CHRONIC PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA

Report of a Case with Necropsy

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(By invitation)

Different forms of external ophthalmoplegia are well known, but in this communication we shall describe an unusual clinical case, the only one, we believe, with necropsy, belonging to a group described in the literature as "chronic progressive external ophthalmoplegia."

Wilbrand and Saenger collected 32 cases of this form of ophthalmoplegia, and because of the following characteristics, they regarded it as a distinct clinical entity:

"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."

McMullen and Hine reported three personal observations. (One of the cases, however, showed signs of disease of

the central nervous system, confirmed at a later examination, so that it can be excluded from the group.)

Discussing the literature, they refer to cases reported (since Wilbrand and Saenger) by Beaumont (12 cases) and Atland.

The characteristics of Beaumont's cases were: (1) Familial; (2) never congenital; (3) slowly progressive; (4) never fatal.

In Atland's case the trouble developed at twenty-two years of age in the right upper lid, and at forty the left upper lid became affected. When seen at fifty-one years of age the ptosis of the right eyelid was complete, that of the left incomplete, and both globes were immovable.

In discussing the various forms of hereditary ocular paralysis Collins quoted Gowers' own statement regarding his well-known theory of "Abiotrophies," and pointed out that, in chronic progressive ophthalmoplegia, all the orbital striated muscles became paralyzed, but the unstriated intra-ocular muscles invariably remained unaffected, and he emphasized the fact that many of the cases belonging to this group had been watched for long periods of time and that not one of them had ever developed additional symptoms attributable to the nervous system. For this reason he alluded to the apparent resemblance of the paralysis of these cases to an isolated form of bilateral ptosis described by Fuchs in 1890, and which he thought were cases of primary myopathy. Collins suggested, because of this apparently strong circumstantial evidence, that chronic progressive bilateral ophthalmoplegia might be, in reality, another limited form of primary myopathy and not, therefore, dependent upon alteration of the nervous system.

But Wilbrand and Saenger regarded this condition as a disease of the ocular nuclei, while Brouwer thought it was dependent upon alterations of the nerve-trunks innervating the extra-ocular muscles. Wilbrand and Saenger, as well as

Collins, reviewed the literature of the subject and stated that there had never been a postmortem examination reported. Since their descriptions were published in the years 1900 and 1922 respectively, a number of clinical cases have been recorded, but we have been unable to find the record of a single necropsy.

The case which we have to record here was carefully studied during the life-time of the patient by both of us. Only the brain was obtained for examination. The third, fourth,

Fig. 1.—Patient, eighty-one years old, showing bilateral ptosis.

and sixth cranial nerves and the optic nerves were cut in cross-sections and in longitudinal sections. The brain stem was cut in serial sections, and every tenth section was stained with hemalum and acid-fuchsin, and by the Weigert and Nissl methods; additional sections were stained with toluidin-blue and the van Gieson methods. Unfortunately, the ocular muscles were not obtained for examination.

Mrs. W. H. C. was first examined in January, 1924, at the age of eighty-one, and was under observation until her death at the age of eighty-four. It was stated by the patient, and also by her daughters, that the right eyelid had begun to droop at the age of forty-three (a photograph of the patient was shown to us, taken at the age of thirty, in which ptosis was not revealed, but another photograph, taken at the age of forty-eight, showed right-sided ptosis), and soon after this the left lid was similarly affected. It is

not known positively how long a period of time had elapsed after the onset of ptosis, or even whether the ptosis had preceded the completion of external ophthalmoplegia, for it was not discovered by one of us (Dr. Langdon) until fully developed, when the patient had reached the age of seventy-five. The general health of the patient at that time and subsequently had been very good. She had had no evidences of illness of any kind. Her parents had been normal, and her near living relatives and three daughters were in perfect health, and on inquiry it was stated that no other members of the family had had a similar disease.

