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A Review of Recent Advances in Scientific Knowledge of the Symptomatology, Pathology and Pathogenesis of Onchocercal Infections*

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In this review, the author discusses separately the cutaneous and the ocular aspects of the symptomatology, pathology and pathogenesis of onchocercal infections. Original results are also reported on dermal onchocerciasis.

The less well known lesions are described in greater detail than the better-known. Among the former are the association of cutaneous tumours with dermal onchocerciasis, depigmentation of the skin, and the posterior ocular lesions. In dealing with the pathology of dermal onchocerciasis, the author demonstrates that the main effect of the death of the parasites is on the blood vessels, causing them to become atrophic so that the consequent anoxia gives rise to the better-known, more obvious changes of pachyderma.

The relationship of allergic and nutritional factors with the different lesions is discussed. It is pointed out that the evidence connecting the symptomatology with allergy is not very conclusive while the evidence connecting nutritional factors with the ocular manifestations continues to mount.

DERMAL ONCHOCERCIASIS

Review of symptomatology

The first change in the skin in onchocerciasis is a rash associated with pruritus. Not much has been said concerning this rash, which in Europeans is present particularly over the buttocks and thighs, sometimes on the elbows or forearms (Rodger, 1957b). It can affect the whole body, being just palpable by the tips of the fingers. It is less prominent in Europeans' skin than the follicular hyperkeratosis of vitamin A deficiency but in Africans it cannot be distinguished from this condition. There are one or two possible explanations as to its nature: the first, that the rash is directly dependent upon the presence of microfilariae in the subcutaneous tissue, cannot always be demonstrated; thus, the second, that the rash is an allergic reaction, appears the more likely; a third, that it is dependent on a low vitamin A status, is less likely. The second view, concerning which there has been nothing new in recent literature, was expressed in the 1930s by several workers. Rodhain & Valcke (1935) examined four cases in Europeans in whom no microfilariae were present in the skin although they were found in fluid taken from punctured nodules. All these patients complained bitterly of pruritus. They believed that this evidence supported the view that the pruritus was a manifestation of some kind of allergy. D'Hooghe (1935) observed six cases, in three of whom there was marked pruritus but no microfilariae, and expressed the same opinion—namely, that the irritant rash was due to an allergic response to some antigen probably produced by the adults at the time of the periodic birth of the embryos. It is sometimes forgotten that dermal onchocerciasis commences in this way and differs in its symptomatology from the established onchocercal skin lesion which has been given so many and varied descriptive names, such as craw-craw (O'Neill, 1875), *la gâle filarienne* (Rodhain, 1915), pachyderma (Wanson, 1950) and so on.

Concerning the changes in the skin following the early rash there have been many papers, one of the best being by Wanson (1950), who, after describing the rash as being due to swelling of the mouths of the pilosebaceous glands, says that subsequently the skin thickens until there is an increase in the

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depths of the furrows; the skin for a while remains lustrous; however, in the end it loses its elasticity and becomes rugose and dry; this last is the stage called " elephant skin ". It is not easy to distinguish all of these signs from those caused by vitamin A deficiency, where follicular hyperkeratosis (comparable to the rash) is one manifestation, and where, when the deficiency is severe, the skin becomes dry and scaly and cracked just as it does in the late stages of dermal onchocerciasis. In vitamin A deficiency Nicholls (1934) called this dry scaly skin " phrynoderma " or " toad skin ". The association between xerophthalmia with dry scaly skin was noticed as long ago as 1883 by de Gouvea and later by Mori (1904) and Bloch (1921). In groups of adult Chinese suffering from keratomalacia Pillat (1929) and Frazier & Hu (1931) found the skin dry and heavily keratinized. Their descriptions of the skin in vitamin A deficiency could apply equally well to dermal onchocerciasis, yet to date no author has excluded low blood values of vitamin A when investigating the skin lesions of onchocerciasis; this is an important omission. Thus, in recent times Jamison and his colleagues (1955) and Browne (1960), dealing extensively with the underlying microscopic appearance of onchocercal skin, have brushed aside nutritional factors with scarcely a mention of them. If not only vitamin A deficiency but also a deficiency of the essential fatty acids and pyridoxine require investigation as possible factors in the etiology of phrynoderma in man (Ramalingaswami & Sinclair, 1953), equally does this apply to pachyderma.

Strong (1938) and Van den Berghe (1941) first mentioned that in some cases of long-standing onchocerciasis there were changes in the pigmentation of the skin, the appearance resembling a vitiligo. Since that day there have been many papers on the subject; Wanson (1950), Rodhain (1952), Browne (1954), Jamison & Kershaw (1956) and Budden (1957) have all discussed it. This condition occurs only in persons suffering from long-standing onchocerciasis exhibiting its various stigmata. The association was first suspected on epidemiological grounds. The early suspicions have now been completely confirmed by clinical and pathological studies. The classic areas for the development of this depigmentation are on the skin immediately internal to the tibial crest on its middle third; rarely it is found in the chest and around the lower abdomen. Its first appearance consists of tiny, punctate, white spots, which increase in size until there are many small, rounded, yellow-brown islets (the " leopard skin " of Rodhain, 1952), which in turn enlarge and coalesce until there are large patches of depigmentation in these areas. The borders are quite sharply defined, and the condition is usually bilateral. Browne (1960) has shown that these achromic areas may gradually regain their pigment when the nodules have been surgically removed and filaricides administered, the whole process taking about a year. There is not an absolute reversal in every case, but it was observed to happen in some.

Depigmentation associated with the treponematoses and with fungi, such as the dermatophytoses, has been excluded on epidemiological, clinical and pathological grounds; nor could Browne find any nutritional factor causing this abnormality although he does not state his premises. He ends his interesting paper by suggesting that depigmentation is an allergic phenomenon due to toxins arising from onchocercal microfilariae or the adult worms. This will be discussed more appropriately in the section on pathology. Thus, there appear to be three main stages in dermal onchocerciasis: first, there is a rash which Wanson has called a hyperkeratosis of the pilosebaceous follicles and is associated with pruritus; next, there gradually develops a marked lichenification or pachyderma, this condition also being associated with pruritus; and lastly, there sometimes develop in the three areas described by Browne —the shins, the chest and the lower abdomen— areas of depigmentation, at first punctate, then macular and finally patchy.

A recent concept of dermal onchocerciasis concerns the association with neoplasms of the skin. Many workers mention finding lipomatous changes in nodules removed surgically. In the writer's book *Blindness in West Africa* (Rodger, 1959a) is related how the microscopic appearance underlying " bung " eye is that of a lipomatous change. It is possible that the nodular changes are degenerative following the death of adult worms within an onchocercoma, but the lipomatous changes in " bung " eye suggest that the embryos may also play a part. At any rate, it seems that in dermal onchocerciasis the development of a lipoma is a distinct possibility. Goems (1938) described papillomatous changes in the skin on the backs of the hands, forearms and backs of patients suffering from dermal onchocerciasis in El Salvador. Benign tumours of the skin have also been reported by Kirk (1947). Multiple papillomata, he said, were frequently found in skins showing chronic onchocercal infestation. Browne (1959)

describes having found two cases of papilloma in chronic dermal onchocerciasis and considers that these tumours developed as a result of onchocercal pruritus, perhaps aggravated by incessant scratching. It is a pity no one attempted vitamin A therapy. In Darier's disease, which is typified by multiple vegetating papillomatous growths, there is no history of dietary deficiency (dietary intakes are seldom helpful, of course, and may be misleading) but the disease can be reversed by administering massive vitamin A therapy. Furthermore, Peck and his colleagues (1943) reported that the level of vitamin A in the blood was low in Darier's disease and treatment with massive doses almost always had a favourable effect. Leitner & Moore (1946, 1948) found vitamin A low but the carotenoids within normal limits. The assumption in the later paper is that these papillomatous skin changes occur because of a hereditary or acquired weakness in the absorption of vitamin A.

In a recent paper (Rodger 1957b) the development of nodules in Europeans was described. The first sign of the commencement of the nodule in a fair skin was said to be a *tâche*, under which a lentil-like object could be felt. The most usual site for nodules in Europeans was the hips. An interesting and original finding was that in many instances such nodules pointed on the surface of the skin after having become mildly inflamed, the adult worms ultimately protruding through the surface. This phenomenon was photographed and after extraction the species was identified as *Onchocerca volvulus* in the London School of Tropical Medicine and Hygiene. This is a little-known sign of cutaneous onchocerciasis and may not occur in the African.

