Brit. J. Ophthal. (1961) **45**, 284.

OCULAR LESIONS AFTER TREATMENT WITH CHLOROQUINE*

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IN 1955 one of us (H. E. H.) saw a patient in whom the complaint of haloes arose from deposits in the corneal epithelium resembling those described by Mann (1947) in workers engaged in the manufacture of atebrine. This patient was at that time under treatment for actinic dermatitis with chloroquine and the similarity of the corneal changes to those described by Mann suggested that a relationship between them and the drug might exist. Treatment was, therefore, stopped and the opacities gradually faded. The case differed from those described by Mann in the important respect that no question of external contamination of the cornea could arise and the implication that opacification of the ocular tissues could occur from drugs taken by mouth seemed of sufficient importance to warrant further

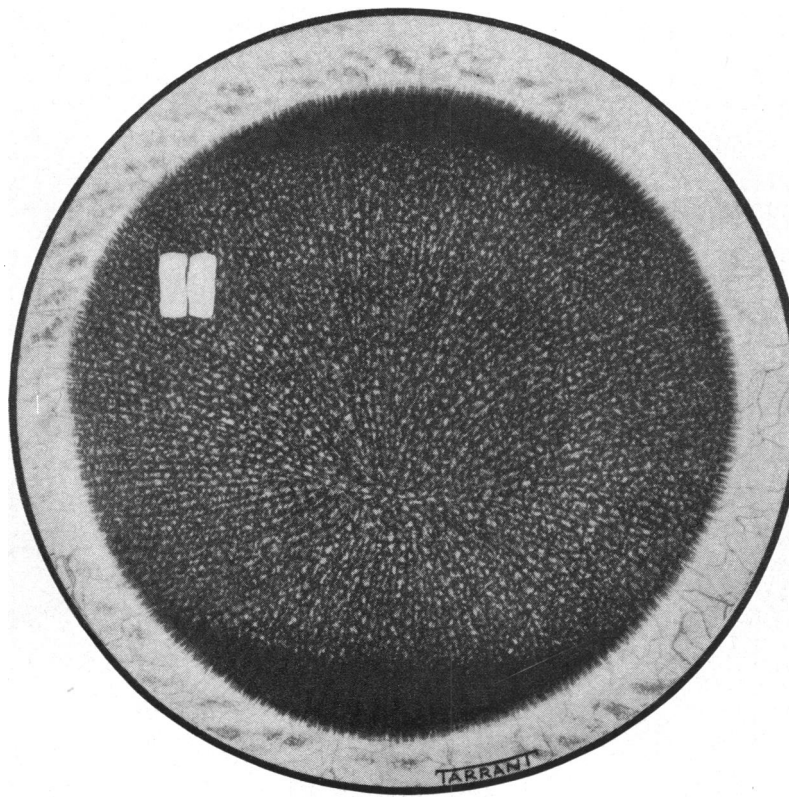

FIG. 1.—Keratopathy—early stage.

* Received for publication November 10, 1960.

investigation. The fact that the pattern of the deposits bore a likeness to the ill-explained Hudson–Staehli line provided a further point of interest.

Thirty patients receiving chloroquine for various conditions were, therefore, examined and among them the incidence of similar epithelial changes was found to be high. The pattern of the deposits was found to vary, and, in several cases which could be examined repeatedly, it was seen to pass from a stage of diffuse punctate deposits (Fig. 1) through a stage in which these became aggregated into curved lines converging and coalescing on a zone just beneath the centre of the cornea (Fig. 2) to a final stage in which a denser, less regular, and greenish-yellow pigmented line appeared in this area (Fig. 3, overleaf). Isolated maculae appeared in some cases (Fig. 4, overleaf). For these changes chloroquine was evidently responsible (Hobbs and Calnan, 1958), and comparable observations have since been reported by Calkins (1958), Zeller and Deering (1958), Leopold (1958), Pau and Bäumer (1959), Rogers (1959), Hertzberg (1960), and Goddard (1960). Other anti-malarial drugs which have been seen to produce similar effects are amodiaquin (Camoquin) and hydroxychloroquine (Plaquenil), seen by Marx (1959), Kersley and Palin (1959), and Scales (1960).