Examination revealed complete ptosis of each eyelid, and the visual axes were found to be slightly divergent. The pupils measured 3 mm. on each side and reacted promptly to light. The power of accommodation was very feeble, but not entirely lost. The two eyeballs appeared immobile, but, on voluntary effort, an extremely slight movement of each eyeball, when rotation was attempted in any direction, could be detected. When both eyelids were held open by the examiner, diplopia developed, but when only one eyelid was held open at a time by adhesive plaster attached to the brow, the patient got on quite comfortably. There were some lens changes in each eye, the rest of the media being clear. The retinal arteries were irregular, with some indentation of the underlying veins. The discs were well colored, with clear margins. The fundi otherwise were in good condition. The corrected vision of the right eye was 5/20 and the left eye 5/6.

There was, therefore, very nearly complete loss of all extra-ocular muscular power, with preservation of the reactions of the pupil of each side to light. Movements in convergence were practically impossible. The function of all other cranial nerves, as well as the muscles innervated by them, was carefully tested and was found normal. The muscular power of the upper limbs was entirely normal; the biceps and triceps reflexes were normal. There was no muscular atrophy. The muscular power of the lower limbs was equal and normal; the patellar and Achilles reflexes were equal and normal; the gait and station were normal. No additional evidence of disease could be discovered. There was a moderate degree of general arteriosclerosis, no greater in degree, however, than might be expected in a normal woman of eighty-one years of age.

The patient died of pneumonia at the age of eighty-four, without having developed additional symptoms.

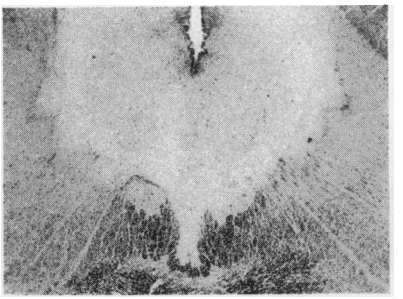

Fig. 2.—Normal fourth nerve nuclei for purposes of comparison with Fig. 3.

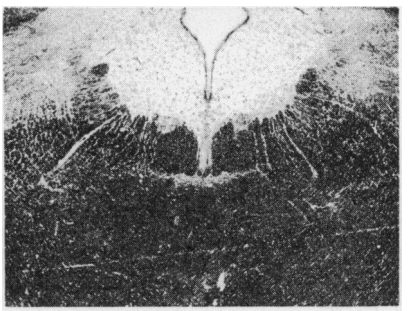

Fig. 3.—Showing pathologic fourth nerve nuclei. The diameter of the nuclear groups appeared shorter than those of the normal nuclei of the control sections.

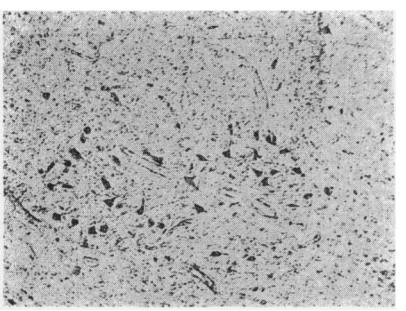

Fig. 4.—Cells of the sixth nerve nucleus from a normal case, for the purpose of comparison with Fig. 5.

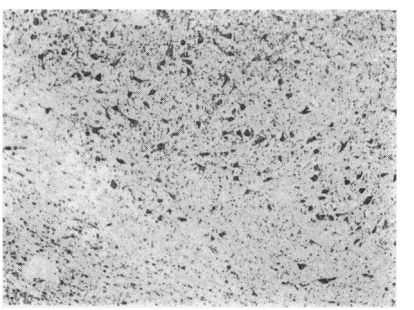

Fig. 5.—Cells of the pathologic sixth nerve nucleus, showing the variations in size.

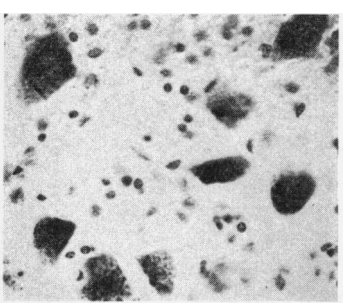

Fig. 6.—Cells of the oculomotor nucleus, one showing evidences of chromatolysis.

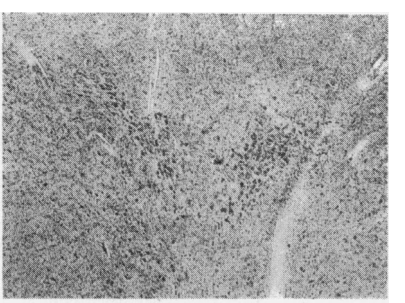

Fig. 7.—Showing preservation of the cells of the Edinger-Westphal nuclei.

