FACTORS IN THE PATHOGENESIS OF OCULAR ONCHOCERCIASIS

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SYNOPSIS

This article briefly reviews the history and distribution of *Onchocerca volvulus*, and the disease for which it is responsible. The importance is stressed of ophthalmic examination, as opposed to clinical inspection, in determining the incidence of onchocerciasis in a region, such as the Sudan, where eye diseases are common. A description of the ocular manifestations of the infection is given, and their etiology is discussed.

*Onchocerca volvulus* was first found by a German medical missionary in negroes on the Gold Coast, and was named by Leuckart in 1893. In 1899 Sir Albert Cook reported the occurrence of onchocercal tumours in a native of Busoga in Uganda. In 1915 Robles discovered onchocerciasis in Guatemala and later (Robles 27) gave a detailed account of the condition, emphasizing that it was often associated with ocular disturbances, including blindness. Robles' observations were soon confirmed by Pacheco Luna and Calderon, and Brumpt 4 separated the causal parasite as a new species, *O. caecutiens*, the "blinding filaria". During the next 12 years ocular manifestations, though commonly reported in South America, were not described in the various series of cases of onchocerciasis studied in Africa. Thus Blacklock, 2 Brumpt, 5 and Mühlens 24 have emphasized that African onchocerciasis is not accompanied by ocular manifestations.

Dry 11 described a skin affection in the Lumbwa and Kisii tribesmen of Kenya, said to be accompanied by impaired vision and even blindness in some of their number, and attributed by the tribesmen to biting flies identified by Edwards as *Simulium neavei*, but Dry does not mention nodules or *Onchocerca*. Hisette 13 was the first person to recognize ocular onchocerciasis in Africa. He found that eye lesions are very common and severe in cases of onchocerciasis in Katanga, described the lesions in detail and concluded that *O. caecutiens* and *O. volvulus* are identical (Hissette 13). Shortly afterwards Bryant 4 independently reported cases of unexplained blindness in the Jur, Bellanda and Bongo tribes of the Bahr el Ghazal Province of the Sudan. Investigation of these cases led to the
discovery of *O. volvulus* in the Sudan (Bryant 8) and finally to the conclusion that this parasite was the cause of the unexplained "Sudan blindness" (McKelvie 21). Onchocerciasis has subsequently been studied in the Sudan by Cruickshank,9 Bryant,7 McKelvie,22 Kirk,15 Satti (unpublished report to the Director of the Sudan Medical Service, 1948), Woodman,30 Bloss,3 Lewis,18,19 Satti & Kirk 28 and others.

Onchocerciasis has been found to be widely distributed in the Bahr el Ghazal Province and occurs also in places in the eastern Sudan near the Abyssinian border,9 always in sparsely populated areas where the land is probably not suitable for much economic development. It is much less widely distributed than is *S. damnosum*, which is considered to be the only vector of the disease in the Sudan; the fly is found in the absence of the disease in the northern Sudan and also on certain southern streams.18 The clinical manifestations include onchocercal nodules, various skin conditions, lymphadenitis, hydrocele, genital elephantiasis and ocular onchocerciasis. The most important result of infection is ocular onchocerciasis, which may end in blindness.

**Importance of Ophthalmic Examination**

Any person studying the eye diseases in a population infected with onchocerciasis will find the picture so typical that it cannot be mistaken for anything else, while the incidence and geographical distribution of the eye lesions agrees closely with that of onchocerciasis. Although the general picture in the population is so typical, however, one must beware of the tendency to regard every eye condition seen in an area of onchocerciasis as due solely and directly to the onchocercal infection. The effects of nutritional deficiency, trachoma, superimposed infection and other causes of eye diseases have always to be borne in mind. There is no reason to believe that these causes are less common in areas of onchocerciasis than elsewhere. Indeed, it is possible that in some cases the action of the onchocercal infection may be mainly a predisposing or contributory one, allowing bacterial infection or nutritional deficiency to produce effects which they would not do in otherwise healthy eyes. A detailed study of ocular onchocerciasis requires a competent ophthalmologist. Mere inspection of the eyes for obvious changes which can be seen externally is not enough. To distinguish the various ocular lesions and assess the part played by onchocerciasis and other causes in their production requires considerable facility with the methods of ophthalmic examination, including the use of the ophthalmoscope, slit lamp and corneal microscope, also some knowledge and experience of ophthalmology. In the Sudan we have been fortunate in this respect. Descriptions of the eye manifestations of onchocerciasis in the Sudan have been given by Dr A. R. McKelvie, formerly Ophthalmic
Surgeon, Sudan Medical Service, or by others with the help of Dr McKelvie, who visited the endemic area of onchocerciasis on various occasions. There he not only studied "Sudan blindness" and ocular onchocerciasis personally, but willingly made his findings available to others. In addition, he kindly undertook to instruct some of his colleagues in ophthalmic examination, so that they were able, with his help and supervision, to do a certain amount themselves.