Review of the pathology

There have been many excellent histopathological papers describing the skin changes in onchocerciasis dating back to the first days of its discovery. Van den Berghe (1941) and Wanson (1950) give excellent accounts of them. Both these workers described a progressive loss of papillation of the dermis and degeneration of the subepidermal elasticum. They also described a progressive increase of the subepidermal fibrous tissue, the appearance in untreated cases of an intense perivascular infiltration and the absence of such infiltration from the neighbourhood of microfilariae which stain freely. Hissette (1937) described these changes as well. Jamison and his colleagues (1955) have not added much to these findings. The only new point which they made was that in advanced cases the final stage was associated with an *increase* in the amount of dermal elastic fibres. The method of control in this paper is not very satisfactory, for the skin samples were taken after death. Moreover, normal skin acting as control was taken from African subjects in the post-mortem rooms of the University College Hospital in Ibadan, whereas biopsies of diseased skin used to obtain the conclusions were taken from volunteers 500 miles away in the British Cameroons. The ecology of these two territories differs quite a bit. The specimens were kept in formol saline for at least six weeks and no photomicrographs are presented with the paper. The latter would have been particularly interesting in the case of the elastic changes described, for elastic changes are frequently the subject of controversy. The authors attempt to explain the epithelial and elastic changes, speculatively, on the grounds that the microfilariae provoke an antigenic response in the skin, perhaps by means of metabolic products. The writer worked on the pathology of onchocercal skin in Oxford University with E. H. Leach during 1957; unfortunately, the results, obtained from material collected in Africa, were never published. Now is perhaps a good time to bring this study into the light of day (see the photomicrographs of skin taken from the outer part of the thigh; Fig. 1-7). One new and important change was noted and that was the consistent involvement of the small vessels in densely infested skin. Strong (1934) quotes Sharp (in a paper that cannot be traced) to the effect that swelling of the endothelial walls of the capillaries of the skin was observed in one patient suffering from onchocerciasis; unfortunately he also had blood-borne microfilariae and so this observation was somewhat inconclusive. There is no doubt that the endothelial damage observed by Sharp approximated closely with what Rodger and Leach found in onchocercal patients who did *not* exhibit blood-borne microfilariae. This observation will be welcomed by French workers, who have long stressed the importance of vascular changes in the eye and have consistently claimed they were caused by toxins emanating from the parasites. The vascular changes observed in the skin consisted not only of a swelling of the endothelium (as in any intoxication) leading ultimately to occlusion of the blood vessels but also of a replacement fibrosis. These vascular changes were constant, while all other changes were variable and apparently affected by age and perhaps by nutritional factors. It was confirmed that the dermal epithelium at first

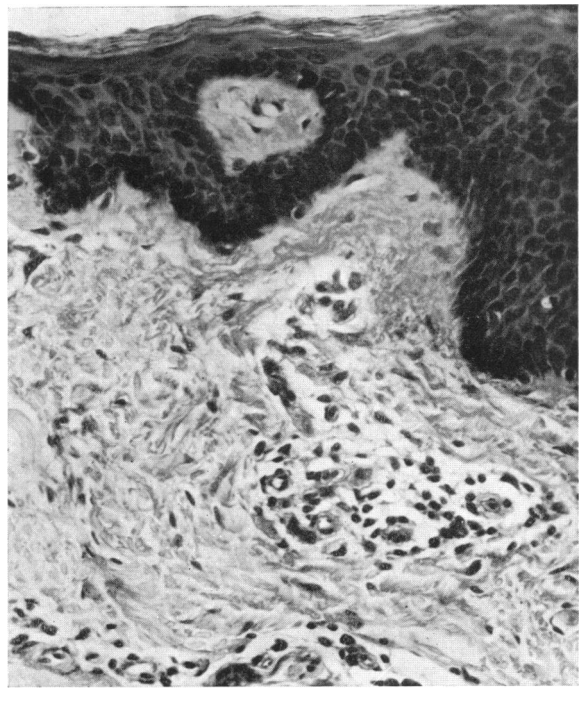
underwent an increase in thickness with an increase in surface keratin and then later became atrophic, losing its characteristic papilliform appearance. It was also confirmed that there was degeneration of the subepithelial and dermal elasticum, but it was not confirmed that there was an increase of the latter in the late stages of the disease. The conclusion reached was that perivascular infiltration occurred as a result of microfilariae dying in the proximity of vessels, a reaction excited by the toxic products of the disintegrating bodies. These toxins, it was concluded, poisoned the vascular endothelium and led to closure of the vessels. It is suggested that the atrophy of the epidermis and the elastic changes described by so many workers are caused by the anoxia which follows occlusion of the blood vessels. In this same unpublished work, when patients were treated with diethylcarbamazine a remarkable change was observed microscopically; the skin vessels multiplied and reduplicated themselves until finally the whole skin became extremely congested. This resulted in a reddening of the skin during the stage of recovery, a fact which has been frequently noted clinically. As the increased vascularity of the skin is associated with a scaling-off of the superficial layers of keratin, this colour change is readily seen even in pigmented skin. Hawking (1952), in describing the histological changes in diethylcarbamazine-treated skin, makes no mention of any effect that the death of the microfilariae might have on the blood vessels. It would be interesting if his slides could be re-examined with this in mind. One might also pay more attention to the pilosebaceous glands in diethylcarbamazine-treated skins, which invariably exhibit the papular type of rash found at the commencement of untreated dermal onchocerciasis, but concerning which there is no recent report by a pathologist.

Ever since the early important papers of such workers as Rodhain (1949) there has been a strong body of opinion which considers that the reaction in the skin of a subject receiving diethylcarbamazine, which kills the parasites in great numbers, is an allergic one. The evidence in support of this is partly cellular inasmuch as there is an eosinophilia and partly that there is an associated oedema and rise of temperature; a less definite (but generally believed) improvement when antihistamines are given has strengthened this possibility. Leach and Rodger, however, found no difference between the microscopic appearances of human skin (in which had been previously placed a counted number of dead microfilariae) in the non-infected and the heavily infected subject. The appearances under the microscope in fact were identical, and so it seems that the reaction in both types of skin must simply be due to the irritant, toxic effect of the dead parasites and nothing else. Because we are dealing with a toxaemia due to thousands of dead parasite bodies the phenomena of eosinophilia and headache and fever and so on are to be expected and do not necessarily lead to the inference that a state of allergy exists. This would be an interesting point for future investigations and discussion. Nevertheless, these unpublished observations seem to be an insuperable objection to the theory that the skin reaction in onchocerciasis is due to a previously induced hypersensitivity. It should be mentioned before concluding this short description of the work in Oxford that care was taken to match each case with a control subject of the same sex and age-group coming from the same area, or type of area, but without onchocerciasis. The dietary intakes of vitamin A in the areas from which the subjects came were also carefully balanced, for in some the daily intake was known to be only 1200 IU, in others 12 000 IU. Studer & Frey (1949) found that vitamin A deficiency caused rat's skin to become atrophic and we felt compelled to eliminate any subject where there was doubt as to whether avitaminosis A might not be playing a part in producing the important vascular changes observed, rather than onchocerciasis alone.

Review of the pathogenesis

It has just been stated that the effect of the death of the parasites seems to be to produce a high titre of toxin which poisons the small skin capillaries; this gives rise to a local anoxia which, after an initial hyperplasia, causes the degeneration and atrophy of the epidermis and dermis. At the same time the products of disintegration of the parasite bodies produce an inflammatory reaction to which eosinophil leucocytes are attracted. It was also stated that because the cellular reaction to a measured number of dead parasites placed subcutaneously in the thigh of an infected and a non-infected person in no way differed it seems we are not necessarily dealing with an allergy. There is a parallel in this with the work of Jarrett and his co-workers (1960a), who were studying the effect of the larvae of *Dictyocaulus viviparus* on calves. On the grounds that larvae dying *in situ* in non-immune calves caused just as severe lesions on disintegration as when they died in previously infected animals, Jarrett reached the

FIG. 1. Serial No. 562
(Farmer aged 25 years)



Individual density figure: 17.

Healthy skin. Slight hyperkeratosis. Several clear cells beneath and within the epithelium contained melanin. The endothelium of arterioles is swollen and some of them are atrophic. There is some perivascular infiltration.

All biopsy specimens taken from the thigh 30 cm above the patella.

