CENTRAL AREOLAR CHOROIDAL SCLEROSIS* A HISTO-PATHOLOGICAL STUDY

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THE history and clinical features of central areolar choroidal sclerosis—or atrophy, as designated by Nettleship (1884)—are recorded elsewhere in this issue (Sorsby and Crick, 1953). An affected member of one of the families described came to *post-mortem* examination, and the present study deals with the findings in this case.

Material

Mrs. Bertha C., aged 56 (CIII, 2 in Pedigree Chart II; Figs 5 and 6, pp. 130, 131). At the time of examination (June, 1949) her general health appeared to be good, but some 2½ years later she died shortly after an attack of coronary thrombosis. A *post-mortem* examination was performed by Dr. W. J. O'Donovan, who found the cause of death to be necrosis and fibrosis of the myocardium, atheromatous coronary occlusion, and hypertension. There was in addition severe atheroma of the thoracic and abdominal aorta, the internal carotids, and the basilar artery; the openings of the ophthalmic arteries were markedly narrowed by atheromatous plaques.

Technique of Histo-Pathological Study

Both eyes, together with the orbital contents, were removed at *post-mortem*. The branches of the ophthalmic arteries were dissected out and examined macroscopically.

Right Eye.—The specimen was irrigated with water and injected with Neoprene *via* the ophthalmic artery; the globe was opened transversely in order to examine the fundus. The cast of the choroidal vessels was then floated out of the eye, bleached with potassium permanganate and oxalic acid, examined microscopically, and photographed first in a glass sphere and subsequently as a flat preparation.

Left Eye.—After fixation in 10 per cent. formol saline the globe was opened horizontally and serial sections were cut through the affected area in the macular region, the following staining methods being used:

haematoxylin and eosin,
Mallory's triple stain,
Verhoeff's elastic stain and Masson's ponceau-fuchsin and light green,
PAS (Hotchkiss-McManus).

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Histo-Pathological Findings

Dissection of the vessels in the left and right orbital contents showed patchy atheroma of the ophthalmic artery, but the branches, including the posterior ciliary arteries, were relatively normal and no narrowing or occlusion was discovered at any point.

Injected Right Eye.—Only the larger arteries of the retina were injected and these showed no abnormality. A zone of retinal atrophy associated with an irregularity of the retinal surface extended from the macula to the disc margin. This area of retinal change corresponded exactly to a practically avascular circular area in the underlying choroid, which contrasted strongly with the remainder of the specimen in which the vessels were fully injected (Fig. 1). Microscopical examination of the choroidal cast showed that the chorio-capillaris was completely absent in the affected zone, and that, apart

FIG. 1.—Right eye. Neoprene cast of choroidal vessels mounted in a glass sphere. Compare with fundus drawing (Fig. 5, p. 131). A well-demarcated avascular zone extends from the submacular region to the disc. In the remainder of the specimen the vascular cast is complete.

FIG. 2.—External view of Neoprene cast showing avascular zone extending from submacular region to disc. The area is well defined and, apart from the traversing ciliary arteries which have been severed at the sclera, only a few straggling atrophic vessels remain. The circle of Zinn around the optic disc is well shown.

FIG. 3.—Internal high-power view of edge of atrophic area. The chorio-capillaris stops abruptly, providing the avascular area with a definite margin. Within the atrophic zone only traversing ciliary arteries and a few atrophied vessels may be seen.

from the traversing ciliary arteries which enter at this point, only a few straggling atrophic vessels remained to nourish the submacular choroid and the zone between the macula and the disc (Fig. 2). At the edge of the atrophic area the chorio-capillaris stopped abruptly, thus providing a well-demarcated margin to the avascular tissue (Fig. 3). The vascular architecture in the remainder of the choroid was apparently normal.

Sections of Left Eye.—The cornea, corneo-iridic angle, iris, and lens were normal. There was a mild degree of hyalinization in the ciliary body, and the choroidal stroma showed a moderate fibrosis and a scattered infiltration with Russell bodies, lymphocytes, and endothelioid cells. In

the macular region there was a remarkably well-demarcated zone of choroidal atrophy extending to the disc margin. Within this area the chorio-capillaris was almost completely absent and only a few patent vessels persisted in the fibrotic outer layers. The atrophied vasculature had left little trace of its previous existence, for, apart from a few shrunken vessels, it appeared to have merged imperceptibly with the fibrous stroma.

None of the vessels throughout the whole of the uvea showed even the slightest degree of sclerotic change; nor did the ciliary arteries, which could be seen both in their course through the sclera and extra-ocularly, show any abnormality.

Bruch's membrane showed no colloid bodies, and was apparently normal except in the macular region, where the underlying choroid was most markedly atrophic and avascular; here the membrane was somewhat less definite than elsewhere, showing a diffuse thickening and a patchy absorption of the elastic outer layer. None of the serial sections, however, showed any interruption in its continuity or any evidence of calcification.