Ocular Onchocerciasis

The ocular manifestations of onchocerciasis have been described by Hissette,13, 14 Bryant,7 McKelvie,21-23 Ridley24 and others. It is not inevitable that every case of O. volvulus infection will develop eye changes. Many cases with nodules of long duration are seen in whom vision is perfect and there are no eye abnormalities at all. When the eyes are affected the course to blindness usually takes some years if posterior manifestations alone are in evidence; but the course may be comparatively rapid if both anterior and posterior manifestations are present, especially if the damage to the cornea is progressive, and—as is usual—is hastened by secondary infection, sometimes causing panophthalmitis with destruction of the eye. All cases do not necessarily pass to complete blindness. In some the condition appears to become arrested for some unknown reason after a certain degree of defective vision has been reached. Following the early descriptions of McKelvie21 and Bryant,7 we in the Sudan customarily divide the objective manifestations of ocular onchocerciasis into anterior and posterior manifestations, the latter being seen only with the opthalmoscope.

Anterior manifestations

Keratitis with iritis, iridocyclitis with synechiae, corneal haze with nummular keratitis, haze in the media of the anterior and posterior chambers caused by microfilariae and their debris, are common anterior manifestations. The keratitis may progress to corneal opacities, which are sometimes pigmented, covering the whole or part of the cornea; the synechiae may result in deformity of the pupil, which may be circular, oval, pear-shaped or irregular in outline. It is sometimes fixed and attached to the posterior part of the cornea, and mydriatics can exert no action. The synechiae may be the cause of secondary glaucomatous changes. In some cases there may be atrophy of the iris, or there may be pigment deposits on its surface. Cataractous changes in the lens and pigment deposits on its surface are sometimes seen. The lens may be dislocated. In some cases observed by Satti (unpublished report to the Director of the Sudan Medical Service, 1948) the lens was adherent to the posterior surface of the cornea, and in one it was completely absorbed.
Posterior manifestations

The early affection of the posterior part of the eye is shown by the presence of luminous spots in the retina, commonly near the disc and more often on its temporal side. This is associated with early degenerative changes in the equatorial region of the fundus and towards the periphery. Later, the degenerative changes in the retina and choroid become more prominent, with choroidal pigment showing through. These degenerative changes may include the macula, with its complete destruction, and in such cases the blindness sets in early, but usually the macula is not attacked until late in the disease. Side by side with these degenerative processes, changes in the disc take place, and in a late case well-developed pallor of the disc, with cupping, and narrowing of the arteries, are seen. In such cases the blindness is usually complete. Secondary glaucoma with severe cupping is sometimes seen. In a few cases optic atrophy alone is encountered without any of the other posterior manifestations.

Contrast between anterior and posterior manifestations

It has been suspected that the posterior manifestations may have a different pathogenesis from that of the anterior ones. The name "Sudan blindness" was originally given to cases in which the posterior manifestations alone were observed. Bryant 7 considered "Sudan blindness" and onchocercal keratitis to be two separate clinical entities, due possibly to a common cause. The following points of difference between the two conditions may be mentioned. The posterior manifestations are usually bilateral, no microfilariae are found by aspirating the anterior chamber, the media of the eye are usually clear; so is the cornea, and the eyes may show no abnormality externally. The anterior manifestations may be unilateral or asymmetrical, the media of the eye are usually opaque, and corneal opacities and other abnormalities are readily seen on external examination of the eye. However, cases with both anterior and posterior manifestations are common. One case, in which onchocercal keratitis was followed years later by a typical retino-choroiditis, has been recorded in detail (cf. McKelvie 28).

Etiology of Ocular Manifestations

Anterior manifestations

The anterior manifestations of ocular onchocerciasis (onchocercal keratitis and its complications) are probably directly due to the presence of the microfilariae in the tissues and media of the eye. It is usually easy to demonstrate the microfilariae in the eye, sometimes in numbers, and the earliest pathological change is usually haziness caused by cellular infiltration round the microfilariae. Cases have been observed, however, in which
microfilariae could be demonstrated in the eyes over a period of years without any pathological changes resulting. The usual explanation given for this is that the worms cause no trouble as long as they are alive and moving about; it is only after they die and begin to disintegrate that an inflammatory reaction is provoked in their vicinity.

Probably intensity of infection, and the actual number of microfilariae in the eye, influence the incidence of ocular manifestations. The anatomical distribution of the adult worms in the body is probably of importance in this connexion. The early observers in South America, the accuracy of whose work has now been confirmed in so many details, emphasized that eye conditions were especially associated with nodules on the head, and relief of the eye symptoms often followed surgical removal of the nodules.