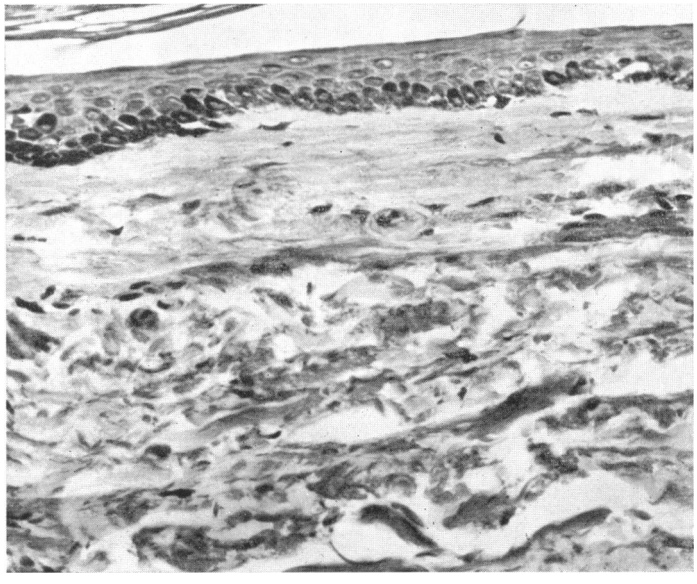
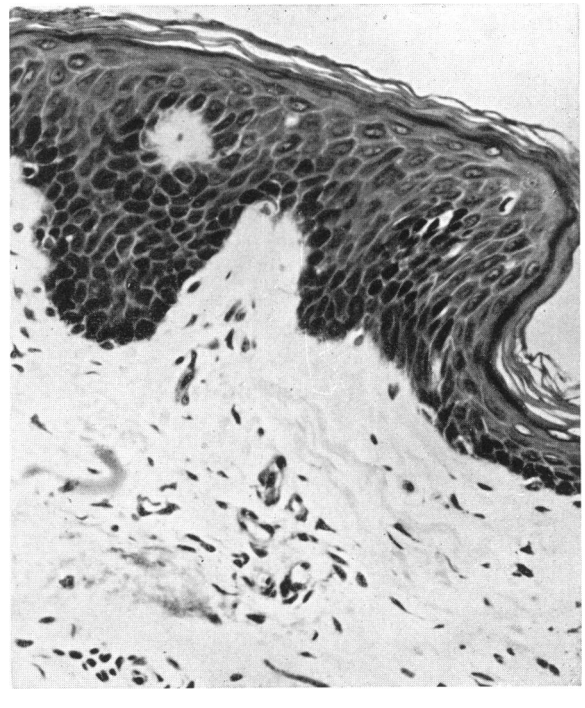


FIG. 2. Serial No. 239
(Farmer aged 60 years)

Individual density figure: 31.

Old case of onchocerciasis with bad pachyderma. Hydrocoele. The epithelium is thinned and very heavily pigmented. There are few papillae. There is almost complete absence of subepithelial vessels.

FIG. 3. Serial No. 503
(Woman aged 35 years)

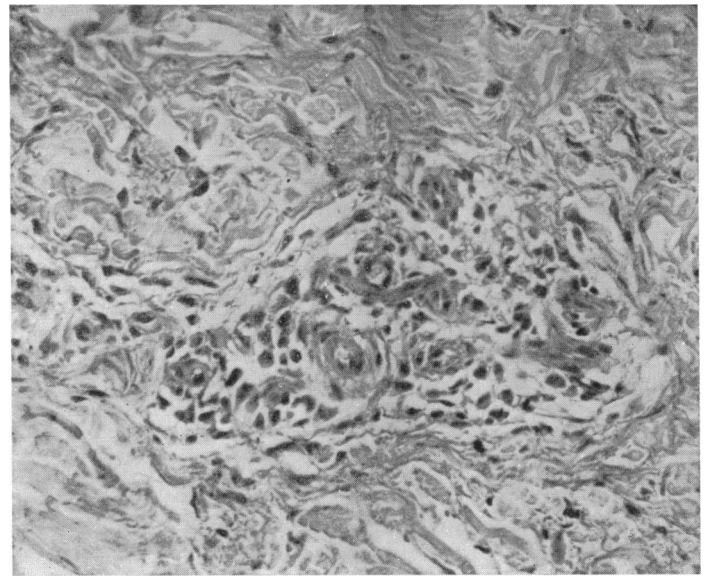


Individual density figure: 31.

Early pachyderma. In most parts, although not in the picture, there was a considerable degree of perivascular plasma cell infiltration. In the subepithelium some of the arterioles reveal swollen endothelium, some are contracted, some degenerate. The nuclei of the endothelium are pyknotic and there is some karyolysis; in others they are swollen and pale.

All biopsy specimens taken from the thigh 30 cm above the patella.

FIG. 4. Serial No. 494
(Man aged 24 years)



Individual density figure :31
Pachyderma below the waist only. High-powered view of poisoned arterioles. The swelling of the endothelium is marked.

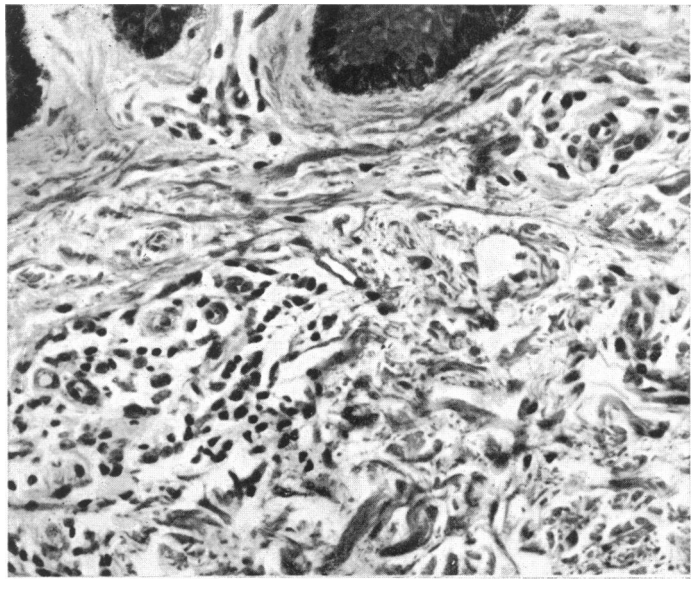


FIG. 5. Serial No. 375
(Man aged 25 years)

Individual density figure: 31.
Healthy skin. Here there is marked round cell infiltration and the arterioles reveal swelling of the endothelium with almost complete occlusion of the lumina.

All biopsy specimens taken from the thigh 30 cm above the patella.

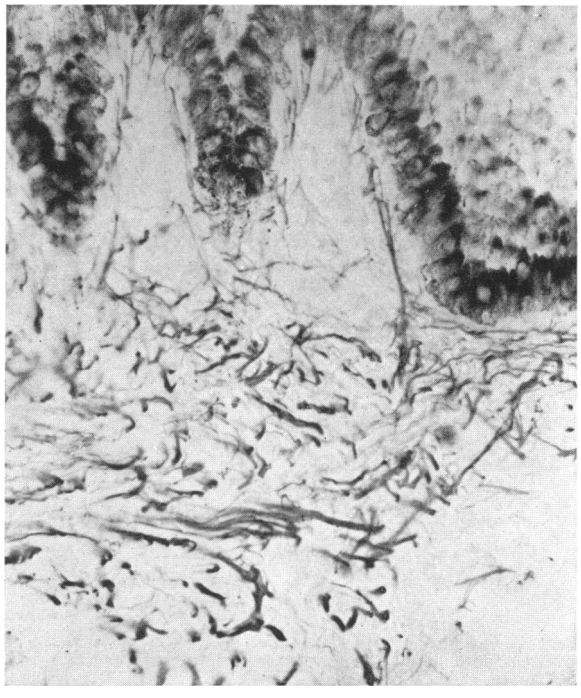


FIG. 6. Serial No. 360
(Youth of 18 years)

The skin is stained for elastic to act as a control for Fig. 7.
Healthy skin. Not suffering from onchocerciasis.

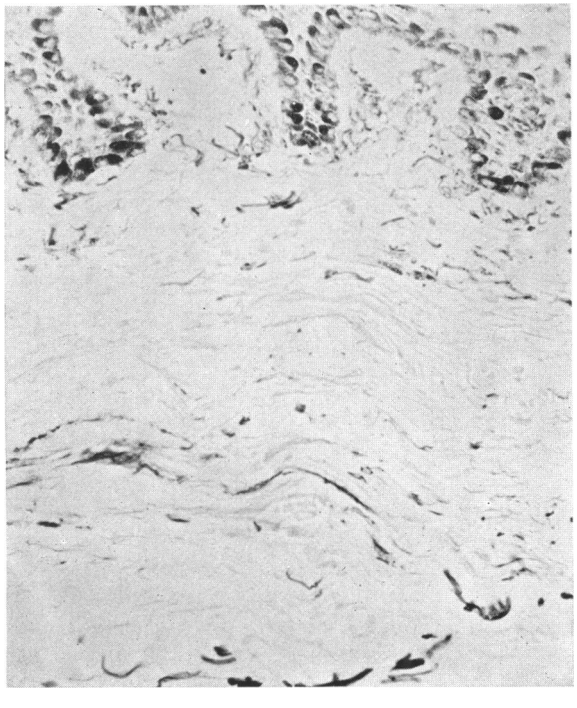


FIG. 7. Serial No. 494
(Same subject as in Fig. 4: man aged 24 years)

Individual density figure: 31.

Subepithelial elastic remains but is absent in those areas where papillation of the epithelium is defective. Although not shown in the picture, the internal elastic lamina was either deficient or ill-staining in all affected vessels. The dermal elastic is markedly defective, and the tissue is almost avascular.