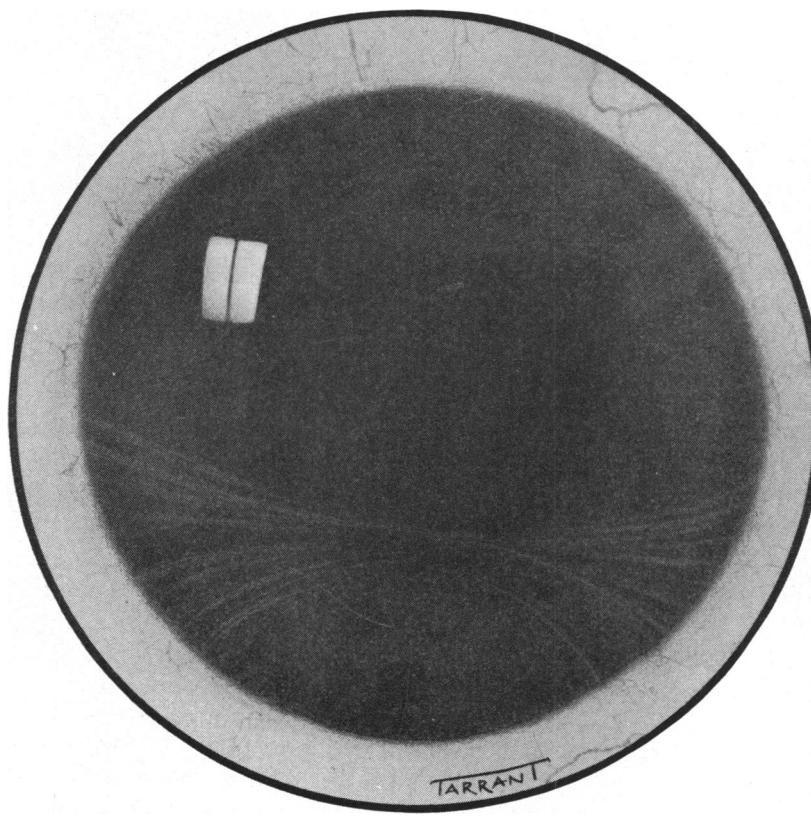

FIG. 2.—Keratopathy—intermediate stage.

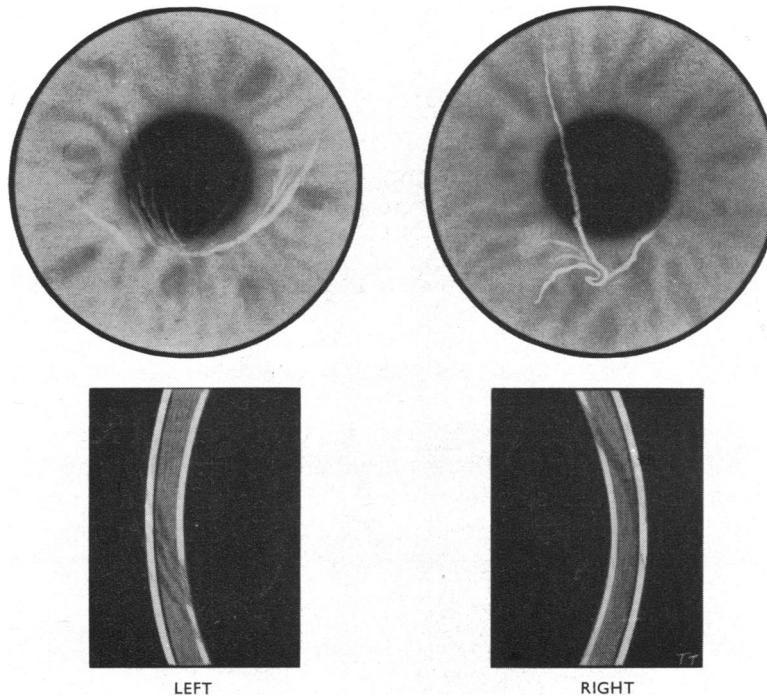

FIG. 3.—Keratopathy—late stage.

These reports dealt principally with the occurrence of the phenomenon although Kersley and Palin noted an incidence of 43·7 per cent. in their series of cases of rheumatoid arthritis under treatment with amodiaquine and hydroxychloroquine. Although fading of the deposits had been noted when the drugs were withdrawn it was not certain that this occurred regularly and the ultimate effects upon vision were not known. Meanwhile, among other patients examined, four were seen in whom serious retinal defects had arisen—evidently by a quite different mechanism; scotomatous vision, impaired night vision, and peripheral field loss were associated with a retinopathy characterized by severe attenuation of the retinal arteries, retinal oedema and pigmentary disturbance (Fig. 5, opposite).

Unlike patients with the corneal lesions, who were usually discovered only by ocular examination, the four with retinal changes had sought advice because of the visual disturbance. They presented, therefore, a selected group; the incidence of such changes among patients receiving chloroquine was quite unknown, but the evidence implicating chloroquine in their causation was sufficiently strong to warrant a published notice of this additional effect of the drug (Hobbs, Sorsby, and Freedman, 1959). The examination of a larger number of patients appeared to be indicated not only so that the outstanding questions concerning the corneal deposits could be answered,