Necropsy Report.—The sixth nerve nuclei were easily recognized. The cells of each nucleus were well stained; chromatolysis was very slight when compared with the cells of a normal nucleus in sections made from a young adult for the purpose of control. The nerve-cells were slightly diminished in number and presented definite variations in size and, to some extent, in shape. At least one-third or one-half their number were distinctly smaller in diameter than the others. Similar appearances were not observed in the control sections. The axis-cylinders were normally stained in the Weigert sections. The bundles of fibers composing the root of the sixth nerves in their course through the pons appeared smaller in diameter and less numerous than those of the corresponding normal sections.

The cells of the trochlear nuclei presented the same appearance. The diameters of the whole nuclear groups appeared shorter than those of the normal nuclei of the control sections, and the bundles of the fourth nerve appeared smaller in diameter than in the normal controls.

The cells of the oculomotor nuclei of each side were slightly diminished in numbers, especially in the lateral cell groups seen in the sections made from the middle and more caudal levels. In the sections from the more proximal levels this diminution in number of cells was not so apparent. In no section, however, were the differences in the number of cells composing the different groups very striking, yet in the normal control sections the corresponding cells appeared more uniformly distributed and more numerous than in the pathologic sections. Variations in the size of the cells were observed, but it was difficult to determine whether these variations were much greater than similar differences in the size of the cells seen in normal specimens. Some cells had undergone chromatolysis, but this was not a conspicuous finding; many of the cells were deeply pigmented. The cells recognized as those composing the nuclei of Darkschewitsch were normal in size and shape, and did not appear to be distinctly diminished in numbers, but did contain much pigment—much more than was observed in cells of the oculomotor group. The cells occupying the median position, corresponding to Perlia's nucleus, appeared normal.

The cells composing the Edinger-Westphal nuclei were numerous, well shaped, uniform in size, with clear nuclei, and without chromatolysis, and were conspicuously free from pigmentation.

The fibers of the oculomotor nerves stained well in the Weigert

sections, but were much less conspicuous than in normal sections, and the bundles appeared smaller in diameter than normal. The intranuclear nerve-fibers (fibræ rectæ) were normal in appearance. There was no evidence of nerve degeneration elsewhere in any of the Weigert sections, nor was there any evidence of inflammatory reactions.

Sections of the third, fourth, and sixth nerve-trunks stained fairly well with acid-fuchsin and Weigert methods, but these again appeared smaller in diameter than corresponding control specimens. The optic nerves were normal.

COMMENT.—We are fully aware of the fact that cells composing some nuclear groups may normally present variations in size. In the oculomotor nuclei, differences in the size of the cells are well known, but pronounced differences in the size of the fourth and sixth nuclear cells are unusual and must be abnormal. According to most authorities, including Winkler, the cells of the fourth and sixth nuclei are more uniform in size than those of the third nuclei. Smallness of the ocular nerves was apparent, even to the naked eye, not only in their intramedullary course, but also in the extramedullary nerve-trunks. Other cranial nerves did not appear so small in comparison.

Senility does not produce distinct alterations in the size of the nerve-cells, though H. H. Donaldson has observed a shrinkage of the whole brain, determined by weighing, owing to old age alone. We know of no evidence showing that cessation of muscular contraction alone for a long period of time, as occurred in the extra-ocular muscles of this case, is capable of producing shrinkage of the nerve-trunks, innervating the muscles so affected, so we are forced to the conclusion that the alterations we have found were sufficient to explain even the extreme degree of ophthalmoplegia with which they were associated.

We wish to point out the striking resemblance of these changes to those found by Greenfield and Stern and others in cases of progressive spinal muscular atrophy of childhood of

the Werdnig-Hoffmann type, for we believe the case we have described must be regarded as a similar form of chronic neuron degeneration, in spite of the fact that the alterations were entirely limited to the ocular neurons, and we think it is probably the same pathologic process recognized as progressive spinal muscular atrophy, when the spinal neurons are affected. Why some of these cases of ophthalmoplegia seem to be hereditary or familial in character, as were Beaumont's cases, or develop sporadically in early life and but seldom in later life, might be due to the same factors, whatever they may be, that determine the time and character of onset of the symptoms in spinal muscular atrophy.