All biopsy specimens taken from the thigh 30 cm above the patella.

same conclusion as we have done in the case of the skin lesions of onchocerciasis—namely, that the lesions are not allergic. These workers also noted the attraction to the spot of eosinophil leucocytes. Although the lesions in onchocerciasis might be regarded as allergic since they represent an exaggerated host response, further study is required and further evidence is necessary to prove it. This is a vastly different point of view from the generally accepted one.

At this stage the possible role of vitamin A must be discussed, especially in connexion with the development of the cutaneous nodules and the spread of the embryos throughout the skin. Concerning these points there is very little evidence (Rodger, 1957b), at least as far as *Onchocerca volvulus* is concerned. In the eastern region of Nigeria, where there is a plentiful supply of red-palm oil, and where the daily intake of vitamin A as measured by the Department of Nutrition amounts to 12 000 IU (which under any condition or stress is an extremely high intake), there is endemic onchocerciasis but very little blindness. Nevertheless, the infectivity rate was found to be extremely high, as high as 75% in some villages. By taking skin biopsy specimens from the conjunctiva down the body to the ankles it was found that there was hardly any instance where the conjunctiva had been invaded and in fact very little invasion above the chest. Obviously, then, one would not expect to find many cases of ocular onchocerciasis in such circumstances. In the face of this, one would have said that these people were not suffering from a dense infection, and yet the strange thing was that the average number of nodule sites (which is a rough index of the density of infection) was more than twice as great as that of the northern territories of Ghana (where the vitamin A intake is low), although it has been established in Ghana that the incidence of blindness due to onchocerciasis is extremely high. The possibility exists that it might be vitamin A which gives rise to this situation, promoting the body's defence against the invasion of the adult parasites by assisting to encapsulate them and at the same time in some unknown way, probably related to cellular nutrition, preventing the embryos from spreading freely. This ties up well with the increasing number of reports indicating that blindness from onchocerciasis is a problem of *unfertile* endemic areas and that in fertile areas onchocerciasis does not cause much blindness, although, of course, there may be another explanation of this. Now this may sound a somewhat fanciful story, but there is a lot of experimental evidence in support of such a view (Moore, 1957). Le Gallic (1955) has shown that when rats deficient in vitamin A are fed livers of animals not deprived of the vitamin there is a definite improvement in the rats' condition, but that when livers from animals suffering from helminth disease are fed to the deficient rats their condition remains unchanged. Soliman (1953) found low liver reserves in cattle with lungworm; in guinea-pigs infected with *Dictyocaulus viviparus* the reserves averaged 2.5 IU per g compared with 23 IU of vitamin A in healthy animals. In India it has been shown that hookworm reduces the vitamin A content in man to below 100 IU% in the majority of cases and even more greatly reduces the carotenoid values (Rodger, Dhir & Hosain, 1960). Moreover, 8 out of 38 subjects investigated and found infested with hookworm had raised light thresholds (although the vitamin A values in all 8 were not very low)—a state of affairs not found in patients with roundworm nor in the large group of control subjects with healthy eyes who were investigated as part of this study. All this suggests that not only can the vitamin A status be affected by parasites but so can the light thresholds. On the alternative side—that the activities of the parasites can be affected by vitamin A status, the two being complementary, of course—Clapham (1933, 1934) found that in rats the intensity of infestation with *Parascaris equorum* was increased by a deficiency of vitamin A. Thus in deficient rats larger numbers hatched and migrated and the rate of development was more rapid than in rats supplied with vitamin A supplement. This author concluded from his different findings that the vitamin A status affects the course of infestation when the parasite comes into close contact with the tissues. This would apply especially well to onchocerciasis. Although there is also contrary experimental evidence, it is clear not only that parasites can reduce vitamin A but also that in the presence of a reduced vitamin A status the parasites multiply at an increasing frequency. The converse—that with plenty of vitamin A the parasites are prevented from spreading—has also been shown to be true. It is an interesting observation, then, that in many areas of Nigeria where there is a lot more vitamin A in the diet than is usual in Africa the skin is healthy despite infestation with onchocerciasis and the number of nodule sites at least as great as, if not greater than, in areas where the skin is unhealthy and the vitamin A intake much lower. Every year more evidence comes

to light which shows that in fertile areas onchocerciasis does not affect the eyes nearly as much as it does in unfertile. A possible nutritional factor cannot be ignored in the circumstances.

OCULAR ONCHOCERCIASIS

Review of symptomatology

Recently it has been claimed that all the onchocercal lesions of the anterior and posterior segments of the eye can be acute (Rodger, 1957a). Up to 1957 it was believed that this occurred in the case of the external eye only; uveal changes were always described as being insidious and chronic in accordance with the early descriptions of Hissette (1937). Thus, any acute iritis (or uveitis), even if present in an onchocercal area in a patient suffering from onchocerciasis, was categorized as being due to endogenous bacterial infection of some sort or another—never to onchocerciasis. Yet, when one thinks of it, the acute changes in the skin should have suggested that an acute change in the eye probably occurs as well, for the eye (and the uvea in particular) closely corresponds to the skin in its reactions to disease. Moreover, a filaricide such as diethylcarbamazine produces an acute reaction in the eye as well as in the skin. Why, then, can an acute eye not occur in the normal course of the disease? We now know that if dead microfilariae are placed deliberately in the skin there will be an immediate acute reaction; and we also know that this is true in the case of the eye as well (Rodger, 1960). Details of these experiments will be given when the pathogenesis is discussed. If that is not enough to convince us that ocular onchocerciasis goes through an acute phase, biopsies of iris in acutely inflamed eyes exhibiting anterior uveitis have been made several times and in every one dissection of the fresh iris tissue under the microscope revealed parasites identified subsequently as *Onchocerca volvulus*. On the face of this evidence there should be no doubt now that ocular onchocerciasis can be, and often is, an acute condition. Animal experiments in the paper mentioned above suggest that the acute phase does not last very long; in fact, in rabbits it dies down in two or three days. It has been said that the cells which are present in such eyes (lymphocytes) are those associated with chronic infections, but any pathologist will say that these cells, although categorized as chronic in type, are frequently associated with diseases which are clinically acute. Thus, as far as the anterior segmental lesions of onchocerciasis at least are concerned, the condition would appear to be acute in the first instance, becoming less acute with subsequent attacks until no reaction remains. It seems probable that after the death of microfilariae the dissemination of the toxins, which emanate from the dissolving bodies of the parasites, will take some time; in this way there will be a much longer period where the clinical condition will be subacute and finally chronic. This is the most common picture. It is logical that this chain of events (an acute attack fading into chronic with remissions and recrudescences of decreasing severity) occurs in lesions of the choroid as it does in the case of the cornea and conjunctiva and sclera and iris. Experimental and pathological evidence will be introduced later which supports these statements. It must not be forgotten when describing the symptomatology that as a result of the initial acute attack the filtration angles are likely to become blocked with exudate and cells and a secondary congestive glaucoma follow as yet another acute complication. This is quite common.

Another important recent controversy concerns the clinical appearance of the posterior segmental lesions. The claim by Rodger (1958) that there are two kinds of posterior lesion, one degenerative and the other an inflammatory posterior uveitis developing into a chorioretinitis, caused by the death of the microfilariae in the posterior half of the uvea has not yet been widely accepted. The latter lesion is very often but not always associated with an anterior one; the former, the degenerative—a different type of lesion altogether because no parasite can be found in the posterior half of the eye—has only seldom been reported in association with an anterior lesion; clinically it is not an inflammatory condition at all.

First, let the symptomatology of the inflammatory type be described. As this condition in the beginning is an acute one, it is associated with vitreous haze. Moreover, it invariably has followed, or is accompanied by, an onchocercal keratitis or iritis; thus it is not surprising that such a lesion has seldom been observed at such a stage in the posterior segment, so difficult is it to see. When the acute phase dies down, on the other hand, provided the corneal, anterior uveal or lenticular changes still permit a view of the fundus, the posterior changes can be seen with the ophthalmoscope. It is a non-specific picture of a kind that would follow any exudative chorioretinitis. However, and this is a very important point, as we saw when studying the histology of the

skin, the blood vessels appear to be particularly liable to become affected by the toxins originating from the dead microfilariae and so inevitably there follow occlusion and fibrosis of the choroidal vessels; in other words, a choroidal sclerosis is the usual end-picture. Thus, patches of old healed chorioretinitis of all shapes and sizes can be seen in the late stages, patches in which sclerosis of the choroidal vessels is a feature. This sclerosis may or may not affect the whole choroid; it sometimes does. The bilaterality (and it is not always bilateral) is unremarkable, because we know both eyes are invariably invaded simultaneously by *O. volvulus*. The keratitis after all is invariably bilateral and quite often equal. Clearly, then, when the lesion is viewed in the late stages it will be difficult to diagnose the exact cause with certainty.