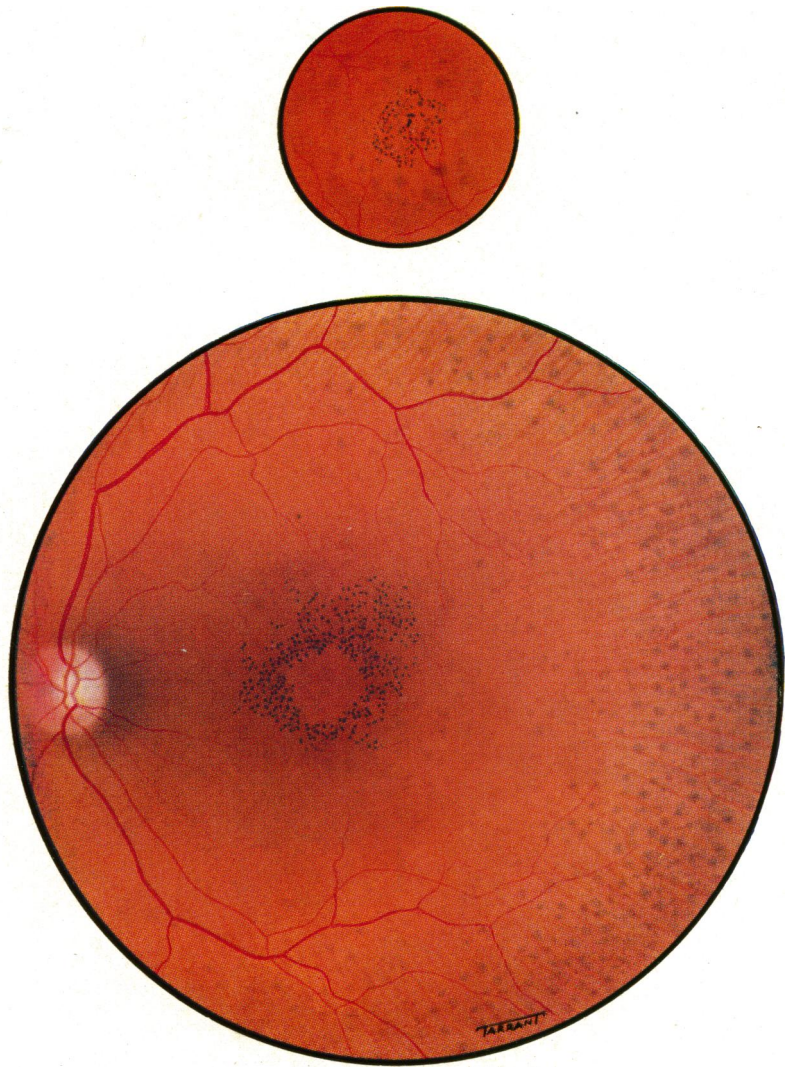

FIG. 5.—Retinopathy.
(*a*) Right eye, maculae only.
(*b*) Left eye, posterior pole and periphery.

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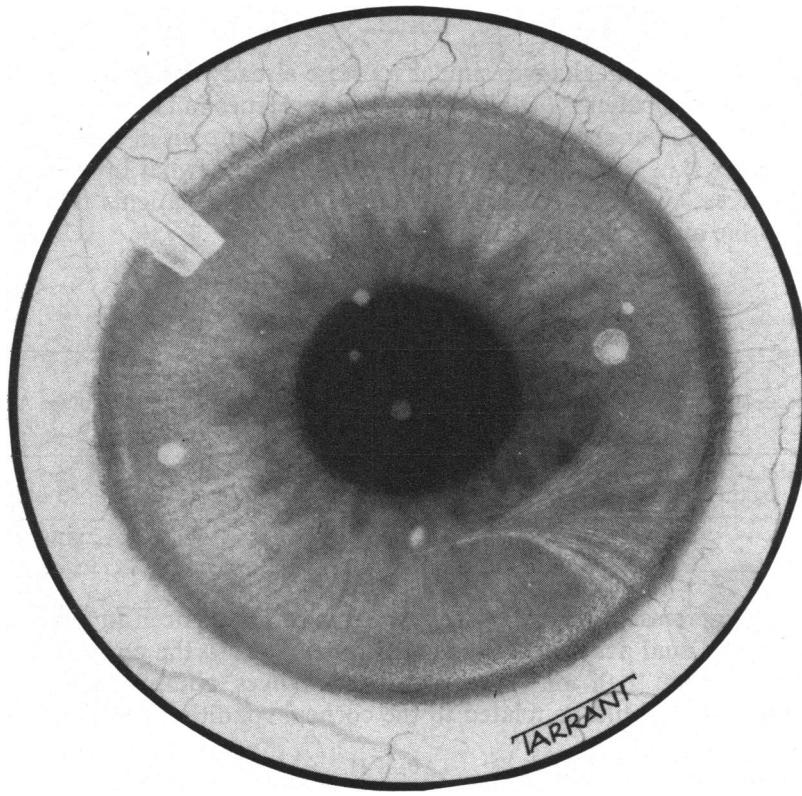

FIG. 4.—Keratopathy—intermediate stage, showing maculae.

but also in order to gain some idea of the incidence of retinal changes and to detect them, if possible, at an earlier stage.

