it is not typical.

It would seem that these patients are much like those reported on previously with external ophthalmoplegia and retinal degeneration. Perhaps some of the previously reported patients may have had undetected cardiomyopathy or would have developed it at a later date.

Refsum's syndrome, although different in several major aspects, shows interesting similarities. The major difference is that none of Refsum's patients had ophthalmoplegia but all had peripheral neuropathy. This neuropathy seems to be well established on clinical as well as pathologic examination, while the present syndrome is a myopathy and not a neuropathy. Refsum's patients also had ataxia as a prominent feature, which was absent in the present syndrome. Refsum's disease is hereditary while the present syndrome apparently is not.

The similarity between the two syndromes are the retinal changes, the cardiac conduction defects, the possibility of sudden death, the deafness, the small stature, and the increase in cerebrospinal fluid protein. Of these similarities, the cardiac conduction defect would seem to be the most interesting. In the present syndrome, this can be explained as a part of the myopathy; but in Refsum's syndrome a cardiac conduction defect is more difficult to correlate with a peripheral neuropathy. On the other hand, an increase of cerebrospinal fluid protein is more easily correlated with a peripheral neuropathy as in Refsum's syndrome than with a myopathy.

SUMMARY

A newly recognized syndrome is described in which the essential features are external ophthalmoplegia, pigmentary degeneration of the retina, and cardiomyopathy. Although quite rare, as judged by a review of the literature, reports of similar sporadic, isolated cases have appeared previously.

The symptoms, clinical features, and laboratory findings in nine patients are presented and are evaluated. Besides the above-mentioned triad, other features, though less constant, were weakness of facial and

pharyngeal musculature, weakness of trunk and extremity musculature, deafness, small stature, electroencephalographic changes, and a marked increase in cerebrospinal fluid protein.

The ophthalmoplegia, the peripheral muscle weakness, and the cardiac lesions are all believed to be a result of a generalized myopathy. The retinal changes, the deafness, and the small stature are probably associated abiotrophic disorders. The electroencephalographic changes and the increase in cerebrospinal fluid protein are more difficult to explain.

It is important that the ophthalmologist be aware of this syndrome and especially aware of the possibility of the cardiomyopathy. As is shown, the cardiac portion of the syndrome may lead to a fatal termination. Such a cardiomyopathy has an ominous prognosis and the chance of sudden death is always present.

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