Throughout the retina there were early *post-mortem* changes of cystic degeneration and incipient liquefaction of the rod and cone layer. The vessels appearing in the sections showed no arteriosclerotic changes. There was a *post-mortem* retinal detachment which was complete, except in the sharply localized area extending from the macula to the disc where the retina was lightly adherent to the underlying atrophic choroid. In this zone there was a correspondingly circumscribed loss of the outer layers of the retina, including the layer of rods and cones, the outer nuclear layer, and about half of the outer molecular layer; the inner nuclear layer, with a variable amount of the outer molecular layer intervening, had come to lie directly upon the choroid (Figs 4, 5, and 6, overleaf). The outer layers of the retina seemed to have vanished and there was no trace of glial replacement. Similarly, the pigment epithelial layer had also disappeared in this area and, apart from one small persistent island, there was no trace of either the epithelial cells or of their pigment. The optic nerve appeared normal and there was no abnormality in the vitreous or sclera.

Summary of Findings

(1) A well-demarcated avascular zone extending from the submacular region to the disc was present in the posterior choroid, as shown in the cast preparations.

(2) Histologically, this avascular zone was found to be atrophic and fibrosed. No arteriosclerotic changes were found either in the affected area or elsewhere in the choroid. Dissection of the posterior ciliary arteries failed to reveal constriction or occlusion.

(3) The outer layers of the retina together with the pigment epithelium had disappeared without glial replacement, in an area exactly corresponding to the underlying choroidal atrophy.

(4) Bruch's membrane was little affected by the failure of the choroidal blood supply.

FIG. 4.—Left eye. Section through affected area in macular region shows a fibrotic and practically avascular choroid. The outer layers of the retina have disappeared so that the inner nuclear layer lies directly upon Bruch's membrane, which appears little affected by the choroidal changes. Mallory's triple stain. $\times 100$

FIG. 5.—High-power view of fibrosed choroid in affected zone. Note almost complete absence of choriocapillaris and other vessels. Bruch's membrane appears normal, the pigment epithelium has disappeared, and the atrophic retina is lightly adherent to the choroid. There is no evidence of arteriosclerosis. Compare with Fig. 6. Mallory's triple stain. $\times 400$

FIG. 6.—High-power view of equatorial choroid beyond affected zone. The vessels are normal in appearance and the pigment epithelium is intact; the overlying retina was detached due to artefact. Compare with Fig. 5. Mallory's triple stain. $\times 300$.

Discussion

It would seem justifiable to assume that the disease, at least in its final stages, has a vascular basis. The pathological processes which may lead

to such a remarkably localized disappearance of the choroidal vessels may then be summarized as follows:

Vascular Occlusion. Embolic, thrombotic, or arteriosclerotic.

Vascular Atrophy. Primary: Heredo-degeneration.

Secondary: To a selective toxic action or to a localized inflammatory process.

Vascular Occlusion.—If vascular occlusion is assumed, the well-circumscribed nature of the submacular choroidal degeneration would imply either a separate blood supply to this region or a peculiar vulnerability of the submacular vessels to disease. In connection with the first possibility, it has been suggested that the choroidal circulation is divided, either functionally or anatomically, into a series of terminal vascular systems. On clinical grounds there is strong evidence of such a sectorial arrangement, as was pointed out by Nettleship (1884) and Coats (1907), and particularly by Hepburn (1910, 1912) who concluded that there were three main sections of supply—the macular region, the mid-periphery, and the extreme periphery. That this is so, however, has never been conclusively shown anatomically, although Leber (1903) drew attention to the fact that the posterior ciliary arteries have but few branches of communication with each other, and that these occur mostly in the anterior part of the choroid and around the optic nerve entrance.

If such sectorial distribution exists, central areolar choroidal sclerosis might arise from occlusion of one of the short posterior ciliary arteries, either in the main trunk or in the perforating scleral branches, the retinal changes arising as a consequential ischaemic degeneration. Our findings in the sections and cast preparations would be in accord with such a possibility.

The insidious onset of the disease excludes an embolic or pure thrombotic process, but its occurrence in middle life or later would be in keeping with an arteriosclerotic vascular occlusion, and, in the case here reported, it would seem reasonable to link the choroidal lesion with the widespread arteriosclerotic changes found throughout the vessels elsewhere in the body. It was for this reason that a careful dissection of the posterior ciliary arteries in both orbits was carried out. Although patchy arteriosclerotic changes were found, no actual occlusion could be demonstrated, but any vessels so affected might well have disappeared or atrophied beyond macroscopical recognition. Nevertheless, the fact remains that examination of these eyes did not reveal involvement of the posterior ciliary arteries.

Arteriosclerotic involvement of the submacular choroidal vessels, as seen in secondary senile macular degeneration, must also be considered, especially since the fundus appearances in life were those generally attributed to choroidal angiosclerosis. A very complete study of serial sections of the left eye failed, however, to show evidence of arteriosclerotic changes within any of the intra-ocular vessels. Sclerosis of the choroidal vessels cannot, therefore, be accepted as an explanation of the choroidal changes in this particular case, and the view that central areolar choroidal sclerosis is simply an extension or severe form of a secondary macular degeneration (Klien, 1951) is not tenable in this instance.