Apart from its use as an antimalarial, chloroquine has been widely prescribed for a number of years in the treatment of rheumatoid arthritis, and has also been used for certain skin diseases since it has displaced mepacrine in the treatment of discoid lupus erythematosus. In both types of case dosage to be effective must be relatively high and maintained for long periods. Such patients appeared to offer suitable clinical material for further investigation, and the eyes of two groups of patients receiving chloroquine on these indications were examined. One group comprised 92 rheumatoid arthritics and the other 73 patients with skin disorders, the majority of whom were suffering from discoid lupus erythematosus. In both groups the patients had been under treatment with chloroquine for periods varying from 3 months to 6 years, and during this time the dosage of the drug had varied between less than 100 mg./day to 600 mg./day or more. It had been consistently low in some cases and high in others. Details were sought of any visual symptoms, and the presence of changes in the retina or cornea was assessed with slit-lamp microscopy and campimetry.

Results

Incidence.—Corneal changes similar to those already described were found in both groups of patients (Table I) and their incidence in those with rheumatoid arthritis (32 per cent.) was comparable with that seen in those receiving treatment for skin conditions (36 per cent.), being somewhat lower than that found by Kersley and Palin (1959) among rheumatoid patients treated with amodiaquine and hydroxychloroquine.

TABLE I

INCIDENCE OF CORNEAL CHANGES IN 165 PATIENTS

Group	No. of Cases	Corneal Deposits		Percentage Affected
		Present	Absent	
Rheumatoid Arthritic	92	29	63	31·5
Dermatological	73	26	47	35·6
Both	165	55	110	33·3

Visual Symptoms.—In none of these patients had there been any measurable reduction of visual acuity which could be attributed to the corneal changes. Rather less than half of those showing changes complained of visual symptoms which could be related to the corneal condition (Table II).

TABLE II

VISUAL SYMPTOMS IN 55 PATIENTS WITH CORNEAL CHANGES

Haloes	12
Haloes and other symptoms	2
Other visual disturbance	7
Symptomless	34

Corneal Changes related to Dosage and Duration of Treatment.—It had already been noted in the original pilot group of cases (Hobbs and Calnan, 1958) that no firm relationship appeared to exist between these factors and the appearance of epithelial deposits, since these were seen in one case after only 3 weeks' treatment in relatively low dosage and were not detected in other cases treated for many months. Among the two groups of patients which comprise the material of this investigation a similar lack of correspondence was seen. From Table III (opposite), showing the total dosage given to the rheumatoid arthritics, it is apparent that, whilst the greatest incidence of lesions occurs in those who have taken between 300 and 400 g. chloroquine, it is least in those who have taken more than 500 g.

The effect of the duration of treatment shows no closer correspondence with the appearance of deposits in the corneal epithelium. Repeated

TABLE III
INCIDENCE OF CORNEAL CHANGES, BY TOTAL DOSAGE OF CHLOROQUINE

Total Dosage (g.)		Less than 100	100–199	200–299	300–399	400–499	500 and Over
Corneal Deposits	Present	2	7	7	6	5	1
	Absent	14	12	5	4	11	15
Percentage Affected		12·5	37	58	60	31	6

examination to determine the appearance and duration of these changes would be necessary at intervals which would be impracticably long in so large a group of patients and was feasible only in isolated instances. It was felt, however, that a comparison of the incidence of lesions in groups of patients under treatment for different periods might offer an alternative method of determining the role of continued administration of chloroquine, since, if the changes persisted, they might be expected to be seen with greater frequency in cases treated for longer periods.

Table IV shows the incidence of corneal changes in patients who had been under treatment for different periods; the variations do not correspond in any direct fashion with the period for which the drug has been given. The highest incidence appears in the group under treatment for between 3 and 4 years; and thereafter it falls distinctly.

TABLE IV
INCIDENCE OF CORNEAL CHANGES, BY DURATION OF TREATMENT

Duration of Treatment (mths)		Less than 12	12–24	25–36	37–48	49–60	More than 60	Uncertain
Corneal Deposits	Present	15	14	10	9	2	3	2
	Absent	28	27	18	13	11	10	3
Percentage Affected		35	34	36	41	15	23	—

The lower incidence of corneal changes observed in the groups longest treated, whilst it may be fortuitous, may well arise because these fade not only when treatment is discontinued but also when it is prolonged. This has been seen to occur in one or two individual patients in whom repeated examination has been possible.

Corneal Changes related to Age and Sex.—The ages of patients in the two groups varied from the early 20s to the later 70s, but the incidence of changes did not vary significantly between the different age groups (Table V, overleaf).

Females predominated in both groups of patients, but neither the complaint of symptoms nor the appearance of corneal changes showed any

TABLE V

INCIDENCE OF CORNEAL CHANGES, BY AGE GROUP

Age Group (yrs)		Less than 40	40–49	50–59	60–69	70 and Over	Age Unknown
Corneal Deposits	Present	13	11	15	12	3	1
	Absent	22	27	23	24	12	2
Percentage Affected		37	29	39	33	20	—

difference which could be correlated with the sex of the patient. Corneal changes were seen in 35 per cent. males and 29 per cent. females.

