POSTERIOR DEGENERATIVE LESION OF ONCHOCELCIASIS*

BY

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The posterior lesion of onchocerciasis is the most interesting manifestation of this disease because it is the least understood. Bryant (1935), after a conversation with the Belgian worker, Hissette, reached the conclusion that a progressive chorio-retinitis which he had seen in the Sudan was caused by this disease. This view, later supported by Hissette (1937, 1938) and by Richet (1939), has since been confirmed by the observations of many other workers. The lesion was said to be accompanied frequently by a secondary optic atrophy, although an optic atrophy by itself due to onchocerciasis was also postulated. The current view today is that the cause of the condition is invasion of the choroid by the parasites and their death. This belief was given some support by the finding of microfilariae in the choroid by Hissette (1932); one autopsy case with several mf. in or adjacent to this tissue was reported by Hughes (1949). Other, as yet unpublished, cases are also on personal record.

When we started our investigations into onchocerciasis in West Africa we visited first a very heavily endemic area in the Northern Territories of the Gold Coast. There many examples of the posterior segmental lesion were found, and nearly all of them (as it was a heavily endemic area) in densely infested subjects. Subsequently, however, we surveyed Northern Nigeria, and here, in areas of light endemicity, the incidence was probably higher. Having evolved by this time an index of the density of infection in the individual (Rodger and Brown, 1957), these index figures were compared in cases of anterior and posterior lesions in Nigeria. The results were extremely interesting. Whereas the mean Individual Density Figure for the anterior lesion was about 26, it was eleven for the type of posterior lesion under discussion; four cases had sterile skins and conjunctiva, and of these two had no nodules although the lesions were characteristic. This raised a problem of pathogenesis, for it no longer appeared so certain that the cause of the condition was an inflammation arising around the dead bodies of mf. in the tissues concerned. In the heavily endemic areas of the Gold Coast we seldom saw the posterior lesion except in association with an anterior lesion, but in Nigeria this was far from being true; 9 per cent. of 165 recorded cases

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were associated with a sclerosing keratitis, 2 per cent. with a kerato-uveitis, and 9 per cent. with an anterior uveitis; 80 per cent., in short, were not associated with anterior lesions. Another factor which suggested that there might be more to the pathogenesis than the accepted view concerned the average number of nodules present in the different types of lesion. Where the posterior lesion occurred alone, the average number (nodule mean) was 0·9; when the posterior lesion was combined with the anterior segmental lesion in the same geographical areas the average was 2·0; with anterior segmental lesions alone, it was as great as 2·6. The possibility that another factor might be involved thus gained strength. This view was lent further support when it was observed that in high-forest areas (where onchocerciasis is common although not severe) no posterior lesions were discovered, whereas in the Northern scrub, even in areas with equal density quotients, the posterior lesion was extremely common. For these reasons, therefore, it was concluded that although onchocerciasis plays some part in producing this lesion, as it has not been reported from places outside the endemic onchocerciasis areas, another factor or factors must be sought. This paper will describe different types of chorio-retinitis which might be confused with the posterior segmental lesion of onchocerciasis; it will also describe the appearance of the posterior lesion from its onset to its conclusion; and it will present certain evidence in favour of our belief that a vitamin A deficiency plays an important part in the production of the changes.

I. DIFFERENT TYPES OF CHORIO-RETINITIS

(a) Onchocerical Posterior Exudative Uveitis.—This condition, essentially part of an endophthalmitis due to the invasion of the uvea by the parasites, has been described in another paper (Rodger, 1957). Whether or not the posterior uvea alone may be invaded, and this lesion produced in the absence of inflammatory changes in the anterior uvea, we are not certain. There has been no way of discovering this, as the fundus picture is non-specific, and we have not been able to obtain any such eyes for pathological investigation. We possess, on the other hand, considerable pathological evidence where the posterior condition has been found in association with an anterior uveitis; it seems to us that the latter combination is what usually occurs. As the anterior uveitis of onchocerciasis is in most instances of a characteristic type, so it is possible even in a quiescent case to categorize an associated posterior chorio-retinitis as one with the same aetiology, even although the appearance is not particularly suggestive. The degenerative type of posterior segmental lesion which is the subject of this paper may also be found in association with an onchocerical anterior uveitis. It is not surprising, therefore, especially in view of the difficulties of observing the fundus where the iris is involved, that the non-specific inflammatory type of posterior uveitis should have been confused with the degenerative. In the former, because at one time it was acute, there is a greater disturbance of pigment and a more
widely scattered distribution of pigment in the fundus. Patches of choroido-retinal fusion, completely depigmented and atrophic, show as disseminated white plaques here and there, a picture that is not at all typical of the degenerative condition. Colloid bodies may be found in both cases, but are much more common as an end-result of the original inflammation in the exudative type. Where the initial acute attack was not severe or prolonged, then the choroidal blood vessels may be exposed and sometimes seen; this makes the distinction of the two types of lesion, one exudative and the other degenerative, extremely difficult. In the former, however, the changes are usually disseminated and associated with involvement of the anterior uvea; in the latter they are circumscribed and confined to the posterior part. Hemeralopia is inconstant in the first, but constant in the second.