It is tempting to think that all lesions of the posterior segment related to onchocerciasis can be subdivided as simply as this into the inflammatory type just described with its various intermediate appearances and what might be called the " Ridley fundus ", i.e., a bilateral *central* choroidal sclerosis (Ridley, 1945). Because of its doubtful origin, the term " posterior degenerative lesion of onchocerciasis " was used for the latter by Rodger (1958). Contrary to Ridley's description, he found it was not always confined to the central part of the posterior fundus, nor always bilateral and equal. Sometimes it extends to the periphery and affects one eye and not the other. An experienced ophthalmologist should be able to distinguish a secondary choroidal sclerosis (following the chorioretinitis of onchocerciasis) from a primary, except perhaps in the aged; in the case of the posterior degenerative lesion the appearance is that of a *primary* choroidal sclerosis. The edge of the lesion is always clear-cut, punched-out, circumscribed. On one side there is healthy retina (apart from slight re-orientation of pigment inside the retinal pigment epithelium), and on the other, one cone diameter away, there is degenerate retina consisting of an intact membrane of Bruch, a degenerate pigment epithelium, atrophy of the rods and cones, an inner nuclear layer reduced to one or two cells thick and gliosis. The condition has been found at puberty on more than one occasion, so it seems to start early. At least one of the stigmata of onchocerciasis has always been discovered in patients exhibiting the degenerative lesion. On epidemiological grounds, therefore, there is very strong evidence that this disease is connected with onchocerciasis. It has never been reported in any area of Africa where onchocerciasis does not exist. Despite this, Choyce (1958) raised the possibility that the lesion might be an inherited one. He agrees with the view that Ridley's description does not go far enough and that there are two types of lesion, but both he considers are examples of a familial choroidal sclerosis; the central he called " recessive " the general, dominant '. D'Haussy,[1] in reply to Choyce, said he found no evidence of a genetic origin although he had examined fifty families in each of which some members exhibited the lesion; but then D'Haussy had not at that time seen the pathological evidence, which will be given shortly, and considered that all types of lesion in the posterior segment were but variations of the same disease. This view may be the correct one; but if it is wrong, and the two-lesion theory correct, then D'Haussy may have investigated only families exhibiting the inflammatory type of posterior lesion, which is much the more common, and which, of course, cannot be linked to a genetic origin. It is surprising that Choyce selected the *central* type of choroidal sclerosis seen in onchocerciasis as a genetic lesion. Sorsby & Wren (1960) point out that the onset of the latter condition is at about the age of 20 years. They add that deterioration is slow and the classic picture does not develop until about the age of 50. This does not fit the facts. Moreover, the affection is usually recessive yet the posterior degenerative lesion, even when restricted to the central area of the posterior segment, although not as common as the inflammatory, runs into many hundreds of cases at least; this does not sound like a recessive disease. Furthermore, this familial type of abiotrophy does not spread to the periphery of the fundus and there is no doubt that the posterior degenerative lesion can.

On the other hand, the second type of inherited abiotrophy Choyce selected, " a *generalized* choroidal sclerosis ", corresponds very closely to the facts. This genetic condition usually starts centrally at the macula. It commences in childhood but vision remains good until about 30 years of age, when it can be seen as a central choroidal sclerosis. After that it tends to spread towards the periphery. It has a dominant characteristic. This picture, it must be admitted, is reasonably close to that of the posterior degenerative lesion seen in broad perspective provided one excludes those cases of *secondary* choroidal sclerosis which have followed inflammatory onchocercal chorioretinitis.

[1] Personal communication, 1959.

In those rare cases where bone corpuscle pigmentation is found surrounding the periphery of an area of choroidal sclerosis, although this too may follow inflammatory lesions of the posterior segment of any kind (and frequently does, as in syphilis), it may also be a primary abiotrophy. The infrequency of this condition suggests a recessive genetic mode of origin, and this lesion should probably be re-investigated with that in mind.

In a way many of the points raised in this section might have been better discussed with the pathology or pathogenesis of the posterior lesions. Sorsby has said in a letter quoted by Budden (1958) " if we are to sort out whether these cases are due to onchocerciasis or are genetic in origin, we shall not get much further by looking with the ophthalmoscope ". But that is not to say, nor, of course, has Professor Sorsby said it, that the clinical descriptions of men like Bryant (1935), Hissette (1937), Ridley (1945), Toulant (1956) and the many other pioneers are of no value.

Review of the pathology

More and more eyes are being obtained for microscopic investigation; yet up to 1955 it seems that the pathology of the ocular lesions of onchocerciasis had been based on only about ten or twelve whole eyes, the bulk of the findings being gleaned from biopsies. The grosser pathology of ocular onchocerciasis is fairly well established now, although not as well as that of the skin. We need in the case of the eye more precise evidence on several points. It is important, of course, for eyes to be obtained by operation rather than from cadavers at post-mortem examination. There should in addition be a standard method of treating these eyes. For example, two hours in fixative is quite long enough for an eye in the tropics. Another technical point which was described in a paper by Rodger, Grover & Fazal (1961) further emphasizes the need for some kind of uniformity in exchange of information on pathological technology. It was noted there in a vitamin A deficiency study on monkeys' eyes that when sections were left for some months in alcohol in light, the residual picric acid from Bouin's fixative tended to bleach the pigment. It was also observed that the process of bleaching was expedited by the Mallory phosphotungstic acid technique especially when the stain had been oxidized by potassium permanganate instead of being left to ripen on its own. The suggestion was made that unstained sections should be mounted at the outset so that any subsequent bleaching of the pigment that might be due to artefact could be assessed when the stained sections were finally examined. This seems an admirable precaution at all times, not just only when investigating the pigment of the eye.

There have been three papers (Hissette, 1937; Hawking, 1952; and Rodger, 1959c) which have attempted to describe some of the fundamental points in the pathology surrounding *O. volvulus*. The microfilariae show changes comparable with, although not exactly similar to, autolysis of any cell body. When the parasites are stained with Mayer's haemalum and the nuclei are revealed as being well stained then there is little doubt that these parasites were alive at the time the material was obtained. Subsequent events appear to fall into four categories. The first change results from an increased affinity of the soma to the stain (somatic staining). Next the nuclei become indistinct, the difference in colour intensity between them and the soma becoming less and less until the whole stains uniformly. During this stage the shape of the parasite alters; it becomes irregularly swollen, ballooning like the body of a caterpillar. Next the body breaks up into fragments, which Hawking (1952) considers are fragments of extruded nuclei. This latter stage appears to occur very abruptly. Finally in proportion as the fragments become smaller and fewer the surrounding tissues stain diffusely blue. This blue stain, which one assumes is due to the diffusion of what remains of the parasite body, lingers on for a while until as a result of absorption nothing remains to be seen at all. The cellular infiltrates found associated with the different stages have also been described somewhat variously. Hissette (1937) observed stages 1 and 2 only. Hawking (1952), following the effect of diethylcarbamazine on infected skin at 18, 23, 48 and 120 hours, described how at first there were diffused areas of inflammation in which great numbers of neutrophil polymorphonuclear leucocytes could be seen centred around dead microfilariae only to be followed at 23 hours by the appearance of eosinophils and lymphocytes and fibroblasts. He also noted that after 48 hours fragmentation of the parasites had occurred, there being many tiny nuclear pieces among the cells by that time, the pieces apparently persisting for at least five days. Rodger (1959c, 1960), investigating microfilarial changes in the cornea, found eosinophil leucocytes present close to the parasite body as soon as somatic staining occurred. He did not note the presence of neutrophil polymorphs in any abundance at all, so apparently they either disappear quickly from the

scene or are present only when a massive number of parasites are killed under diethylcarbamazine therapy. With fragmentation of the parasite the number of eosinophil leucocytes increased enormously and many round cells were also added. Finally a somewhat variable picture was noted, no doubt depending upon the time at which stage 4 was observed; sometimes eosinophil leucocytes were in the majority, sometimes fibroblasts; plasma cells and lymphocytes had also increased in number in the later stages and at times were more common even than the eosinophils. Clearly on examination of the eye of an infected subject many of these stages will be found overlapping. Nevertheless, when these patterns are found at all in the eye of an onchocerciasis subject, whether any living microfilariae are discovered or not, they must be of the very greatest assistance to the microscopist. It should be noted here that none has been observed in posterior degenerative eye sections. In his paper, Rodger (1959c) demonstrated after studying several eyes that the parasites were able to reach the eye most easily from the conjunctiva of the lids and in this way passed into the anterior segment of the eye. From the outer coats of the anterior segment microfilariae were found passing between the epithelium of the cornea and Bowman's membrane; they were also found passing in a posterior direction through the corneoscleral junctional fibres to the angle of the eye whence they could be followed into the uvea or the corneal stroma. It seems likely that when the microfilariae reach the angle of the eye they will also be able to break through the ligamentum pectinatum quite easily, and if present in the iris they will equally readily be able to break through the fine anterior endothelium to enter the anterior chamber. The passage of *O. volvulus* down the adventitial sheaths of blood vessels was also demonstrated in this paper, particularly *via* the perforating anterior ciliary vessels and those at the equator. It was suggested, although not demonstrated, that when the orbit is invaded, as undoubtedly it must be in heavy infections, the parasites may also pass up the sheaths of the posterior ciliary vessels and in this way invade the posterior coats of the eye from behind; logically they might also enter the optic nerve directly *via* the sheaths of its nutrient vessels. It was in the course of these intensive microscopic studies that Rodger found *O. volvulus* in the retina. The parasites appeared to have reached the latter structure by forcing a passage through the pigment epithelium, for there was evidence of such a breakthrough in the sections. There was no sign, however, of a break in the continuity of the membrane of Bruch, although many hundreds of serial sections were examined; so, apparently, they must either break into the retina from the ciliary body between the pigment epithelium and the cuticular lamina of Bruch or pass up the sheaths of the retinal vessels, or break into the retina from the vitreous.