Vascular Atrophy.—The assumption of a hereditary spontaneous atrophy affecting the submacular choroidal vessels, would have something to commend it, for such a process has already been held to be responsible for the disappearance

of the choroidal vessels in choroideremia and in gyrate atrophy; it would also fit in with the bilateral distribution and the familial incidence of the disease. On the other hand, choroidal atrophy in choroideremia and in the gyrate form occurs at a much earlier age, and tends to spread throughout the whole choroid; whereas the central areolar form remains localized and circumscribed. Nevertheless, it is well known that hereditary degenerations may be remarkably selective and, in the absence of a demonstrable choroidal or ciliary angiosclerosis, this explanation of a localized spontaneous atrophy remains an aetiological possibility, and gains some support from the fact that there was no evidence to suggest a selective toxic action or a localized inflammation as a cause of the vascular atrophy in this case.

The possibility that choroidal atrophy might arise from compression within the choroid must also be considered. As has recently been pointed out (Ashton, 1952), the choroidal vessels, lying within a fibrous stroma, are sufficiently confined by the intra-ocular pressure on the one side and by the sclera on the other for flattening of the veins to be caused at arterio-venous crossings. It would seem likely, therefore, that any further compression, such as may result from an intra-stromal leakage of blood or exudate, might well lead to collapse of the vascular bed within the affected area. Such a process would explain the well-defined zone of vascular atrophy in this case, but the histological material, showing only the end-stages of the disease, does not offer evidence to either support or deny such a concept.

The *post-mortem* examination of this material has, therefore, been disappointing in that it has not provided definite evidence of the pathogenesis of central areolar choroidal sclerosis. The only certain conclusion which can be reached is that the condition was not due, in this instance, despite the conflicting ophthalmoscopic appearances, to a choroidal angio-sclerosis. This, however, is an observation of considerable significance, for we have already called attention to this discrepancy between clinical and histological diagnosis in a case of fundus dystrophy (Ashton and Sorsby, 1951). The absence of any histological evidence of choroidal angio-sclerosis in these two different conditions, shows that the ophthalmoscopic appearance of opaque choroidal vessels does not necessarily imply an arteriosclerotic pathology. Alternative explanations must therefore be sought, and it is possible that such abnormal appearances may derive from perivascular exudates, from a localized exsanguinity of the vessels, or from fibrotic changes in the perivascular tissues. In any event the histological findings suggest that an ophthalmoscopic diagnosis of choroido-angiosclerosis cannot be made with certainty.

Role of Bruch's Membrane.—It is noteworthy that, in spite of the extreme avascularity of the submacular choroid, the overlying Bruch's membrane had remained intact and comparatively healthy. This apparent immunity to prolonged ischaemia is of importance in that the breaks in Bruch's membrane, which precede the development of angioid streaks (Böck, 1938; Hagedoorn, 1939; Klien, 1947; Verhoeff, 1948) and disciform degeneration (Brown, 1940; Verhoeff and Grossman, 1937), have been presumed by the workers quoted to be due to a deficient blood supply.

We have shown that dehiscences in Bruch's membrane were the fundamental pathological change in the case of fundus dystrophy previously examined (Ashton and Sorsby, 1951), and since arteriosclerosis was not a feature in this case, we

suggested that the breaks arose from a primary degeneration of the membrane. From this it followed that choroidal angio-sclerosis, when found in association with angiod streaks, disciform degeneration, or fundus dystrophy, was to be regarded rather as a parallel development than as a causative factor. While the case of fundus dystrophy provided evidence of pathological changes in Bruch's membrane without deprivation of blood supply, the present case of choroidal sclerosis further supports the above argument by providing an example of a grossly inadequate blood supply with no significant pathological changes in Bruch's membrane. In this connection it is interesting to note that Bruch's membrane was intact in the case reported by Klien (1951), although in that instance the choroidal angio-sclerosis was of sufficient severity to give rise to a secondary macular degeneration.

If the histology of this isolated case is indeed illustrative of the group of central areolar choroidal sclerosis as a whole, the absence of arteriosclerotic changes in the choroidal vessels suggests that the affection falls into the group of vascular atrophies rather than into that of the choroidal angio-scleroses.

Summary

The histo-pathological findings in a case of central senile choroidal sclerosis are reported.

In one eye, the well-demarcated avascular zone was demonstrated in a Neoprene cast of the choroidal vessels. Histological examination of the other eye showed the avascular zone to be atrophic and fibrosed, but no arteriosclerotic changes were found either in the affected area or elsewhere in the choroid. Dissection of the posterior ciliary arteries failed to reveal constriction or occlusion. The outer layers of the retina, together with the pigment layer, had disappeared without glial replacement in an area exactly corresponding to the underlying avascular choroid. Bruch's membrane was little affected by the failure of the choroidal blood supply.

The pathogenesis of the condition is discussed and it is concluded that the findings suggest a vascular atrophy rather than a choroidal angio-sclerosis.

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