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Ophthalmological safety of chloroquine

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The antimalarial drugs, chloroquine phosphate (Avlochlor) and hydroxychloroquine sulphate (Plaquenil), have recently been losing favour in clinical practice because of their ocular toxicity. However, simple precautions can be taken to prevent this. The results of serial photography, colour vision assessment, and examination of retinal vessels and fundus periphery, the incidence of corneal deposits and of non-ocular toxicity, and the appearance of sixteen cases with overt maculopathy have been discussed elsewere (Percival and Meanock, 1968), and will not now be repeated. This paper investigates further the changes that may occur before the appearance of toxic maculopathy.

Material and methods

272 outpatients taking part in the survey were referred from the departments of rheumatology and dermatology to the ophthalmic out-patients department during the years 1964 and 1965. The standard daily dose of the antimalarial was 250 mg. chloroquine phosphate or 200 mg. hydroxychloroquine sulphate, these doses being approximately equal in terms of base-equivalent. 93 patients received double the daily dose during the first part of their course. 43 patients received half the daily dose during the course when control at this level seemed satisfactory. Patients were followed up under ophthalmic supervision at 4-monthly intervals for 2 to 3 years. Several of them had begun therapy some years before referral.

Ocular examination comprised:

(1) Recording of visual acuity.

(2) Assessment of colour vision using the Ishihara pseudo-isochromatic plates.

(3) Recording of central fields on the tangent screen to a 1 mm. white and a 7·5 mm. red target at 1 metre distance. A central field defect to red was said to be present if there was either a relative or an absolute scotoma to red between 4° and 9° from fixation. In most cases the colour returned to the original red hue outside the scotoma. Central fields to red targets were assessed serially from April, 1966, onwards in 230 patients and in 100 control subjects. The latter were selected at random and were matched for age and sex; all had healthy maculae and gave normal readings to the Ishihara plates.

(4) Examination of the fundus under mydriasis with particular attention to the foveal reflex.

(5) Binocular examination of the macula under high magnification, using a slit lamp and Goldmann contact lens, for the presence of pigment mottling. The test was carried out under mydriasis on 179 patients. Use was made of both white light and red-free light from the slit lamp.

(6) Electro-oculogram (EOG) was recorded using the Moorfields portable apparatus in 241 patients, and serially in 84 patients once or twice at the commencement of the trial and thence at between one- and two-year intervals. If the reading appeared to be near or below the lower limit of normal it was recorded more frequently.

(7) 177 patients were subjected to anaesthesiometry, using four standard nylon hairs as described by Ruben (1964), each requiring a force of 8, 12, 18, and 40 mg. respectively to cause them to bend.

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The axial area of each cornea was tested, the patient being seated with his head on a chin-rest. Abnormal sensation was considered to be present if the 8 mg. hair both failed to be felt and failed to produce a blink response.

Results and comment

Of the 272 patients originally referred, 74 were found unsuitable for full investigation. This number comprised sixteen patients who never received more than 100 g. total dose of chloroquine, 29 who failed to attend follow-up clinics, nine who were unreliable for field testing or whose drug administration was unreliable, nine in whom macular assessment was impossible because of lesions present before the start or because of cataracts, and eleven who already had maculopathy at the time of referral.

The age and sex of the remaining 198 patients are shown in Table I. They are grouped according to total dose received by the end of the trial in Table II (opposite), which summarizes the investigations performed.

Table I *Age and sex of* 198 *patients investigated*

Sex	*Male*			*Female*			*Total*
Age group (yrs)	20–40	41–60	61–80	20–40	41–60	61–80	
Rheumatological	5	23	13	20	103	23	187
Dermatological	1	3	0	4	3	1	11

Examination of the macula

In 193 patients with healthy fundi (Table II) the maculae appeared ophthalmoscopically unchanged during the trial, although in 65 some degree of granularity or colloid change was present. The foveal reflex was absent in 82 patients, but it was impossible to tell whether there had been any toxic change except in 21 in whom a gradual disappearance of the foveal reflex was noted. Fine pigmentary mottling at the macula and loss of the foveal reflex are well-known age changes in the normal eye (Braley, 1966; Percival and Meanock, 1968). By careful serial observation it was possible to diagnose early maculopathy in five patients because of pigment irregularity in maculae previously seen to be normal.

Field testing

The 153 patients in Table II tested with red targets included four with established familial colour blindness, and five who developed early maculopathy during the trial but before the red field testing had been instituted and the condition of premaculopathy fully defined. The latter had normal fields to white targets and the defects to red disappeared within 18 months after cessation of therapy. The remaining 144 on continuous chloroquine therapy (mean total dose 410 g.) had maculae persistently within normal limits: 79 had normal red central fields and 65 had relative or absolute paracentral red scotomata (Fig. 1, overleaf).

In some of each group the foveal reflex was absent, but changes in this reflex occurred in none of the former group and in 21 of the latter. Thus the red field defect correlates well with the loss of the foveal reflex, but is an earlier feature in the development of maculopathy.