Passing from these original studies concerning the morbid anatomy and intraocular movements of the embryos to the ocular pathology itself, one finds that most of the recent work has been on the posterior segmental changes. This is largely because the anterior changes are much better known and understood; thus, there is no need to enlarge on the anterior changes in this review.

Lavier and his colleagues (1956) examined an eye which exhibited chorioretinitis in a subject suffering from onchocerciasis. They stressed the presence of vascular changes of the choroid as well as similar changes found in the retina and optic nerve. They said that these changes were caused by toxins, although they found no microfilariae in this eye. A possible reason for this in the light of what has been said already about the symptomatology of the posterior segmental changes is that they were dealing with a case of the posterior degenerative lesion. In view of the vascular changes found in skin sections in Oxford, it is interesting to read in this paper that the authors considered the vascular changes (including those in the optic nerve) were due to circulating toxins. Ridley (1957), on the other hand, believes that optic atrophy does not follow a toxic effect on the nutrient vessels of the nerve but is a natural progression following the death of the nerve cell bodies in the retina. He does not seem to believe in a primary onchocercal optic atrophy. Lagraulet (1957) carried out an interesting experiment on rabbit eye. He implanted a nodule in the orbit and claimed that in the vicinity chorioretinal lesions developed similar to those found in man; this study is of somewhat doubtful value as the changes demonstrated were not specific and it seems quite likely that the reactions of the eye of rabbit to a nodule taken from man would be a chorioretinitis of this type whatever the nature of the foreign protein used. Lagraulet and his colleagues (1957) also described the clinical and pathological findings in three patients exhibiting the typical anterior and posterior segmental lesions of onchocerciasis. Once again in these cases, although the anterior changes were pronounced, they found no parasites in the

posterior half of the eye. These eyes might well repay further study, concentrating on the infiltrates. The authors compared the material with an eye enucleated by Giaquinto in Guatemala in 1933 (Giaquinto, 1934), on which they carried out a detailed examination. In this eye healthy microfilariae were present in all the tissues including the optic nerve. They emphasized that the microfilariae they saw in this eye were healthy and had not apparently excited any inflammatory reaction in their vicinity, which is, of course, a well-known fact now. The French authors are clearly reluctant to conclude that the posterior lesion in their three cases was not due to onchocerciasis despite the absence of microfilariae in the posterior half of the eye; they say the lesions might have been produced by the presence of dead worms or embryos which presumably had become absorbed by the time they came to examine the eye. Thus this group of French workers is firm in its belief that a toxin emanating from the parasites and acting primarily on the vessels of the choroid is the cause of the posterior segmental lesions. They may be right. But if so, it is none the less an inflammation, and as the pathology of the *degenerative* type of lesion is non-inflammatory, it seems they should accept the postulate that there are two types of lesion. It will be noted that in none of these papers was any distinction made between the two types of lesion either before the eye was obtained or after, which is a pity. In his 1960 monograph on the subject, Rodger described the microscopic appearance of ten eyes, five exhibiting the inflammatory chorioretinitis and five the degenerative, all ten of which he had examined with the slit-lamp and ophthalmoscope before excising. In addition he obtained three other eyes in which the fundi could not be seen, so great was the involvement of the anterior segment, yet all three of which were subsequently discovered to exhibit microscopic changes characteristic of a non-specific chorioretinitis with many living and dead microfilariae present in the posterior segment.

The fundamental pathological changes in the case of the inflammatory type of lesion are great congestion of the choroidal vessels with their ultimate closure as a result of fibrosis, and violent pigmentary disturbance. In the acute stage a cellular exudate is found between the choroid and retina and even on top of the retina with parasites sometimes present within it. The optic atrophy that was present in these eyes was secondary in type and in two was associated with glaucomatous cupping where the filtration angles had been involved in the anterior segmental lesion. Here and there patches of the retina had become involved in the inflammatory process and as a result the retinal layers had disappeared locally, what was left being bound down closely by glial tissue to the underlying infiltrated uvea, Bruch's membrane having dissolved. In other eyes examined outside this series of ten, eyes exhibiting anterior segmental lesions and excised to study the latter, a few chronic inflammatory cells were present in the posterior uvea with or without living microfilariae; in others, uveal infiltration was marked and in yet others living parasites were present without there being any infiltration at all. These findings are perfectly easy to understand; they underline the chronological and topographical chain of events leading up to the development of the inflammatory chorioretinitis of onchocerciasis. Rodger called it an exudative posterior uveitis because he believed the trouble started in the uvea.

In the five eyes which exhibited the posterior *degenerative* lesion, the underlying pathology was quite different from all this.[1] To begin with, there was no sign of any true inflammation, no exudate or residual exudate, nor were there any parasites in the eyes. In some a series of 18 skin biopsies was negative, and only the presence of a nodule revealed that one was dealing with onchocerciasis. More important still, no signs of any of the four stages characteristic of the dissolution of the embryos could be found. In this lesion the outstanding changes were choroidal sclerosis and depigmentation, not congestion and pigmentary aggregation. This is not to say that there was no evidence of depigmentation in the inflammatory type; there was some, co-existing with aggregation; equally in the degenerative there was slight aggregation. The optic nerve head in the degenerative lesion was never cupped as a result of secondary glaucoma, although atrophic cupping was common. The clear-cut margin already described as characterizing this condition was even more striking under the microscope.

It is strange in view of these differing pathologies that there still appears to be some diffidence in accepting the fact that we are dealing with two

[1] Budden (1962) states that "the term inflammatory choroidal sclerosis [presumably 'post-inflammatory' is intended] reflects *the usual histological findings* [my italics] more accurately" than the term "choroido-retinal degeneration". An analysis of the eyes examined which was given in the monograph by Rodger (1960) shows that this appears to be an inaccurate statement so far as the usualness of the findings is concerned, when all the pathological literature available is analysed.

lesions. Unfortunately we do not have any information concerning the pathology of the genetic lesions of the posterior segment of the eye which Choyce believes these conditions to be. In fairness to him, it must be said that they are not likely to differ very much from the pathology of the degenerative lesion just described. On the other hand, the microscopic appearance of the posterior inflammatory choroidal sclerosis (observed with the ophthalmoscope before the eyes were excised) does not resemble any genetic lesion, not even in advanced cases where the inflammation has died out, for in them the disseminated inflammatory scarring is characteristic.

As vitamin A deficiency has been suggested as a co-factor in the development of the posterior degenerative changes (Rodger, 1958), a brief word is indicated summarizing the literature which supports this possibility. Tansley (1933), Johnson (1939, 1943), Ramalingaswami and his colleagues (1955) and Dowling & Wald (1958) have all reproduced degenerative posterior fundal changes in animals suffering from xerophthalmia. Here there are gross changes in the retina which consist of pigmentary disturbance and atrophy of the neural elements. The changes in the deficient monkey eyes investigated by Ramalingaswami and his colleagues (1955) also included choroidal sclerosis, although this finding was noted after publication.[1] Although in all these studies xerophthalmia co-existed, and gross changes in the posterior half of the eye might be expected, the findings do indicate that vitamin A deficiency, albeit a severe one, can lead to posterior changes as marked as those we are discussing. In a recent study by Rodger, Grover & Fazal (1961) vitamin A deficiency was induced in three *Macaca rhesus* monkeys which were shown to be nightblind by means of a dark adaptometer especially designed for the purpose (Rodger, 1959b), the experiment being terminated before any of the animals exhibited anterior changes. At the end of 45 weeks, when these monkeys were sacrificed, their dark adaptation being demonstrably impaired, the fluorescent microscope revealed an absence of vitamin A from the liver and there were very low blood values. All the retinas showed a re-orientation of the pigment in the retinal pigment epithelium, the pigment granules having withdrawn into the cell bodies so that the nuclei were concealed. These changes do not correspond to those we have been discussing in man but one cannot help wondering whether similar changes might not have occurred if the circumstances had been only slightly altered. The changes in the posterior degenerative lesion of onchocerciasis are, in fact, intermediary between those slight ones reproduced by Rodger, Grover & Fazal and those of other groups of workers where the deficiency was gross and caused a coincident nutritional xerophthalmia. Thus, as far as the pathology of the degenerative lesion goes, we must admit we cannot dismiss outright as impossible the suggestion that vitamin A deficiency may be a factor.