(b) Primary Chorio-Retinal Degenerations.—Most of the various fundus pictures characteristic of this type of disease resemble the posterior segmental lesion of onchocerciasis. Juxtapapillary choroidal sclerosis is one such although the macular changes here are not as striking. This lesion in the choroid is a focal one and leads to depigmentation and then to degeneration of the retina. It is difficult to say whether the posterior lesion of onchocerciasis follows the same course, as the story is very complex. The two pathologies are remarkably similar. However, they will not be described here, where it is only intended to discuss the clinical aspects of the diagnosis. While it is known that genetic factors play an important part in the causation of primary chorio-retinal degenerations, there is no evidence that the posterior lesion of onchocerciasis might be an affection inherited in an intermediate sex-linked manner, despite its similarity to such conditions. The tapetal reflex of primary chorio-retinal degeneration described by Falls and Cotterman (1948) was never noted in onchocerciasis.

(c) Circumscribed Tuberculosis of the Choroid.—The first evidence of this disease is an ill-defined exudate, usually in the periphery of the fundus; the disease may also affect the posterior pole of the eye; the exudate occurs within the choroid, and causes a break-down of the pigment epithelium barrier. Repeated attacks at the periphery of old posterior lesions may lead in the end to involvement of the peri- or juxtapapillary areas. With the pigment cells aggregated in clumps, the choroidal blood vessels may then be seen over as wide an area as in onchocerciasis. A consecutive optic atrophy is to be expected. There is no doubt at this stage that tuberculosis can resemble onchocerciasis very closely. The lesion, however, is seldom as regular in outline as in onchocerciasis.

(d) Syphilitic Chorio-Retinitis.—A chorio-retinitis occurs frequently in congenital syphilis but rarely in acquired syphilis. Most, if not all, of the posterior manifestations of syphilis may be seen in West Africa. Where syphilis and onchocerciasis occur side by side in the same patient, the posterior lesion is the hardest of all to categorize. The changes in syphilis
are frequently combined, as is the posterior lesion of onchocerciasis, with hemeralopia. However, the latter is always associated even in its early stages with visible changes in the case of syphilis, unlike in onchocerciasis; again, night blindness may be absent altogether in syphilis, whereas it never is in onchocerciasis.

What manifestations of syphilis may be confused with onchocerciasis of the posterior segment? The localized types of chorio-retinitis may, as might a late neuro-retinitis with a secondary retinitis pigmentosa.

(e) Disciform Degeneration of the Macula.—This condition is essentially one of a sclerosis of the choriocapillaris (Verhoeff and Grossman, 1937). It may be unilateral.

In the more common senile variety an invariable occurrence in all cases reported pathologically has been the presence initially of a large organized haemorrhage between the retinal pigment epithelium and Bruch's membrane, which has forced its way through the latter from a diseased choriocapillaris. The picture now somewhat resembles the posterior degenerative lesion of onchocerciasis—a grey swelling frequently truly discoid in shape; in onchocerciasis, however, such an appearance follows after or accompanies peripheral or juxtapapillary involvement, an apparently invariable rule. For this reason one should not readily confuse the conditions in the early stages. We have on record four cases of disciform degeneration of the macula, only one of which was early; the others represented the late fibrous changes so well illustrated by Kahler and O'Brien (1935).

II. POSTERIOR DEGENERATIVE LESION OF ONCHOCERCIASIS

In the course of the Survey, 165 cases of the posterior degenerative type of lesion were noted; this represented about 5 per cent. of all blindness due to onchocerciasis. Of these cases, characteristic in type, 71 were diagnosed with the ophthalmoscope and recorded, but were not investigated further, and are not considered in the present work. Of the remaining 94, seventeen were early cases and the remaining 77 were in different stages of advancement. These 94 cases were given a physical examination which included observations on nutritional defects of the mucous membranes and skin, teeth, nails, and hair; they were also given a full ocular examination with the biomicroscope as well as with the ophthalmoscope; visual fields were plotted in some; and all were passed through the laboratory where the blood and skin were fully investigated. In more than half of them serological tests were carried out, and in one-sixth the serum was assayed for its vitamin A content. In selected cases the dark adaptation was plotted. These procedures were repeated many times.

The relation of *mf. onchorerca volvulus* to these cases has already been given; it should be noted that, in two with characteristic eye lesions, no sign of onchocerciasis could be found, and in another two the only manifestation was a solitary nodule. This does not exclude the possibility that they were
carrying free adult worms. 20 per cent. of the 94 cases exhibited *mf. perstans* in the bloodstream, 8 per cent. *mf. bancrofti*, and 1 per cent. *mf. loa*. There is nothing here to involve these parasites in the pathogenesis.