Retinal Changes.—In the four cases with retinal damage referred to above, visual symptoms had been obtrusive at once, and for this reason it was thought likely that few such would have passed unnoticed. This has proved to be the case, for (apart from one doubtful instance, a defaulter in whom confirmation of the retinal lesions could not be obtained), no further cases of retinal involvement from chloroquine have been found by examination of the 165 cases under discussion. An additional case has, meanwhile, been seen by one of us (H. E. H.), but this patient also presented because of severe loss of vision. This case merits detailed description because it presents some features in addition to those already described in the original four.

A woman aged 43 years had suffered from discoid lupus erythematosus for some years and had been under treatment with chloroquine for the past 6 years. The drug had been begun at a dosage of 400 mg./day for one year, then discontinued for some months, and then recommenced at the same dosage for the 8 months from February to September, the period during which lesions tended to relapse, for some years. For 15 months continuously, before she was examined by one of us (H.E.H.), she had been taking 600 mg. daily, and during the last 9 months of that period she had noticed that her vision seemed less good, so that she had found it unreliable when driving a car, and had given up driving. Her family had remarked that she seemed not to see details which were readily visible to them. Apart from this she had been aware of occasional frontal headaches and had felt generally "below par".

Examination.—The visual acuity was 6/9 in the right eye and 6/12 in the left, being scotomatous in both eyes and not improved by lenses. The visual fields (Fig. 6, opposite) were grossly constricted and the Amsler chart indicated an irregular haze overlying the fixation area in both eyes. The eyes were externally normal, with no sign of corneal deposits, and no lens opacities were seen. The fundus vessels were seen to be severely attenuated, with some pallor of the optic discs and patches of oedema at both posterior poles. Skull *x* rays, including the optic foramina, showed no abnormality. Blood examination revealed normal red and white cell counts. Both urine analysis and the general examination were negative, apart from a single patch of discoid lupus on the nose. The blood pressure was not raised.

Treatment.—Chloroquine had been discontinued a day or two before examination and, in an effort to counter the retinal ischaemia which the fundus picture suggested as the cause of the visual loss, full doses of priscol were administered and the patient was nursed in an oxygen tent for alternate periods of 6 hours for 2 weeks.

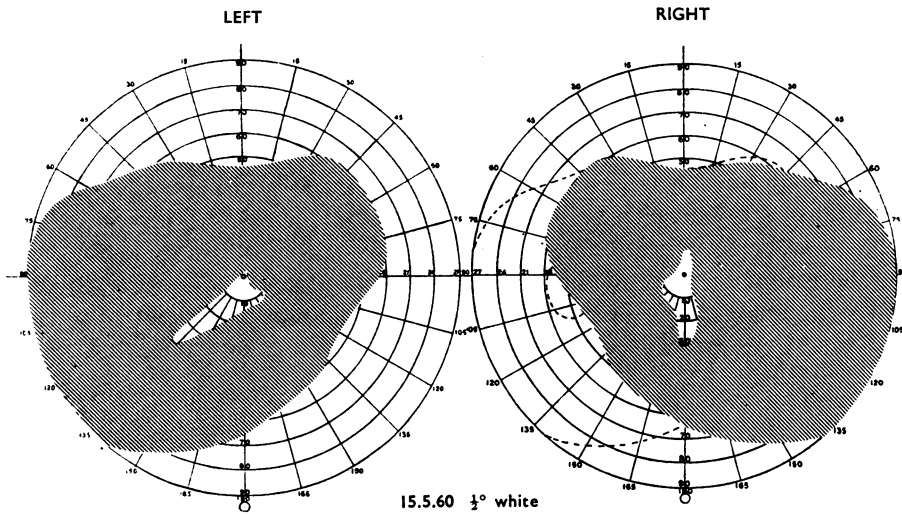

FIG. 6.—Initial visual fields, right and left eyes.

Progress.—The subjective scotomatous vision resolved on this regime, visual acuity improved to 6/9 in both eyes, and some increase in the peripheral fields was observed (Fig. 7).