A most interesting parallel can be drawn between human eyes and the eyes of horses suffering from onchocerciasis (Heusser, 1948, 1952). Cello and Roberts are at present working in Vienna on this same condition. Cello [2] says that he has confirmed the accuracy of the descriptions of the various cellular infiltrates relating to the stages of dissolution of microfilariae in the eye. All the lesions found in human onchocerciasis seem to occur also in horses. The eyes examined to date have all exhibited various stages between acute iritis to the blind eye where the iris has atrophied, the pupil become occluded and the posterior uvea involved in the inflammatory process. Cello also says in his letter, " We were quite surprised to find microfilariae presumed to be *Onchocerca* in the very first four affected eyes which we sectioned. All eyes had corneal lesions which appeared to be identical in their pathology to those described in man and rabbit ". Posteriorly, Cello adds, the picture was somewhat different. Small focal areas of chorioretinitis were scattered over the fundus (not one patch). Microscopically, these appeared to be small granulomas bounded by large numbers of eosinophils in the adjacent choroid. Parasites were not found in any of the granulomas but remnants of microfilariae were found in the neighbourhood. Dr Cello concludes in the following way: " Later we hope to explore the idea that one of the causes of recurrent uveitis in horses is a hypersensitivity to pigment initiated by the reaction of uveal tissue to this parasite ". This letter shows what unknown fields in the realms of animal onchocerciasis are being explored at the moment.

Review of the pathogenesis

Budden (1957) concluded after his ophthalmic surveys in Northern Nigeria that the incidence of anterior uveitis, keratitis and optic atrophy was related to the intensity of human infection, whereas

[1] Personal communication, 1959.

[2] Personal communication, 1961.

the incidence of the posterior segmental lesions appeared to be more closely related to the presence of infection rather than to its intensity. From this fact he assumed that although anterior segmental lesions and inflammation of the optic nerve resulted from a direct invasion of the eye by microfilariae, the posterior lesions involving the choroid and retina were more likely to be due to a circulating toxin. Kershaw (1958) conceded that the density of infection (as measured by the method devised by Kershaw, Duke & Budden, 1954) indicated that the anterior segmental lesions were closely correlated with the density of infection and at the same time concluded that the posterior lesions were not. Budden has challenged this statement. Using the method of assessing the density of infection suggested by Rodger & Brown (1957), Rodger reached much the same conclusion as Kershaw as far as the degenerative type was concerned. In the method of assessing the density of infection referred to above, by equating the figure obtained with ocular lesions it was observed that where the cornea and iris were involved the individual density figure (IDF; see below) was high, with the exception of superficial punctate keratitis in which the figure was on average half as low again (suggesting that this lesion is not nearly so commonly due to invasion and death in the cornea of parasites as most workers seem to believe). Many of the posterior segmental lesions which were considered to be inflammatory in type exhibited very high individual density figures; on the other hand, the posterior degenerative lesion, as has been mentioned already, was associated with extremely low densities of infection in the individual. The method of assessing the individual density of infection which Rodger & Brown devised is easier to perform than Kershaw's and has several useful features. The method gives an index of the degree of infestation in the individual. Biopsy specimens of equal surface area (obtained by stamping on the skin) are taken from the left or right side in each of five sites (the calf, thigh, chest, neck and conjunctiva), being repeated on the opposite side if found negative; the process is repeated on each site, except the conjunctiva, if both sides are found negative. Thus a maximum of four biopsy specimens is taken on each site except the eyes, where the maximum is two, so for any individual a minimum of five and a maximum of 18 specimens might be taken from all sites. One positive biopsy is sufficient to establish the presence of infection in a site and each infected site scores marks which increase as one moves up the body from the ankle to the eyes. The individual density figure is then defined as the sum of the scores. It was estimated statistically that by this method the chance of missing an infected site does not normally exceed 1 in 250. The possible scores include every integer from 0 to 31, each corresponding to a particular combination of positive and negative sites which can be read off at a glance from the published chart. Another useful characteristic of the index is that the higher the infection is in the body the higher is the score, indicating the greater probability of ocular invasion.

Whatever method one chooses of assessing the density of infection they all have limitations in determining the pathogenesis of any particular lesion. Epidemiological factors, although of no little importance, also have their limitations. Experimental evidence is what is lacking. There is little doubt now that the dead bodies of *O. volvulus* act as chemical poisons. Animal parasites are frequently living irritants acting by virtue of toxins which they excrete or by the mechanical irritation they excite. Neither the adult nor the embryo worms appear to come into this category until death; in life both appear to be well adapted in the case of *O. volvulus*. It is after the embryos die that the products of their dissolution cause a violent, if brief, reaction; the subsequent dilution and dispersal of the toxic products by the tissue fluids lead to a long-drawn-out chronic phase. As the process of tolerance sets in, as Rodger (1960) demonstrated in rabbit and man, subsequent microfilarial deaths lead to less and less severe acute attacks but, of course, prolong the duration of the chronic irritation, For the greater part of the course of this disease, therefore, the toxins act more as stimulants to growth than as necrotizers, different cells being stimulated to varying extents. Thus, initially, although we have a violent destructive lesion, it is quickly followed by more insidious changes as the mechanism of repair ironically enough furthers those processes which lead to blindness, unless immunity or partial immunity—that is, tolerance—intervenes. There are many examples of this in veterinary literature, such as the work of Jarrett and his colleagues (1959). They showed in calves that an infection with *Dictyocaulus viviparus* confers a high degree of resistance to a subsequent reinfection, and that this acquired tolerance can result from a single infection with a sublethal dose of larvae or from a series of repeated doses of smaller numbers of larvae. This is just what Rodger demonstrated in his field laboratory

in 1955-56 in rabbit and in man with the larvae of *O. volvulus*. When a noxious dose of microfilariae (about 40) was injected under the conjunctiva in non-infected human subjects, it produced a violent local reaction; this state of affairs did not occur in subjects who appeared to be immune because, although the parasites were present in great abundance in their eyes, there was no sign of any lesion. This seems to be an original observation of the very highest importance. It shows that the development of a complete or a partial immunity in onchocerciasis is a fact. This experiment also explains why so few people are blinded out of the many millions whose eyes are invaded by microfilariae.

The pathology which reveals vast numbers of plasma cells and lymphocytes following the acute reaction strengthens this view. Boyd (1947) believes that both plasma cells and lymphocytes are concerned with the development of a complete or partial immunity, and in ocular onchocerciasis these cells are present in abundance from early on. The fact that a state of allergy to the dead bodies of microfilariae has not been demonstrated, by either active or passive transfer, in the skin or in the eye, does not necessarily weaken this thesis. There is no question that the reaction in the eye of a non-infected rabbit, as in the eye of a non-infected man, is a very violent one; nor is there any doubt that subsequent reactions with equal numbers of parasites are never greater and very soon become lesser. This suggests that it might be possible to confer immunity by administering dead larvae, possibly after treating them with X-irradiation. Whole-worm vaccine is not so likely to be effective, and hyperimmune serum would be difficult to collect. *O. volvulus*, on the other hand, can be obtained in abundance by excising nodules, a procedure we know is acceptable to the majority of the people in the endemic areas. Jarrett and his colleagues (1960b), in the third of their fascinating studies on *Dictyocaulus viviparus* in calves, describe the high degree of immunity obtained by administering third-stage larvae partially inactivated by X-irradiation. If a rapid anamnestic antibody response can be demonstrated in *O. volvulus* infections, it might be advisable to investigate the protective effect of vaccinating twice with irradiated larvae before challenge.

Mr Pierre Arquembourg, in an unpublished memorandum submitted to the World Health Organization in 1959, presented a very comprehensive immunological plan. He suggested that an attempt be made to establish routine laboratory tests by using a substitute antigen, as, for example, *Dirofilaria immitis*. This would be invaluable in supplying indirect evidence that onchocerciasis had been present in cases where skin biopsies were negative, as in the case of posterior degenerative lesion subjects. It would also permit a rough qualitative assessment of the degree of immunity existing. It would, of course, be a great step forward if we could cultivate a reference strain or strains of *O. volvulus* from man in some laboratory animal or in a suitable culture such as human skin. This would be particularly useful in finding a suitable form of chemotherapy. We know that the ox and the horse are potential reservoirs; we could investigate the truth of this, Arquembourg suggested, by cross-immunity reactions in, say, rabbit sera. We could also demonstrate the possibility that an immunological reaction is responsible for the apparent tolerance seen in so many subjects infected with *O. volvulus*, no doubt by a method based on quantitative serology. We could also look for precipitins in the aqueous and vitreous in man's eye, as well as for antibodies in the ocular tissues in infected man and animal; and in all these experiments we should consider the possible role of the embryos as compared with the adults.