The disease is a slow one, the onset being insidious. It takes about a year before any visible change appears in the fundus. During this time the subject complains only of night-blindness. The first visible changes are evident in the retinal pigment between the disc and the macula. Depigmentation occurs in small round areas (about half the size of drusen), the result being a “freckling” of the fundus. The retinal pigment then usually becomes heaped up around the disc. When this happens a view of the choroidal blood vessels is afforded; complete sclerosis of the choriocapillaris frequently has already occurred. We are now able to see the larger vessels of the choroid, the margins of which, for optical reasons, are hazy, and the colour of which is a healthy red. The macula often shows degenerative changes simultaneously with the juxtapapillary changes although in many cases it becomes affected later. The first change in the macula is a grey oedema which is followed by an aggregation of the pigment here into large lumps. This is not preceded by freckling. The pigmentary disturbance is probably great because the hexagonal pigment epithelium at the macula is normally more dense than anywhere else. Occasionally all the pigment in the macular area seems to collect into one single mass (10 per cent.). The choroidal blood vessels behind the macula usually remain hidden, but that sclerosis occurs here also is certain, for in 5 per cent. of our cases the vessels could be seen. There is no pigment in the tissue binding the choriocapillaris, so the next change is the partial break-up and then accumulation in small masses of the choroidal pigment in the deeper layers of that structure; at the same time it may migrate inwards. As a result of these changes the white sclera is sometimes seen, though not often; this is an important distinction between the degenerative lesion and specific inflammations. Outside the affected area the fundus is healthy so that the lesion is sharply demarcated; this demarcation is not very evident in lightly-coloured fundi, and it may be concealed by the scattered particles of pigment, but it is always present. It is of vital diagnostic significance.

The condition continues to advance slowly over the fundus taking from 2 to 5 years before it is complete. Where the changes occur more rapidly a greater deposition of pigment within the retina occurs. As, however, the lesion is nearly always a very slow one, the pigmentary upset is frequently not as gross as one would expect from the size of the area involved. The affected zone in the end spreads beyond the disc, a common end-picture being one where the chorio-retinal degeneration spreads four disc diameters on the temporal side of the optic nervehead, three disc diameters below, two disc diameters above, and one disc diameter to the nasal side. The lesion may, on the other hand, reach right out into the periphery. With choroidal vascular changes so gross, it is surprising to find any degree of visual acuity retained.
Sheathing of the retinal arteries and veins has been described by various workers, and has been said by some to be specific (Sarkies, 1952; Toulant, Robineau, and Puyuelo, 1950). With this we are not in agreement. Physiological sheathing is present in 10 per cent. of African eyes. In the series of cases being discussed, 23 per cent. exhibited retinal sheathing (5 per cent. of the veins, 9 per cent. of the arteries, and 9 per cent. of both arteries and veins). This suggests, if we deduct physiological sheathing, that sheathing is present in about one-quarter of the posterior degenerative lesion cases. Sheathing was, however, also present in one-half of chorio-retinal lesions arising from other causes such as syphilis, tuberculosis, etc., and so it cannot be said to be at all characteristic of the posterior degenerative lesion of onchocerciasis, nor indeed of any importance whatever in its diagnosis, even though present in one-quarter of the cases. It is slightly more common in the exudative type of case and this has added to the confusion.

The association of an optic atrophy with the changes that have been described is very frequent. In the 94 cases under discussion, forty exhibited consecutive optic atrophy with some degree of pigmentary disturbance at the disc margin and fourteen showed a simple type of optic atrophy. That is, 54 of the 94 cases were associated with an optic atrophy. Of the remainder, seven advanced cases appeared to have a normal disc, 26 partly advanced cases—the choroidal blood vessels that remained were still healthy—showed no sign of atrophy, and the seventeen early cases had no optic atrophy. As is usually the case with white atrophy of the optic nervehead, it bore no relationship at all to the degree of the visual defect. Atrophic cupping is common in long-standing cases. That optic atrophy by itself can occur in onchocerciasis, seems probable. We have found mf. in the retrobulbar and intra-ocular portion of the nerve, confirming the findings of Hissette (1932) and Mira* (1934). Clinically it is not possible to diagnose such an atrophy with certainty, unless related to a characteristic lesion elsewhere in the eye.

The final changes in the posterior segment occur as a result of the continuation of the sclerotic process in the choroidal arteries; the colour of the vessels changes from red to orange and from orange to almost white; apparently the smaller the vessel the quicker the change. The pigment which at first exhibited freckling and later aggregated into clumps, sometimes migrates into the retina, lying underneath or above or around (rarely) the retinal blood vessels. This is less common than in the inflammatory type. That a secondary retinitis pigmentosa was exhibited by 5 per cent. of the degenerative cases is difficult to explain. The pigment corpuscles do not often adopt the delicate bone-corpuscle appearance seen in primary tapeto-retinal degeneration, but are usually heavier with thicker processes. They are also seldom found surrounding the retinal vessels as in the primary condition. Sometimes this peripheral pigmentation adopts a very dense interlacing

* Mira is the former surname of Dr. M. Giagiunto, now secretary to the E.E.D. Section of the World Health Organisation.
configuration completely covering the circumscribed edge of the primary lesion.

It has been said by several workers that the posterior segmental lesion of onchocerciasis can adopt a great variety of appearances, but such is not the case. The description given covers the disease from its onset to its conclusion, and within that context a great variety of appearances is possible, but they all conform to a set pattern. Any lesion inconsistent with this pattern we should look on with grave suspicion. Hyaline warts on Bruch's membrane were noted in only a few instances, and then usually at the periphery, in association with Blessig-Iwanoff cystoid degeneration. They are not a feature of the clinical picture. Too much reliance must not be laid on the clear-cut circumscription of the sclerotic area, as this does not always strike the eye readily; however, as has been said, if it is looked for carefully, some evidence of it may be found. Retinitis pigmentosa must not be taken as the last change which occurs; it may occur before the larger choroidal arteries become affected. Although it has been said that the area of the retina between the disc and the macula or below the disc is most commonly the first to exhibit changes, in rare instances the first appear below and to the nasal side of the disc, or even above the disc.