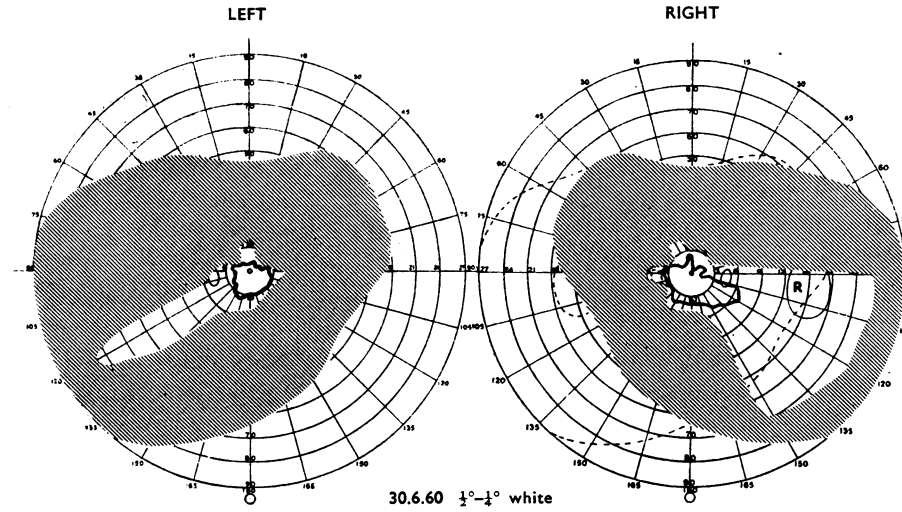

FIG. 7.—Visual fields, both eyes, after treatment.

Dark adaptometry (Dr. R. A. Weale) at this time showed that, whilst there was virtually no adaptation on direct fixation, it was normal in the small area of peripheral field on eccentric fixation. The electroretinogram (Dr. G. Arden) was found to be extinguished at this stage.

On purely clinical grounds little or no further improvement was felt to be possible and this expectation has been confirmed 6 months later, the only change being the appearance in the retinal periphery of fine granular pigmentation.

These five cases of retinopathy represent, therefore, the total seen in the cases examined which together number 170, giving an incidence of 2·9 per cent. In addition to these three other cases are known to us: one seen by Lister (1959), one by Ormrod (1960), and one reported by George and Mitchell (1961). Cases of this sort have also been reported from France by Grupper, Brégeat, and Juge (1960) and by Bureau (1960). It is possible also that the case reported by Sternberg and Laden (1959), in which visual loss associated with 'macular degeneration' was seen after 4½ years' intermittent treatment with chloroquine, arose in this way, and that the severe field loss reported by Goldman and Preston (1957) after a long period of treatment may have been similarly produced, but accurate records of ocular examinations are lacking in these cases.

Retinal damage, it is clear, occurs much less frequently than corneal changes. When it presents clinically it does so because of manifest effects upon vision—principally central vision; and at this stage the changes appear to be irreversible. In the two most severe cases the arterial attenuation and disturbed retinal pigmentation bore a resemblance to the fundus picture of retinitis pigmentosa, and the analogy was further strengthened by the fact that visual loss had first been found to be disabling in conditions of poor illumination. This symptom was not mentioned by the remaining two of the four patients first reported; but because of their crippling arthritis their activities had for years been restricted. In the case here described, however, although abnormal pigmentation was not at first apparent, defective vision at night was a disabling early symptom. It was considered possible, therefore, that a selective toxic action upon the rod mechanism might be occurring in the early stage of the retinopathy and that such cases might be detected by dark adaptometry before objective retinal change or impaired central vision was apparent.

Several of the dermatological cases receiving chloroquine in varying dosage were therefore examined on the Crookes adaptometer, and although this series was small and the results inconclusive, the findings in the case reported above (of normal dark-adaptation in a small persisting area of field) appeared to discount the likelihood that adaptometry would prove useful in the detection of early cases.

Discussion

This form of keratopathy must, therefore, be regarded as a toxic phenomenon provoked by chloroquine and other antimalarial drugs rather than as an obscure dystrophy, as Calkins (1958) has pointed out. It is probably not specific to these drugs, for we have seen changes of a similar type in a pethidine addict who had been taking large quantities of this drug for a long period; and is comparable with the case reported by Markoff (1948)

in which needle-shaped crystals appeared temporarily in all layers of both corneae in a patient undergoing treatment with urethane.

It is evident that the corneal changes are caused by the administration of the drugs. They have been seen to arise and progress during treatment in many patients repeatedly examined, and they have been found in a large proportion of patients taking the drug in relatively high dosage and have been seen to fade when treatment is discontinued. The form of the deposit in all the cases which we have examined has been granular, although oedema might be suspected from the history of haloes and this has been reported in one case by Hertzberg (1960). Such an effect of synthetic antimalarial drugs was noted by Reese (1946) and by Chamberlain and Boles (1946) in small numbers of airmen taking mepacrine in suppressive doses.

Serious blurring of vision occurred in these cases, and also in that reported by Bleil (1958), where it formed part of a severe toxic reaction to amodiaquin; but such an effect was not recorded by Hertzberg. The nature of the deposit remains obscure; *in vivo* it does not exhibit the fluorescence with the quartz slit-lamp microscope which may be seen with pure chloroquine, although Pau and Bäumer (1959) have noted this in excised epithelium. These workers have also examined the epithelium histologically and have found that the deposits are confined to the cytoplasm of the cells. The mechanism by which the deposits form is undetermined: bloodstream transference of the drug or some intermediate metabolic product of it is evidently involved, either directly to the epithelium *via* the perilimbal vascular plexuses or, as Mann (1959) has suggested, *via* the lacrimal gland and the tear fluid. Whatever the deposit may be, it seems likely that the high oxidative activity at the corneal surface is responsible for the colour change seen in later stages when it takes on the appearance of the Hudson–Staehli line. The further investigation into these problems which was at one time contemplated has not been pursued in view of what is now known of the ultimately innocent visual effects of the deposits.