There remains, as far as ocular onchocerciasis is concerned, one major uncertainty—that is, the pathogenesis of the posterior degenerative lesion. We have its pathology in several eyes and the clinical picture seems to fit this pathology. Although the posterior degenerative lesion is the one ocular manifestation of onchocerciasis which all would like to reproduce in experimental animals, no one to date has succeeded in doing so satisfactorily. Nevertheless, the epidemiological findings very strongly support the view that this lesion is due to onchocerciasis. To some extent, in the case of the generalized choroidal sclerosis which follows a posterior inflammatory chorioretinitis, sufficient attention has not been paid to those papers, such as that by Strong (1934), which indicate that the vessels are involved in the pathological processes surrounding the dead parasite bodies. The sclerosis of the skin capillaries in onchocerciasis which is reported from Oxford strongly suggests that a choroidal sclerosis is a very likely happening when the parasites die in the posterior uvea. It does not seem likely that in the posterior degenerative lesion, if it does result from the death of microfilariae, the skin and eye would be sterile and that there would be no pathological evidence to support the obvious etiology. Its patho-

genesis remains unexplained. Is it a genetic lesion? Is it just another example of a reaction due to the death of parasites in the posterior uvea, perhaps the sort of thing that occurs when only a few parasites die in that situation? Or is it the type of inflammatory lesion that occurs around the bodies of a few microfilariae which have entered the eye by the sheaths of the posterior ciliary vessels? Is it due to a toxin emanating from the adult worms, as some workers have suggested? Does vitamin A play a part in its production? D'Haussey, in his personal reply to Choyce's arguments that this lesion was genetic, shrewdly points out that the territory in which he worked had a population of several million people of which only a small part was affected by onchocerciasis and that if these posterior lesions, the central type being lumped together with the general, were independent of, or unconnected with, onchocerciasis one should surely have observed them in larger numbers in the non-onchocercal areas; but he never did. This is the sort of argument which is unanswerable. Clearly the bulk of evidence opposes Choyce's view that this lesion is genetic. Choyce would have had a stronger case if he had not gone too far in his paper by stating that onchocerciasis is not a serious cause of blindness. We know this is incorrect.

The high incidence of blindness due to onchocerciasis is not just reflected in local parish registers or field surveys. It is supported and underlined by statistical assessments made by the Royal Commonwealth Society for the Blind in more than twenty tropical territories previously under British administration. Here an attempt was made with the assistance of the local medical services to indicate the major causes of blindness in each territory. Cataract and trachoma were the most frequent causes, but the highest rates of blindness were found where onchocerciasis was also known to be present. A rough generalization would be that where cataract and glaucoma are the main causes of blindness, as in the West, a rate of from 200 to 500 per 100 000 is usually found. Where trachoma is also widespread the rate is likely to be between 500 and 1000 per 100 000, and wherever in Africa the rate exceeds 2000 per 100 000 then onchocerciasis, or some exceptional local condition, is likely to be present. This appears to be the final answer to those few who have attempted to minimize the importance of onchocerciasis as a cause of blindness.

One final point in relation to the pathogenesis of ocular onchocerciasis remains, and that is the suggestion that vitamin A is in some way involved in its development (Rodger, 1958). This is a reasonable hypothesis in view of the normal relationship of vitamin A to the metabolism of the retina, in view of the known shortage of vitamin A in large regions where onchocerciasis is endemic, and in view of the dissimilarities to other onchocercal lesions. Moreover, there is no doubt that massive doses of the vitamin produced varying degrees of visual improvement in a few subjects exhibiting the early changes typical of the degenerative type of lesion (Rodger, 1958). Nicol (1958) has pointed out that the people in the areas in which this study was carried out were having a reasonable dietary intake of vitamin A and could not be depleted. However, the characteristic stigmata of vitamin A deficiency were observed among a few of these same people and the blood assays obtained revealed low vitamin A values not only in those with the degenerative lesion but also in some cases of xerophthalmia. As long as one can demonstrate low blood values in clinical cases of nutritional xerophthalmia, one can be sure that the dietary intake of vitamin A is not adequate for everybody in that area. Unfortunately reliable carotenoid readings were not obtained and this is something which simply must be done, because we might be dealing with an adequate intake associated with inadequate absorption; only the combination of the two assays will help to demonstrate this. It might, of course, be that we are dealing with a nutritional mutation so that both nutritional and genetic theories are in part correct. It is feasible that an eye would suffer in a subject where the most sensitive part of the retina requires for its growth and function a substance or an excess quantity of a substance not present or not adequately present in the range and quantity of nutrients available to it; alternatively, it may not be possible for vitamin A to be absorbed in that particular individual suffering from that particular mutation. Beadle & Tatum (1941) with their brilliant studies on the mould *Neurospora crassa* have fully demonstrated the potentialities of studying nutritional mutants in micro-organisms and have confirmed their existence without any doubt whatever. The purpose of a reviewer is to present as widely as possible the relevant facts and findings gleaned from the literature so that our ideas can be given other horizons. On the subject of nutritional mutation we are faced with this situation, an angle which might well lead to an explanation of several problems in relation to onchocerciasis: by now there are many examples in the literature,

in higher organisms as well as in micro-organisms, in which it is known that a single mutation results in the failure or modification of some essential metabolic process. This can lead to structural changes. The imaginative work of Beadle (1945) strengthens this argument. In essence Beadle's studies suggested that genes act through the determination of enzyme specificities and thus control synthetic and other metabolic processes. If this is the case, then the relation of nutrition and genetics to the posterior degenerative lesion is not so improbable as at first it sounds. The work by Wagner & Mitchell (1955) has further demonstrated the presence of such mutants and revealed the fact that in some instances competitive inhibition occurs between normal metabolites where mutation is present. At least, such a hypothesis demonstrates how important it is to draw on the knowledge of those experienced in allied sciences as well as those practised in the use of the specialized instruments and techniques of today.

RÉSUMÉ

L'auteur a présenté à la seconde Conférence sur l'Onchocercose tenue à Brazzaville en juin 1961 une communication dans laquelle il se proposait de passer en revue les progrès récents concernant la symptomatologie, la pathologie et la pathogénie de l'onchocercose cutanée et oculaire. Un travail original et non encore publié effectué en collaboration avec E. H. Leach de l'Université d'Oxford complète cet article et traite des effets de l'onchocercose sur les vaisseaux sanguins de la peau.

Dans une première partie consacrée au revêtement cutané, l'auteur donne une description de modifications épidermiques décrites classiquement tout en mettant l'accent sur d'autres aspects moins connus, tels le vitiligo, la tendance à la formation de papillomes et l'expulsion de vers adultes à la peau. Il discute la pathologie de l'onchocercose cutanée et montre que la destruction des parasites a pour effet principal de créer une intoxication au niveau des vaissseaux sanguins qui provoque leur atrophie; il semble que l'atrophie de l'épithélium et la dégénérescence des fibres élastiques soient la conséquence de l'anoxie tissulaire. En ce qui concerne la pathogénie des modifications cutanées, l'auteur invoque des observations expérimentales qui font planer un doute sur l'opinion généralement admise selon laquelle leur symptomatologie relèverait d'un processus allergique. La dissémination des parasites à travers la peau et l'apparition de nodules sont l'objet d'une discussion qui envisage l'éventualité d'une corrélation avec une carence en vitamine A.

La seconde partie de l'exposé passe en revue les manifestations oculaires et insiste plus spécialement sur l'atteinte du segment postérieur. A la phase initiale, il faut remarquer que les lésions oculaires se présentent toujours sous une forme aiguë; elles passent ensuite à la chronicité avec des alternances de rémissions et de recrudescences dont la gravité va en s'atténuant. Après examen de la littérature, l'auteur fait état de preuves qui viennent à l'appui de l'opinion selon laquelle il existerait deux types de lésions du segment postérieur: les unes résulteraient de la destruction des filaires dans la chambre postérieure de l'oeil (chorio-rétinite onchocerquienne), les autres bien que relevant d'un processus différent ne se voient cependant que dans les zones où l'onchocercose est endémique. Après avoir passé en revue la pathologie de ces deux variétés, l'auteur constate que l'unanimité s'est faite en ce qui concerne la pathologie et la pathogénie des manifestations oculaires de l'onchocercose, réserve faite exclusivement des lésions dégénératives à distance. La pathogénie de cette dernière catégorie de lésions retient, entre autres, le rôle éventuel de processus allergiques, de la malnutrition, de facteurs génétiques (notamment de mutations nutritionnelles), ou simplement de quelque processus inflammatoire consécutif à la destruction des filaires.

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