It has been suggested that there are different kinds of Onchocerca in man (species, races, strains, etc.), differing in their tendency to produce ocular manifestations. This concept goes back to the days when it was thought that the South American parasite O. caecutiens caused blindness while the African one (O. volvulus) did not. It was largely discredited when Hissette 18 showed that eye lesions were common in African onchocerciasis and suggested that O. volvulus and O. caecutiens should be regarded as synonyms. All subsequent work tends to support the conclusions of Hissette. For the present the theory that ocular lesions are caused by certain types of Onchocerca, and not by others, is in abeyance, and likely to remain so until factual evidence can be produced to support it.

Observations in the Sudan (Kirk 18) have shown an apparent correlation between the incidence of ocular lesions on the one hand, and distance from Simulium breeding-places and incidence of positive skin smears and onchocercal nodules on the other. The incidence of positive skin smears was determined by taking one specimen only from each individual, from the arm. It was thought likely that repeated skin smears from different parts of the body would show 100% infection rates in all the populations concerned, and that the single smear method might provide a rough estimate of the intensity of infection. This assumption may not be correct. Woodman 50 cites Van den Berghe's (1941) observation that the adult female can distribute her offspring around the connective tissues before becoming encysted, the latter being very possibly the terminal phase of her life history, so that the presence of cutaneous infection with microfilariae may not necessarily indicate a heavy infection with adults or future serious complications.

Racial or hereditary defects, nutritional deficiencies, and intercurrent infections have been regarded as important contributory factors. These conditions can themselves be responsible for eye lesions, and may co-exist with onchocerciasis. Secondary infection is responsible for some of the worst end-results of ocular onchocerciasis, but it is doubtful how much importance can be attributed to the other two factors mentioned. It is
interesting in this connexion to recall the relatively low incidence of ocular lesions (under 1\%) and of nodules (3.4\%) reported by Kirk\textsuperscript{15} and Woodman\textsuperscript{30} in the Azande as compared with other tribes in the Bahr el Ghazal, in whom the incidence of ocular lesions varied from 4\% to 10\%, and of nodules from 3\% to 46\%, although the percentage of positive skin smears was very similar in the Azande and the other races. Bryant & Fairman\textsuperscript{8} have emphasized that different races in the Bahr el Ghazal vary greatly in their reaction to different drugs and diseases. Thus bismuth can be administered in full doses for yaws to Nilotics (Dinka, Shilluk and Nuer) whereas caution must be exercised with the same drugs in forest-dwellers (Azande, Bongo and others) or a dangerous stomatitis results. Chloroform is ill tolerated by Nilotics, well by the Azande. Bone lesions in yaws are common in Nilotics, uncommon in forest-dwellers. Hookworm infection causes a profound and intractable anaemia in the Dinkas whereas the Azande are not affected to the same extent. The Azande appear to be extremely susceptible to leprosy; according to Pridie\textsuperscript{25} this tribe of approximately 200,000 people contains approximately 75\% of the total number of lepers in the whole Sudan.

Analysis of the factors underlying these differences is not easy. As regards nutrition, Lorenzen\textsuperscript{20} describes and contrasts the diets of different peoples in the Bahr el Ghazal, and the Azande diet has been the subject of a detailed study by Culwick.\textsuperscript{10} There is a shortage of first-class animal protein since, owing to the presence of the tsetse fly, the Azande do not own domestic stock, and the diet is said to be deficient in riboflavin. However, the soil and climatic conditions of the Azande district permit the cultivation of many varied crops, and there is an abundance of fruit. Opinions differ about the nutritional state of the Azande. Thus Abbott\textsuperscript{1} concludes that signs commonly ascribed to nutritional ill-health are exceedingly common among them. Lorenzen\textsuperscript{20} and Woodman\textsuperscript{81} consider that the Azande exhibit few proved signs of the deficiency diseases and, comparatively speaking, are better off than most tribes in Central Africa.

The relative immunity of the Azande may, on the other hand, be due to a lesser risk of infection. Bloss\textsuperscript{3} thinks this is so. He points out that in the Raga, Raffile, Rumbek and Mvolo areas, where ocular lesions are commonest, the people live along rivers which form ideal breeding-grounds for \textit{S. damnosum}, and the fly can be found all the year round. They take their drinking-water from these rivers, wash in them and fish in them continually. In the Azande area conditions are different. The people use continually the smaller tributaries, where the fly does not breed regularly. They go to the large rivers, such as the Sueh, in certain seasons only. Their chances of infection are therefore only seasonal. Bryant\textsuperscript{6} remarked that the Bellanda tribe affirmed that they had not suffered from blindness until they moved, seven years earlier, from the Azande country to their present country on the Naam river.
Posterior manifestations