It was only in the early cases that we had success in plotting the visual fields; in the later stages it was impossible to prepare accurate perimetric or scotometric charts. The initial visual field change seems to be a gradual uneven and irregular depression, beginning in the inner part of the peripheral zone (as in retinitis pigmentosa), but unlike the latter associated with a central relative scotoma. Beyond this point our perimetric studies have thrown no light on the subject; nor have we enough evidence to theorize.

III. Some New Observations Relating to the Pathogenesis of the Posterior Lesion

The absence of the posterior degenerative lesion of onchocerciasis in West Africa in regions where the diet contains a large amount of vitamin A, is highly significant (Table I, overleaf). An attempt was made to ascertain, both by assays and by clinical trials, whether vitamin A deficiency was implicated or not. In a rural community in the Plateau province of North Nigeria, where the degree of vitamin A deficiency was only slight, the sera of twelve cases were assayed. All the subjects came from neighbouring villages except the last (Serial No. 1,291). One patient had disciform degeneration and another had syphilitic chorio-retinitis. Table II (overleaf) shows that the two non-onchocerciasis cases had a marginal level of vitamin A, whereas only one of the posterior lesion cases (Serial No. 1,291) could be placed in that category. The last patient was examined at a different time of year, when vitamin A in plenty had reappeared in the diet, and this offers a ready explanation of the anomaly.
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TABLE I
AVERAGE DAILY NUTRIENT INTAKE OF ADULT MALE NIGERIAN PEASANTS IN FOUR DIFFERENT AREAS, 1954-1956*

<table>
<thead>
<tr>
<th>Group</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occupation</td>
<td>Farming and Fishing</td>
<td>Farming</td>
<td>Farming</td>
<td>Farming</td>
</tr>
<tr>
<td>Area</td>
<td>Banks of Lake Chad, Sahel savannah</td>
<td>Bunga-Ningi, Bauchi Province, Sudan savannah</td>
<td>Langai, near Panyam, Plateau province</td>
<td>Mbanegoe, Ogoja, Rain forest</td>
</tr>
<tr>
<td>Lesions</td>
<td>No Onchocerciasis, and No Posterior Lesion</td>
<td>Onchocerciasis and Posterior Lesion</td>
<td>Onchocerciasis and Posterior Lesion</td>
<td>Onchocerciasis but No Posterior Lesion</td>
</tr>
<tr>
<td>Calories</td>
<td>3,000</td>
<td>2,900</td>
<td>2,600</td>
<td>2,400</td>
</tr>
<tr>
<td>Protein</td>
<td>Animal... (g.)</td>
<td>29</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Vegetable (g.)</td>
<td>78</td>
<td>84</td>
<td>81</td>
</tr>
<tr>
<td>Fat</td>
<td>... (g.)</td>
<td>37</td>
<td>40</td>
<td>45</td>
</tr>
<tr>
<td>Calcium</td>
<td>... (mg.)</td>
<td>1,390</td>
<td>880</td>
<td>612</td>
</tr>
<tr>
<td>Iron</td>
<td>... (mg.)</td>
<td>56</td>
<td>37</td>
<td>30</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>... (i.u.)</td>
<td>1,200</td>
<td>4,240</td>
<td>4,100</td>
</tr>
<tr>
<td>Thiamine</td>
<td>... (mg.)</td>
<td>3.6</td>
<td>2.9</td>
<td>2.3</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>... (mg.)</td>
<td>1.1</td>
<td>1.4</td>
<td>1.3</td>
</tr>
<tr>
<td>Nicotinic Acid</td>
<td>... (mg.)</td>
<td>27</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Ascorbic Acid</td>
<td>Uncooked (mg.)</td>
<td>24</td>
<td>133</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>Cooked (mg.)</td>
<td>12</td>
<td>44</td>
<td>12</td>
</tr>
</tbody>
</table>

* These four areas correspond with those in which we worked. The cases quoted in Tables II and III come from Area C. The intakes were measured by methods described by Nicol (1949, 1956)

TABLE II

<table>
<thead>
<tr>
<th>Serial No.</th>
<th>Vitamin A (i.u./100 ml. plasma)</th>
<th>Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>772</td>
<td>88</td>
<td>Disciform degeneration of macula</td>
</tr>
<tr>
<td>829</td>
<td>30</td>
<td>P.S.L.</td>
</tr>
<tr>
<td>830</td>
<td>10</td>
<td>P.S.L.</td>
</tr>
<tr>
<td>831</td>
<td>10</td>
<td>P.S.L.</td>
</tr>
<tr>
<td>837</td>
<td>30</td>
<td>P.S.L.</td>
</tr>
<tr>
<td>845</td>
<td>20</td>
<td>P.S.L.</td>
</tr>
<tr>
<td>872</td>
<td>25</td>
<td>P.S.L.</td>
</tr>
<tr>
<td>879</td>
<td>80</td>
<td>Syphilitic chorio-retinitis</td>
</tr>
<tr>
<td>883</td>
<td>45</td>
<td>P.S.L.</td>
</tr>
<tr>
<td>900</td>
<td>20</td>
<td>P.S.L.</td>
</tr>
<tr>
<td>1,029</td>
<td>42</td>
<td>P.S.L.</td>
</tr>
<tr>
<td>1,291</td>
<td>88</td>
<td>P.S.L.</td>
</tr>
</tbody>
</table>

A value of vitamin A below 70 i.u. per 100 ml. plasma is taken as sub-normal.
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The situation at this point may be summarized as follows:

(1) The posterior segmental lesion is found in subjects with a low I.D.F. (mean I.D.F. 11). It is not found in non-onchocerciasis areas.