The facts that corneal changes do not affect all patients taking the drug and that they may fade even when high dosage is continued present another curious problem and raise the possibility that some variation in the individual response to the drugs may be present, or be induced, in the positive cases. This is to some extent supported by the knowledge that, whilst in the majority of positive cases high dosage has been continued for a long period, epithelial changes have also been seen in one or two cases under treatment for as little as 3 weeks. The absence of reports of such changes among the much greater number of individuals taking chloroquine in normal therapeutic doses for malarial therapy and prophylaxis also emphasizes the role of high dosage in producing the epithelial deposits, whereas the oedematous lesions produced by mepacrine occurred on relatively low dosage and were regarded as a form of idiosyncrasy. Certain features of Bleil's case suggest that it, too, may have arisen in this way. Nevertheless

it is clear that in the majority of patients the most important factor in determining the development of these changes is the combination of high dosage and prolonged administration.

The chemical structure of the antimalarials concerned does not suggest a common chemical factor as the toxic agent, for although the side-chains of mepacrine (Fig. 8) and chloroquine (Fig. 9) are identical, the base of mepacrine is an acridine ring and that of chloroquine is a quinoline ring. The structure of Plaquenil is identical with that of chloroquine except for the addition of an hydroxyl group (Fig. 10), but that of amodiaquine (Camoquin) is again quite different (Fig. 11).

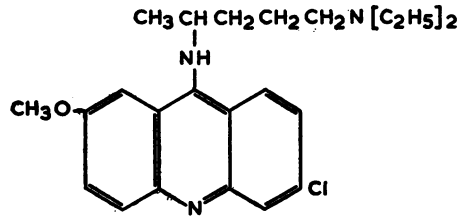

FIG. 8.—Chemical formula, Mepacrine.

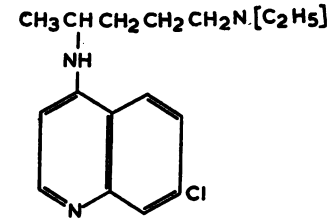

FIG. 9.—Chemical formula, Chloroquine.

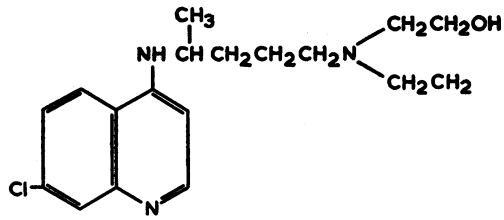

FIG. 10.—Chemical formula, Plaquenil.

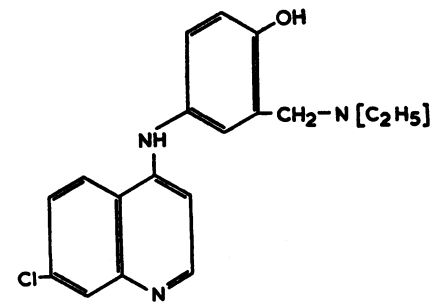

FIG. 11.—Chemical formula, Amodiaquine.

The resemblance of the condition in its early stages to that first described by Fleischer (1910) as cornea verticillata has been commented upon by Calkins (1958) and by Wybar (1959), and raises interesting speculations. Whilst it is conceivable that the lesions in Fleischer's cases were iatrogenic, since the patient was afflicted with disseminated sclerosis and may well have been treated vigorously for this condition, the similar cases reported by Gruber (1946) could not have been so, arising, as they did, idiopathically in two successive generations. Such an appearance could best be accounted for by the assumption of an inborn metabolic anomaly comparable with that which gives rise to cysteine crystals in the cornea in Fanconi's syndrome, or to the copper deposits forming the Kayser-Fleischer ring in hepato-lenticular degeneration.

In the late stage the appearance of the epithelial deposits exactly resembles the Hudson–Staehli line, and it is of interest, in this connexion, to recall the hypothesis of Koby (1930) that this takes its form as the result of the movements of the firm posterior margins of the eyelids upon the corneal epithelium. He suggested that these tended, by making momentary folds in the epithelium, to favour the deposition of pigment—believed to be haemosiderin in the cases he was considering—along the line of junction of the lids. The genesis of the lines indicated in Fig. 1, 2, and 3 appears to offer a useful illustration of this process.