The extra-ocular muscles were not examined, but, had they been, we are certain that they would have been found severely atrophied, for it is inconceivable that such complete neuron paralysis, which had persisted for so many years, would not have produced very decided muscular atrophy.

Collins examined a piece of excised muscle from his case and found it atrophic, but it was not examined microscopically.

Simerling reported a case of left-sided congenital ptosis, with necropsy. The movements of the eyeballs were normal, and the reflex pupillary movements were preserved. He found degeneration of the cells of the oculomotor nucleus in the more proximal levels. The right oculomotor nucleus was normal. He also stated that the intramedullary oculomotor nerve-bundles, as well as the fibers of the extramedullary oculomotor nerve-trunk on the affected side, were much thinner than normal.

Fuchs reported in 1890 five cases which have already been referred to by Collins, in which bilateral ptosis was the only symptom of disease. In three of these the condition was acquired, and in two it was hereditary. The muscles of the eyelids were extremely wasted, and a portion of these atrophic muscles was excised for examination microscopically. The muscle-fibers appeared much thinner than normal; the

nuclei were increased in numbers, and there was pigmentary degeneration inside the sarcolemma, but no fatty degeneration was found. The connective tissue between the muscle-fibers was increased in amount. Fuchs discussed at length the difference in the appearance of atrophic muscles when the result of neuronic disease and the appearance of primary muscular atrophy, and emphasized that, in the latter condition, hypertrophy of some muscle-fibers is generally found. Though admitting that, in his case, because of the small microscopic specimens, differentiation was extremely difficult, he seemed to believe that it was, in reality, a primary myopathic disease.

Judging from Fuchs' description, we think his cases of isolated ptosis must have been the result of primary myopathy, an entirely different disease from the case we have observed, and we have referred to them only for the purpose of emphasizing the important differences in the character of muscular atrophy. The muscles of the eyelids of Fuchs' cases were extremely wasted. In our patient the muscles of the eyelids were not atrophic, and obvious muscular atrophy has not been recorded in other cases of chronic progressive ophthalmoplegia to which we have alluded.

Ptosis, with paralysis of the extra-ocular muscles, is well known in myasthenia gravis, a condition affecting striated muscles primarily, but the characteristic of this form of paralysis is the tendency to recover muscular function after rest, and the rapid exhaustion of function from prolonged effort. Yet Collier asserts that it is well known that the paralysis of myasthenia gravis might become complete and permanent. In our case there were no symptoms suggesting myasthenia gravis.

Spiller, in discussing oculogyrations and the lesion causing complete bilateral ophthalmoplegia, says:

"I believe that, when the central pathway of corticonuclear oculogyration is paralyzed above or in the nucleus of the nerve to

the affected internal rectus, the function of this muscle in convergence will disappear or become much impaired, as it did in the case I now report. When the break occurs in these fibers above this nucleus, no impulses can pass into this nucleus for either form of function of the internal rectus, *i. e.*, for oculogyration or for convergence; but when the break occurs in the posterior longitudinal bundle, and therefore below the nucleus of the nerve to the internal rectus, the function of the internal rectus muscle in convergence may be preserved, as it has no relation to the abducens nerve, but oculogyration, demanding the function of this muscle in association with the function of the heterolateral external rectus, will be lost. So far as I know, this diagnostic distinction of a lesion above the nucleus of the nerve to the internal rectus, as compared with one in the posterior longitudinal bundle below this nucleus as of value in localization, has not been described, and it applied to the lesion above the nucleus only when it is near the nucleus.