(2) Cases with the posterior lesion have a low nodule mean (0-9).

(3) The posterior lesion is not found in areas where adequate vitamin A is present in the diet.

(4) It has been established in a group of subjects in an area of vitamin A deficiency (although not a gross deficiency) that cases exhibiting the lesion had a very low quantity of vitamin A in the plasma.

It seemed reasonable, then, to carry out clinical trials with massive vitamin A therapy to ascertain whether or not any recovery in the visual acuity occurred. Details of the trials are given in Table III.

<table>
<thead>
<tr>
<th>Serial No.</th>
<th>Visual Acuity</th>
<th>Improvement in Visual Acuity</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>L</td>
<td>R</td>
</tr>
<tr>
<td>772</td>
<td>H.M.</td>
<td>C.F.</td>
</tr>
<tr>
<td>829</td>
<td>6/60</td>
<td>6/60</td>
</tr>
<tr>
<td>830</td>
<td>H.M.</td>
<td>H.M.</td>
</tr>
<tr>
<td>831</td>
<td>C.F.</td>
<td>C.F.</td>
</tr>
<tr>
<td>837</td>
<td>6/9</td>
<td>6/9</td>
</tr>
<tr>
<td>845</td>
<td>H.M.</td>
<td>H.M.</td>
</tr>
<tr>
<td>924</td>
<td>6/36</td>
<td>H.M.</td>
</tr>
<tr>
<td>930</td>
<td>H.M.</td>
<td>H.M.</td>
</tr>
<tr>
<td>1,291</td>
<td>6/60</td>
<td>6/60</td>
</tr>
<tr>
<td>1,306</td>
<td>6/36</td>
<td>H.M.</td>
</tr>
<tr>
<td>1,338</td>
<td>6/36</td>
<td>6/36</td>
</tr>
</tbody>
</table>

Treatment consisted of 165,000 i.u. vitamin A daily, prescribed as 5 capsules Crooke's cod liver oil.

The lack of success of this therapy in the control cases need not be emphasized. It was only to be expected. In four cases the recovery of vision could be classified as almost complete, and in three as partial. When the effect of
the therapy was analysed, some interesting facts emerged. The best results were naturally obtained in cases with early lesions, i.e. those with a history of night-blindness, who showed early sclerotic changes around the disc with or without oedema or pigmentary disturbance at the macula. Partial success can be attained even when the ophthalmoscopic picture reveals a fairly gross lesion. Little or no improvement was achieved in two cases where secondary retinitis pigmentosa existed, and the improvement was slight in those where atrophic cupping of the disc was present; these conditions would appear to be contraindications to therapy. It is difficult in this small series to generalize as to when or when not it is worthwhile attempting treatment with vitamin A, but it may be said that, where the visible choroidal blood vessels are red in colour, there lies the greatest hope of recovery. Gross macular upset and optic atrophy do not appear to militate against the achievement of some improvement. The effect of these massive doses of vitamin A was dramatic in some cases and produced quite a sensation in the village concerned. For example, one man (829: Figure), who had taken to begging, returned to his farm, and when we visited the village a year later during the rains when the farmers were busy in their fields, he was working happily among them.

Another case (772), who had been completely blind, returned to market as a petty trader, where he would certainly need to use his eyes. A third (1,291), gardener to a European, who was witness to his visual recovery, gained a new lease on his job. Where possible, we controlled the degree of the hemeralopia with a dark adaptometer. The set was standardized with a flash of 30μA at a figure for normal eyes of 2-2 after 30 minutes in total darkness. In early cases the figure obtained lay between 4 and 5; in some cases the brightness of the flash had to be increased to 60μA. before it was seen; in others (even a few of the early cases) the test could not be performed at all. Although resolution of the anatomical changes did not occur, the dark-adaptation figure came back to normal in early cases.

The Snellen charts for illiterate subjects (Landolt C and E) were used for testing visual acuity. It could be argued that the results of these tests varied according to the part of the functioning retina which was directed towards the letters. It was not possible to carry out adequate perimetry with this
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A type of subject, but every effort was made to eliminate this source of fallacy at the initial examination. This was done by encouraging head-tilting, and the results here showed fairly conclusively that only a little if any variation in the acuity occurred at all (letters not lines). On subsequent examinations the same practice was carried out, so that the subjects were given every chance to see the charts under equal conditions on each occasion of testing. Guessing was soon discovered. Objectively, there was no doubt when recovery of vision had been obtained. Whether such recovery was maintained, we do not know apart from the three cases quoted above. All were given a year's stock of capsules to carry away. We are satisfied that no alteration occurs in the visual acuity after a course of any filaricide.