The lower incidence of retinal changes is fortunate, since, unlike those in the cornea, they appear in most cases to be irreversible at the stage at which they have so far been detected. Among the four cases originally described, progressive visual impairment appeared after $3\frac{1}{2}$, $2\frac{3}{4}$, and 3 years' treatment with chloroquine compounds, but ceased to progress when chloroquine was discontinued. In the case here described the duration of treatment was longer and a slight improvement of symptoms and field defects has followed the discontinuation of chloroquine and the institution of empirical therapy of the retinal lesions by vasodilator drugs and oxygen. In all five cases greatly narrowed retinal vessels, pallor of the optic discs, and macular lesions—oedematous or pigmentary—have been noted, whilst in two of the early cases peripheral retinal pigmentation suggestive of retinitis pigmentosa was seen. In the last case this pigmentation was not at first apparent, but it appears to be developing now, some 6 months after the subsidence of the oedematous macular lesions. The suggestion put forward by Hobbs and others (1959) that the oedematous lesions represented an earlier stage of retinopathy, the fully-developed picture of which included pigmentation, is thus to some extent confirmed, and the resemblance of the clinical picture to that known to be produced by quinine and by piperidyl-ethylchlorophenothiazine is strong. Whilst the pharmacological effects of chloroquine give no ground for the belief that it can provoke the retinal vascular response seen in these patients, the clinical evidence that such has been the case is highly suggestive. Idiosyncrasy may well play a part in this response to synthetic antimalarials, as it does with quinine; but, apart from the cases of corneal oedema already referred to, acute ocular lesions have not been reported, and the fact that long-continued treatment has preceded the appearance of the ocular lesions in the majority of cases suggests that in general some other factor is needed to provoke them.

This may perhaps be found in the fact that chloroquine is a drug which is only slowly metabolized by the body so that its cumulative effect appears after a variable interval. If, as Huriez (1960) maintains, this tendency is exaggerated in patients with lupus erythematosus, a further predisposing factor may well be thus provided.

It would seem, therefore, that chloroquine may damage the eye by two quite separate mechanisms, involving either the cornea or the retina. Such

a dual effect, whilst it appears at first sight novel, is by no means unknown in experimental pharmacology, for Cibis and Noell (1955) have found that sodium iodoacetate, in addition to its recognized ability to produce retinal damage with pigmentary disturbance in animals, also affects the transparent tissues of the eye and may produce cataract in a significant proportion of experimental animals.

Attempts to produce retinal lesions in rabbits with chloroquine have so far proved unsuccessful (Hobbs and others, 1959) and in this respect experience with the drug is similar to that with piperidylethylchlorophenothiazine (a tranquillizer akin to chlorpromazine) which is known to have produced retinal damage with pigmentation in patients undergoing psychiatric treatment. With both drugs, however, the retinal effects appear to arise through spasm of the retinal vessels, in contrast to those which result from iodoacetate and certain other retinotoxic agents, the effects of which are reproducible in animals, and which appear to exert a direct effect upon the rod and pigment layer of the retina. It is possible, therefore, that in the paurangiotic retina of the rabbit such vascular changes could not be observed.

In none of the cases examined has opacification of the lens been seen in a form which could be attributed with any degree of certainty to chloroquine. Senile cataract has been found to co-exist in some cases and snowflake subcapsular opacities have been noted in one or two. This possibility cannot, however, be entirely dismissed in view of recent experimental and biochemical work on the role of the quinones in cataract formation.

Summary

(1) A preliminary survey of selected cases under treatment with antimalarial drugs which indicated a high incidence of corneal changes due to the drug has been extended by examination of a larger group of patients, in which similar changes were found to affect some 33·3 per cent.

(2) Such changes have been found to be symptomless in the majority of cases, to regress with the withdrawal of treatment, and even in some cases with its continuance. The characteristic symptom is the appearance of haloes around naked lights.

(3) A significant reduction in visual acuity attributable to the corneal lesions has not been noted.

(4) The lesions appear insidiously, usually after prolonged treatment at high dosage, but no precise relationship to dosage or duration of treatment has been found.

(5) Previously reported retinal changes (arterial attenuation, oedema, and, in some cases, pigmentary disturbance) have been further noted and found to be largely irreversible.

(6) Such retinal changes were not always accompanied by corneal deposits.

(7) Dark adaptometry has not proved useful in the detection of cases of retinopathy at an early stage.

(8) No evidence of cataract formation arising from treatment with chloroquine has been forthcoming.

(9) Treatment of the corneal deposits appears to be unnecessary and treatment of the retinal condition appears to have little effect. It would seem advisable, however, when these drugs must be given in such high dosage, that courses of treatment should be of limited duration, and that if prolonged treatment is essential it should be interrupted for periods of several weeks during which the drug is withdrawn.

We are indebted to Dr. A. Freedman for allowing us to examine the group of patients with rheumatoid arthritis under his care; and to the various members of the medical staff of St. John's Hospital for Diseases of the Skin whose cases were made available to us. Mr. Michael Sheridan's assistance with the dark-adaptation trial was invaluable and we are grateful for the help given by Dr. R. A. Weale and Dr. G. Arden of the Institute of Ophthalmology in the examinations to which reference has been made.

The illustrations are the work of the Departments of Medical Illustration of the Institute of Ophthalmology and the Royal Free Hospital.

Part of the expenses of the investigation were met by a grant from the Royal Free Hospital Endowment Fund.

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