While the anterior manifestations are generally clearly associated with the presence of the microfilariae, it has been thought that the usually bilateral nature of the posterior changes and the difficulty of demonstrating the worms in the eye are more suggestive of a toxic agent. The use of fish poisons (cf. Kirk 18) to stupefy the fish and thus enable them to be easily caught floating in the water, is extremely popular in the Bahr el Ghazal, Randia nilotica and Tephrosia vogelli being two of the most commonly used poisons. It was at one time suspected 6 that "Sudan blindness" might be due to the use of these poisons, but no evidence to support this theory was obtained. The appearance of the fundus oculi, and the frequency of a family history of the disease in the Jur tribe in which there is much in-breeding, suggested at one time that the condition might be allied to retinitis pigmentosa, but its close association with onchocerciasis, not only in the Sudan but in other parts of Africa, is now abundantly clear.

Night blindness is a common early symptom in cases of ocular onchocerciasis with posterior manifestations, and this suggests that vitamin A deficiency may play some part in the production of the condition. Satti in an unpublished report describes the examination by him and McKelvie of a number of schoolchildren in Wau who were suffering from night blindness with no other signs or symptoms. Ophthalmoscopic examination revealed no changes in the fundi, no abnormalities could be found in the eyes generally, and the ordinary tests of visual acuity revealed no case of defective vision. In none of the cases was there any evidence of onchocerciasis, although Wau is the capital of the Bahr el Ghazal Province and the centre of a region in which onchocerciasis is prevalent. These cases improved rapidly on vitamin A therapy and the condition was attributed to the occurrence of deficiency of this vitamin in the same area as onchocerciasis.

In heavy or intense infections the number of microfilariae in the tissues may be very great. From the host they derive the nourishment necessary for their sustenance and growth. If the host is living on a minimal or inadequate intake of any vitamin or other essential metabolite the parasites may compete for this, and by deflecting some of it to their own metabolism may produce a state of frank deficiency in the host. The observations on vitamin A and night blindness quoted from Satti’s report indicate that some people in the Bahr el Ghazal are probably living on a minimal or inadequate intake of this vitamin. Another substance which has been considered in this connexion is riboflavine, because of an apparent temporary amelioration in some cases after the administration of this vitamin. In view of the low incidence of ocular onchocerciasis in the Azande as compared with other tribes (Kirk 18), and the estimated riboflavine deficiency in this tribe (Culwick 10), it is unlikely that deficiency of this vitamin is of much importance in ocular onchocerciasis. As far as the writer is aware, no dramatic or per-
manent improvement of the eye condition has been reported after any form of vitamin therapy. Nor is any information available about the metabolic requirements of the microfilariae since no one has yet succeeded in keeping them alive for any length of time in synthetic media (Vargas 29).

Since allergy plays such an important part in the production of pathological changes in all forms of filariasis, it has been thought that the posterior ocular changes may be the result of a peculiar type of hypersensitiveness found only in susceptible persons. The striking allergic reactions which occur during the treatment of the disease with Hetrazan (Banocide) do not support this view. The so-called "ocular reaction" may be so severe that treatment does more harm than good (Laurie 17), but it occurs in patients with anterior manifestations, keratitis and its complications, with numerous microfilariae in the tissue and fluids of the eye. In cases observed in the Sudan, treatment has had no effect, one way or the other, on established posterior manifestations, and no published reports indicate clearly any such effect as distinct from the general "ocular reaction" occurring in patients with both anterior and posterior changes.

RÉSUMÉ

L'onchocercose est très répandue dans la province de Bahr el Ghazal, au Soudan, peu peuplée et se prêtant mal au développement économique. La conséquence la plus grave de l'infection est la cécité. La forme de cécité due à la filariose est typique et ne peut échapper à ceux qui étudient les ophtalmies au sein d'une population. Toutefois d'autres affections oculaires peuvent coexister, dues aux carences, au trachome ou à des infections intercurrentes, aussi fréquentes dans les zones à onchocercose qu'ailleurs. Il se peut même que la filariose soit un facteur favorisant l'apparition de ces autres formes.

Les lésions de la partie antérieure de l'œil (la kératite et ses complications) sont probablement dues à la présence de microfilaries dans les tissus et les humeurs de l'œil, plus particulièrement de filaires mortes qui sont à l'origine de réactions inflammatoires. Il est probable aussi que l'intensité de l'infection — ainsi que, selon certains auteurs, la présence de nodules dans la tête — aient une influence sur la fréquence de ces manifestations oculaires.

Quant aux lésions affectant la partie postérieure de l'œil, qui sont toujours bilatérales, on a pensé qu'elles étaient la conséquence d'une intoxication, d'une avitaminose ou d'une allergie. Aucune de ces hypothèses ne semble cependant se vérifier. Dans les cas suivis au Soudan, le traitement n'a eu aucun effet, ni bon ni mauvais, sur les manifestations affectant la partie postérieure de l'œil.

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