DISCUSSION

The different diseases which bear some resemblance to the posterior degenerative lesion of onchocerciasis suggest that it is not easy to diagnose. Most workers have emphasized the variety of appearances in this condition. With the recognition of an exogenous chorio-retinitis of onchocercal origin (Rodger, 1957), the diagnostic features become somewhat clearer. No author that we are aware of has so far attempted to survey the different descriptions of the degenerative lesion, and it would now seem worthwhile to do so. The description with which we are most in agreement is that of Ridley (1945), who described the lesion in its advanced condition, with or without the corpuscular aggregation of retinal pigment at the periphery. Ridley does not emphasize sheathing of the retinal vessels, an observation on which Sarkies (1952) and Toulant and Boithias (1952) laid great stress. We have already discussed this factor, and mention it here again only to emphasize our view that it is not a specific sign of the disease. Sarkies (1952) described what he considered to be an early case of the lesion in a schoolboy, as a very slight, patchy increase of pigmentation in the macular area associated with intervening lighter areas, suggesting that the sclera was shining through an atrophic retina. This seems rather slender evidence on which to diagnose the posterior segmental lesion. Sarkies went on to say that no intermediate stage between that picture and the advanced appearance was seen, and added that only one of his advanced cases resembled the description given by Ridley. This is difficulty to explain unless on the basis that confusion has existed as a result of the posterior exudative uveitis of onchocerciasis, common where Sarkies worked in an area with a high density quotient. As this is a non-specific inflammatory uveitis, it bears only a slight similarity to what we have called the posterior degenerative lesion of onchocerciasis. Ridley's description is based on twelve cases he saw in a village called Funi in the Northern Gold Coast. This village is isolated, and the nutrition of the people very poor. We visited this village and saw ten cases, eight with advanced degenerative lesions, and two inflammatory.
At the advanced stage, the degenerative lesion, is, as Ridley said, typical. The appearance is similar to a choroidal sclerosis, with peripheral corpuscularization occurring in some instances. This is not a hypothetical combination, as Ridley remarks. It was described by Duke-Elder (1940), and later by Falls and Cotterman (1948), in genetically determined lesions. This type of degeneration is extremely rare in Africa, however, if it occurs at all. We have discussed it in Section I (above).

Hissette (1932, 1937) and Bryant (1935) seem to have confused the inflammatory with the degenerative type. For example, both workers mention that plaques of choroidal atrophy revealing white sclera are often seen, whereas in our view this is rare in the degenerative type. Hissette describes photophobia and lacrimation as part of the symptomatology, which is something we ourselves never observed. He also says that the lesion is a late symptom of onchocerciasis, whereas in our own cases it appeared to be the opposite, the most common age group being 20 to 30 years. Hissette finds difficulty in deciding whether cupping of the disc, which is frequent, is atrophic or glaucomatous, because in many cases the cupping exactly simulates the glaucomatous type. A secondary glaucoma was common in our cases of onchocercal exudative uveitis, but glaucomatous cupping was never seen in the degenerative lesion, although atrophic cupping was usual in long-standing cases. Hissette also remarks on the frequent incidence of colloid bodies, which, as pointed out above, are more commonly found in the inflammatory than in the degenerative type. All these points suggest that the variable appearances of the lesion emphasized by Hissette and by Bryant were due to a misunderstanding of the underlying dual pathogenesis. In fact, the former stated that he found it impossible to suggest a pathogenesis to cover the many aspects of the disease. He was not helped, of course, in that the pathological material obtainable at the time was extremely small. Both men, nevertheless, must be given every credit for being the first to describe these changes.

Toulant, Robineau, and Puyuelo (1950) and Toulant and Boithias (1952) also appear to have been confused by the multiplicity and diversity of the lesions. We have never seen the retinal haemorrhages nor the colloid bodies which Toulant describes at the posterior pole save in the inflammatory condition. Nor is it clear what he means when he says that he has never noted the tapeto-retinal degeneration, so-called by Ridley, unless there is some confusion here in the nomenclature. This term well describes what is the most characteristic stage of the disease. Toulant and Boithias qualify this statement by saying that a secondary retinitis pigmentosa is seen but is rare, only three cases having been recorded in the course of several years' work, but this is not our experience. One significant remark of theirs is that a juxtapapillary chorio-retinitis is a frequent finding. This is our own view, the lesion usually first appearing in this position. Toulant and his colleagues, who have produced much fine work on this subject, disagree
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with Hissette over the symptomatology, and are in general agreement with other workers that it rests entirely on the presence of hemeralopia.