"Complete ophthalmoplegia implicating all the nerves supplying the eyeballs has been explained usually as the result of inflammatory lesions of all the ocular nuclei, but this explanation, when all other cranial nerves entirely escape, has seemed to me unsatisfactory, especially as bilateral complete ophthalmoplegia has been repeatedly observed without other nerve lesions. I believe that when a lesion destroys the nuclei of the trochlearis and oculomotorius nerves bilaterally, which a comparatively small lesion may readily do, as these nuclei are very near together, it must destroy the connections in the posterior longitudinal bundles between the nuclei of the internal recti and those of the external recti, and consequently paralysis of the external recti muscles will result without any lesions of the abducens nerves or their nuclei. The movements of the two eyeballs are intimately associated, and a lesion of the central pathway of corticonuclear oculogyration near the nuclei affects the movements of both eyeballs."

Collier has described how a lesion situated above the oculomotor nucleus is capable of producing complete ophthalmoplegia, but he points out that when ophthalmoplegia occurs from a lesion in this situation, the eyelid is retracted and ptosis will not develop. In his case, hemorrhage was found in the region of the posterior commissure, and retrac-

tion of the eyelid was observed. The oculomotor nuclei were not implicated by the lesion; the paralysis, he thought, had been produced by destruction of the efferent ocular cerebral nerve-fibers in their course downward from the brain, before they had reached the level of the oculomotor nuclei to connect with them.

In our case, and in all similar cases alluded to here, the pupillary reflexes for light especially, and, to a less degree, in accommodation, were preserved, and in our case the Edinger-Westphal nuclei were intact. This fact would appear to support the view, so generally held, that the function of the Edinger-Westphal nuclei is essentially for the control of the pupillary movements.

Brouwer has paid particular attention to this problem. He described a case of ophthalmoplegia in which the oculomotor nerve had been compressed by an aneurysm of the carotid artery, but with the preservation of the pupillary reflexes, yet the cells of the Edinger-Westphal nucleus presented some alterations. He attributed the cell changes to retrograde effects of compression exerted upon the oculomotor nerve.

Discussing the literature of the subject very thoroughly, he referred to the cases of Cassirer, the work of Tschuda, Bernheimer, and others, and said he had been unable to find a single case recorded in the literature in which destruction of the Edinger-Westphal nucleus had occurred with preservation of the pupillary reflexes to light and in accommodation. From his studies of literature and his own investigations of comparative anatomy and pathologic anatomy, he concluded that the Edinger-Westphal nucleus was certainly the sympathetic part of the oculomotor nucleus, and referred to the fact that Jacobsohn had given it the name of "nucleus sympathicus nervi oculomotorii."

Wilbrand and Saenger, after having referred to the work of others, point out that the Edinger-Westphal nuclei lie so

close to other cell groups of the oculomotor nuclei that functional differentiation from experimental methods alone is exceedingly difficult. They quote the case of Gruenstein and Georgieff, in which there had been bilateral ophthalmoplegia with preservation of the pupillary reflexes. Microscopically, these authors found two lesions in the peduncles destroying most of the cells of the oculomotor nuclei, and, at the same time, the Edinger-Westphal nuclei were preserved for the most part, only a very few of these cells in the posterior portion of one of the group were implicated in the lesion which was a tubercle. They regarded this observation as important evidence, showing that the Edinger-Westphal nucleus had to do with the pupillary reactions.

Leslie Paton and Ida Mann studied the development of the third nerve nucleus in its bearing on the Argyll-Robertson pupil, and concluded that the view that the median nucleus of Perlia is concerned with convergence, and the Edinger-Westphal nucleus with pupil movements, is supported by the study of their development in man, since the time of appearance of the various parts of the nucleus appears to be correlated with the development of the mechanism of their respective functions.

It is significant that Brouwer and Winkler both quote the work of Cajal, who said that, although he had been able to demonstrate the Edinger-Westphal nucleus in the cat, mouse, and dog by silver methods of staining, he had been unable to follow their axis-cylinders into the oculomotor nerve-trunks, so that he suspected it was not really part of the oculomotor nucleus. It appears, therefore, that the cells of the Edinger-Westphal nucleus must represent a separate neuron system, and, for that reason, it was not affected in our case, thus explaining the preservation of the pupillary reflexes.