CONCLUSIONS

It is now possible to consider the probable course of events in the evolution of the degenerative lesion. It seems certain that the initial symptom of night-blindness depends upon a vitamin A deficiency. It may be that the first appearance of retinal pigmentary disturbance in the area between the macula and the disc (juxtapapillary) is related to the high incidence of rods in that area; the rods are most dense directly below the papilla, being about 170,000 per sq. mm. in this region. It is interesting to note that Ramingalswami, Leach, and Sriramachari (1955) found structural changes in the rods and cones and pigment epithelium of the retina in monkeys placed on a diet deficient in vitamin A. It is permitted to accept in the light of this interesting paper that, as a result of a gross vitamin A deficiency, the retinal pigment epithelium and the visual receptors of the human eye may be similarly affected. This is given indirect support by Hume and Krebs (1949), who showed that cone function as well as rod function was affected in a group of human volunteers deprived of vitamin A. Wald, Brown, and Smith (1952) showed that the carotenoid components of the rhodopsin and iodopsin systems are identical. Iodopsin is now known to be vitamin A aldehyde. At the same time as these retinal changes occur in the posterior degenerative lesion, the choroidal vessels are equally badly hit. This is more difficult to explain. A vascular degeneration may be induced by a circulating intoxicant, as in diabetes. Clinically, the vascular changes of the degenerative lesion under discussion could be explained in the same way. What filarial source of intoxicant might there be? In view of the low I.D.F. in these cases and in view of the fact that in some of them no mf. have been found either in the skin or in the eye, mf. as a source are unlikely. The only other source of toxin is the adult worm. This is not outside the bounds of possibility. It has been mentioned earlier that the average number of nodules (nodule mean) in these cases is low (0.9), and that we found many cases without any palpable nodule; it is thus possible to argue that it is only free adult worms which permit the circulation of such a toxin. The occurrence of free adult worms has been demonstrated post mortem by van den Berghe (1941) and others. Here, too, vitamin A deficiency may play a part. The nodule mean where the posterior lesion is never seen in rain-forest villages (vitamin A being plentiful in the diet) was found by us to be 40 even where the density quotient was less than 5. Might not a deficiency of vitamin A, therefore, be in some way responsible for the low nodule mean, leaving a proportionately high number of adult worms free in the tissues? The factors which determine the effect of the nutritional status on parasitic infestations are complex; yet Moore (1957), after reviewing the contradictory literature, suggests that the migration of parasites or of their larvae may be facilitated.
by defective barriers in the deficient animals. There is some evidence for this. It may well be, then, that the nodulation of adult filariae *Onchocerca volvulus* is to some extent determined by the vitamin A content of the diet: the more vitamin A the greater the number of nodules. A toxin liberated by adult worms lying free in the tissues is much more likely to achieve a reasonably high titre in the blood than if it were liberated within the comparatively avascular and densely fibrous-walled nodule. That would be one possible explanation for the absence of the degenerative lesion from rainforest country. If a toxin liberated by free adult worms exists, it is well known that the complexity of the choriocapillaris not infrequently results in a high local titre of any circulating poison. Owing to the huge surface area offered for absorption, retinal damage results. How these toxic substances act is obscure, of course, and it is still debated whether all of them are essentially neurotoxic or some of them act primarily upon the blood vessels causing a secondary neuronic degeneration through vasoconstriction (Duke-Elder, 1940).

In primary choroidal sclerosis the vascular changes precede and induce the pigmented changes, but Ramingalaswami and his colleagues (1955) did not discuss the choroidal vessels although the retinal pigment was altered as a result of vitamin A deficiency. Leach (1957) says that changes in the walls of the choroidal vessels, especially the choriocapillaris, were seen in sections taken from the eyes of monkeys deficient in vitamin A. This may be seen in the original illustrations to this paper. Leach is the first, however, to agree that such important observations require confirmation. The degenerative lesion of onchocerciasis differs from a primary choroidal sclerosis in that a vitamin A deficiency is an ever-present factor. There seems, therefore, no alternative to postulating at least two aetiological factors. These two, of course, could be linked: the filarial toxin may interfere in vitamin A metabolism as well as acting on the vessels. In this way a vicious circle is set up, all the more likely to appear in subjects already deficient in the vitamin. There is some evidence to support this hypothesis. Eveleth, Goldsby, Bolin, and Bolin (1953) have made preliminary studies on the conversion of carotene in sheep infested with filariform larvae after deprivation of vitamin A. A better conversion was observed in one non-infested sheep than in three which were infested. In experiments on guinea-pigs, animals which were infested with *D. filaria* were found 8 months later to have reserves averaging 2.5 i.u. per g., as compared with 23 i.u. per g. in control animals not so infested. Animals infested with *D. viviparus* also had lower reserves than control animals (Soliman, 1953).

Several factors suggest that the pigment epithelium plays a vital role in the rod and cone degeneration. Popper and Greenberg (1941) demonstrated the presence of vitamin A in this epithelium, and suggested that the vitamin is altered within it as it passes from the circulation to the receptors. Damage to the epithelium could occur secondary to a choroidal sclerosis...
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of the type described here induced by a filarial toxin, thereby leading to inhibition of the vitamin A metabolism with a resultant adverse effect on the rods and cones; the epithelial changes, on the other hand, might be simply a primary degeneration in a vitamin A deficient subject as a result of the generalized deficiency. In neither of these events is it necessary to postulate a direct competitive effect by a toxin to explain the breakdown in the vitamin A metabolism. It would be enough if the epithelium itself degenerated. It is well known that the more rapid the destructive process the greater will be the deposition of retinal pigment in new locations. In Ridley's drawing of the degenerative lesion in his monograph, and in the excellent retinographs of Boithias (1954), gross accumulation of the retinal pigment is not important if the size of the area involved is taken into account. This supports the view that the condition is insidious, which all the better fits the pathogenesis just suggested.

To sum up, it seems likely that as a result of the vitamin A deficiency—either with or without additional interference in vitamin A metabolism by a filarial toxin—there will be destruction of the retinal pigment epithelium which in turn will lead to degeneration of the retinal receptors. Simultaneously a choroidal sclerosis develops from the effects of a filarial toxin, for it is not as yet proven that vitamin A deficiency alone can lead to such a change. The sclerosis in its turn gives a greater impetus to degeneration of the retinal pigment epithelium, thereby further aggravating the break-down in the vitamin A metabolism. The restriction of the lesion in the first instance to the papillo-macular area, where the choriocapillaris is most dense, and where the number of rods requiring vitamin A is greatest, lends support to the belief that a toxin plays an important part in producing these changes. It should not be impossible to isolate such a toxin, if such exists. The hypothesis put forward rests partly on circumstantial evidence, but in the absence of a better argument it affords some basis on which to work in the future.

While this explanation goes as far as possible in the light of our present knowledge, it leaves us wondering why only 5 per cent. of the many subjects whose bodies almost certainly contain free adult filariae, and who are deficient in vitamin A, appear to suffer from the ocular lesion. Many might consider that 5 per cent. is a large enough percentage in any large biological series; others might ponder on the probability of there being a third factor involved. In this connexion, it is interesting to read of the toxin present in rye germ, the ill effects of which on the spinal cord could be prevented by vitamin A (Mellanby, 1931). There are also other possibilities: there may be some reason why the carotene which is ingested is not converted into vitamin A; the blood carotenoids were estimated in only two of our cases (1,029 and 1,291), owing to difficulties in obtaining blood; both figures were abnormally high despite the level of vitamin A. We do not know if this is the rule, but it may be an important observation. Wald and Hubbard (1949) have shown that the conversion of retinene to vitamin A is a coupled reduction for which cozymase
acts as a coenzyme, and fructose diphosphate can act as a substrate. The cycle is dependent on the existence of an adequate supply of nicotinic acid, which is contained in cozymase. While there are ample amounts of nicotinic acid in the diets of the people of Northern Nigeria (Nicol, 1949), there is a deficiency in riboflavin; it is believed that a close relationship exists between these two respiratory enzyme vitamins, so that cozymase activity may well be interfered with. It is in directions such as these, perhaps, that further discoveries may be made.

SUMMARY

(1) Two types of onchocercal lesion in the posterior uvea are shown to exist; one is due to the death of microfilariae in or adjacent to the choroid, and is inflammatory in type; the other is a degenerative lesion associated with a low degree of infection in the individual and a low nodule mean.

(2) The different types of chorio-retinal disease that may confuse the diagnosis are described in detail.

(3) The posterior degenerative lesion of onchocerciasis is also described in detail. Its evolution is discussed.

(4) The sera from ten cases suffering from this lesion were found to have a low vitamin A content (about 25 i.u. per 100 ml. plasma). Recovery of vision (almost complete or partial in seven cases of the posterior degenerative lesion) followed the administration of 165,000 i.u. vitamin A daily. Improvement, when it occurred, began at the end of one week. In addition, the dark adaptation in early cases so treated returned to normal. There was no resolution of the anatomical abnormalities. Where atrophic cupping, peripheral corpuscularization, or orange-white sclerosis of the larger choroidal blood vessels existed, no improvement resulted.

(5) After a discussion of the varied clinical descriptions of this disease, assessment of possible factors in the aetiology suggests that a combination of vitamin A deficiency with a toxin liberated by free adult worms could explain its onset. This is supported by the fact that the lesion does not occur in areas where vitamin A deficiency or onchocerciasis exist by themselves, but only when the two conditions are associated.

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REFERENCES

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CORRIGENDA

It is much regretted that in Prof. Rodger's two articles published in the British Journal of Ophthalmology in September and October, 1957, the reference lists contained two incorrect page numbers:
On p. 557, Rodger (1957b) should read B.J.O., 41, 599 (not 513).
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Occlusion of the pupil in the latter was the commonest single cause of blindness due to onchocerciasis in children.

(6) Vitamin A deficiency can cause hemeralopia, pre-xerosis, xerosis itself, and keratomalacia; they were each found in African children although not necessarily in association one with the other.

(7) Keratomalacia, characterized by spontaneous iris prolapse without an inflammatory reaction or painful symptoms, is perhaps the most typical and striking of all the appearances of avitaminosis A in small children.

(8) Whipped-up clear mucus in the outer canthus, conjunctival pigmentation especially close to the limbus, and folds in the bulbar conjunctiva constitute a triad of signs indicative of pre-xerosis. It appears to be much more significant than Bitot’s spots.

REFERENCES


CORRIGENDA

The following corrections should be noted in “Posterior Degenerative Lesion of Onchocerciasis”, by F. C. Rodger, *Brit. J. Ophthal.* (1958), 42, 21:

p. 23 (b), last line: for “in onchocerciasis” read “in onchocerciasis areas”.

p. 26 (footnote): for “Dr. M. Giagiunto” read “Dr. M. Giaquinto”.

p. 28 (Table II): delete records of serial numbers 772 and 837.

p. 29 (Table III, footnote): for “cod liver oil” read “vitamin A”.

pp. 33 and 34: for “Ramingalaswami” read “Ramalingaswami”.