The most recent and most convincing work on the subject is that of Winkler. He says that the cells of the Edinger-Westphal nuclei do not send fibers to the oculomotor nerve

roots and, consequently, should not be considered as parts of the oculomotor nuclei. By extirpation of the ciliary ganglion in cats, and also after section of the oculomotor nerve, he found no effect whatsoever on the cells of the Edinger-Westphal nucleus. He points out that this result is diametrically opposed to Bernheimer's results, for Bernheimer believed he had been able to establish that the Edinger-Westphal nucleus disappeared on the operated side after extirpation of the ciliary ganglion.

Winkler thinks it probable that Bernheimer had been misled because the Edinger-Westphal nucleus is inconstant and not easily recognized in some animals, and that he might have operated upon an animal in which, by chance, the nucleus was very poorly developed.

Winkler regards the Edinger-Westphal nuclei and also the Darkschewitsch nuclei as separate from the oculomotor nuclei, and thinks they are intercalated groups of cells which have to do with the synergic movements of the eye, the latter representing part of the mechanism for the control of the upward associated movements of the eyeballs. He describes the Edinger-Westphal nucleus as situated among the fibræ rectæ, and surrounded by them, the fibræ rectæ passing through the gray matter between the proximal part of the main lateral groups of the oculomotor cells. The Edinger-Westphal nucleus in the proximal levels forms an important, intercalating apparatus, and, with the nucleus of Perlia, which is situated in the more caudal levels, receives innervations from the subcortical and, to a moderate degree, from the cortical regions. He thinks the Edinger-Westphal nuclei regulate all pupillary movements, not because they give origin to radicular, sympathetic fibers, but because they receive a great number of fibræ rectæ.

We wish to thank Dr. William G. Spiller for his valuable assistance and suggestions in the preparation of this report.

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DISCUSSION

DR. F. PHINIZY CALHOUN, Atlanta: I have recently seen and reported elsewhere (The Southern Medical Journal, Vol. XX, p. 923) in detail a case of chronic progressive ophthalmoplegia externa which seemed to fit in perfectly with the classification made in 1900 by Wilbrand and Saenger.

Very briefly, the case history is as follows: A male, aged thirty-nine years, with periodic yet progressive attacks of diplopia and ptosis for ten years. The family and past history is unimportant, except that at the age of four years the patient had a severe attack of dysentery from which he nearly died, and his recovery was prolonged. Besides, he developed hyperthyroidism four years ago, for which a subtotal thyroidectomy was done. (These are mentioned on account of the possible bearing on the cause of the ocular paralysis.) The eyes were normal in every regard, except for the almost complete paralysis of the extra-ocular muscles, including the lid elevators. The general physical and neurologic examinations were negative.

In many of the more recent reports of cases of progressive ophthalmoplegia externa a thyroid disturbance has been prominently mentioned in the histories, particularly in female cases. Whether or not it was a coincidental or a contributory cause to the ocular paralysis will demand further study on more cases, but it at least adds support to the thought that the defect is in the muscles, for the observations and findings of Dudgeon and Urquhart in nine cases of exophthalmic goiter, one of whom had my-

asthenia gravis, showed in eight cases lymphorrhages in the extrinsic eye muscles as well as in the heart and some of the skeletal muscles. The lymphorrhages were large and small, the former causing wide separation of the muscle-fibers, especially in the eye muscles.

Personally, believing that the seat of the paralysis is in the nucleus, I have accepted the explanation offered by McMullen and Hine, that it is due to a "lack of inherent vitality or an 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." It seems that in the case which I reported the endowed vitality of these cells was seriously impaired at a very young age by a severe illness (dysentery) and recovery was never complete.

TEST-LETTERS WHICH COMPLY WITH THE PHYSIOLOGIC REQUIREMENTS OF A VISUAL TEST-OBJECT

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Visual acuity is measured by the smallest angular distance under which two points still appear to be separated. This apparent distance varies according to different investigators, but it is generally agreed that, in normal visual acuity, the distance between two objects that are barely distinguished as two may be assumed to subtend an angle of one minute at the eye. This is the "angle of distinctness" or "minimum visibile."

Actually, the visual angle is a solid angle having a circular base and its apex at the nodal point. The ideal test-object, therefore, would be circular. Round dots may be, and have been, used as a simple test for measuring the visual acuity; but since an object, if bright enough to stimulate a sensitive retinal element, may be perceived under an angle much smaller than the smallest angle of distinct vision, dots are