Table II *Ophthalmological investigations during chloroquine therapy*

		Total dose of chloroquine phosphate or hydroxychloroquine sulphate equivalent (g.)			*Total patients*	
		100–250	250–500	Over 500		
Number investigated		56	97	45	198	
Visual acuity	6/6 + both eyes	54	88	39	181	
	Less than 6/6 either eye	2	9	6	17	
Ishihara plates	No defect	53	92	42	187	
	Colour defect	1	4	2	7	
Central fields	Full to white	56	97	45	198	
	Scotoma to white	—	—	—	—	
	Full to red	20	40	19	79	153
	Scotoma to red	19	34	21	74	
Peripheral fields	Full	56	97	45	198	
	Constricted	—	—	—	—	
Maculae	Normal limits	55	94	44	193	
	Abnormality developed	1	3	1	5	
Foveal reflex	Present	36	55	25	116	
	Absent	20	42	20	82	
Macular pigment (slit lamp)	Grade I	8	16	6	30	150
	Grade II	22	40	22	84	
	Grade III	8	17	11	36	
EOG (per cent. light rise)	More than 200	21	54	18	93	161
	185–200	7	4	8	19	
	Less than 185	16	20	13	49	
Corneal deposits	Absent	29	33	13	75	
	Present	27	64	32	123	
Corneal sensation	Normal	18	23	7	48	94
	Reduced	10	28	8	46	

It is proposed to use the term premaculopathy for those maculae that appeared to be within normal limits but either developed paracentral red scotomata or lost the foveal reflex during therapy. Since no patient lost the foveal reflex without also developing a red scotoma, premaculopathy may be defined as the development of a reversible paracentral scotoma to red targets.

Of the 65 patients thought to have premaculopathy on account of paracentral red scotomata, 64 were followed-up after discontinuation of therapy; the fields returned to normal within a year in 59. The incidence of an irreversible red scotoma was therefore five out of 143 (3·5 per cent.). In these five the foveal reflex when present at the start and the EOG (when serially recorded) both remained normal.

Fifty patients who had taken more than 110 g. chloroquine had been off chloroquine for more than 3 months (mean 18 months) when their red fields were assessed. They had received a mean total dose of 333 g. chloroquine phosphate or the hydroxychloroquine sulphate equivalent. There were only three with scotomata to red. This is further evidence of the reversibility of the premaculopathy defect.

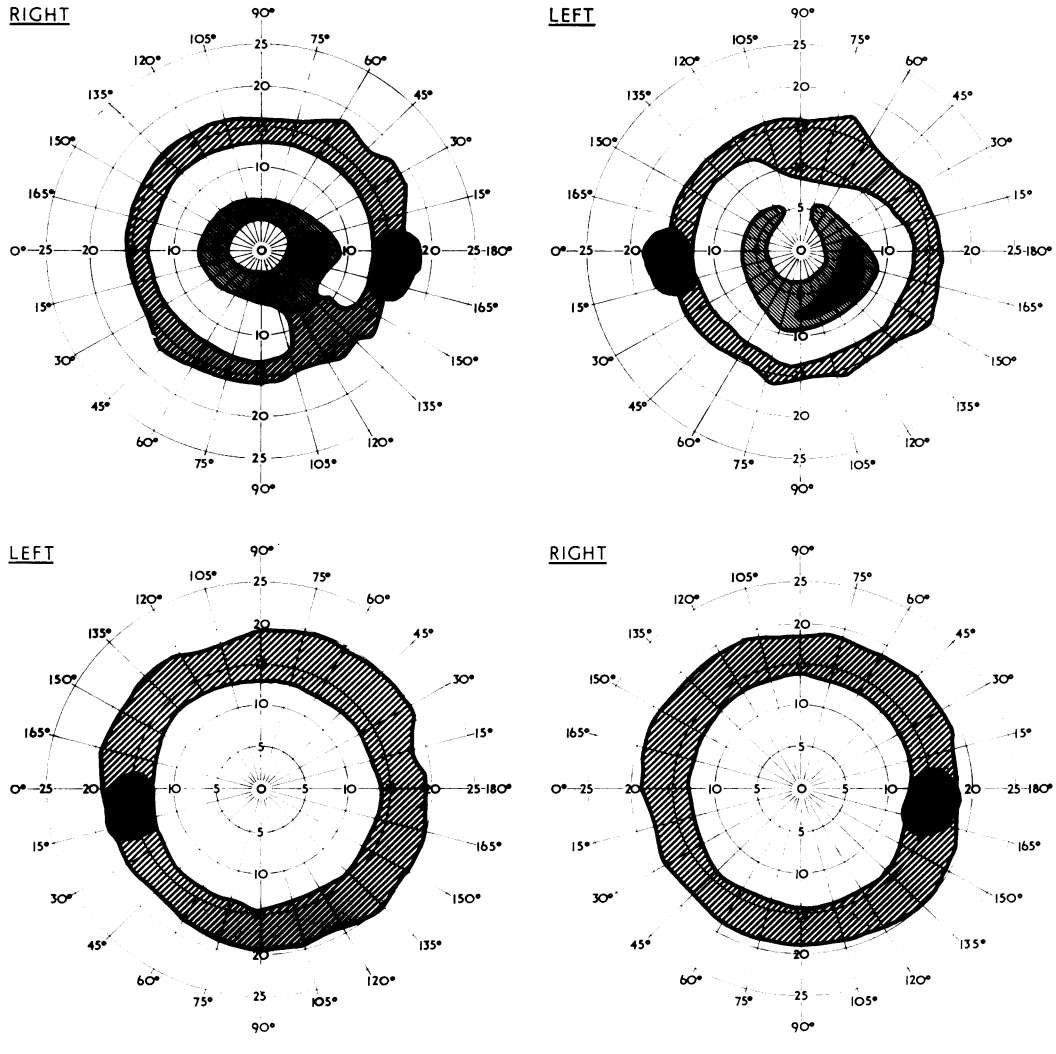

FIG. 1 *Chloroquine premaculopathy in a man aged* 70 *who had received a total dose of only* 146 *g. hydroxychloroquine sulphate over* 22 *months. Typical relative scotomata which had become absolute in places (solid area) were found to a* 7·5 *mm. red target at* 1 *m. distance in September*, 1966. *These had disappeared within* 6 *months after cessation of therapy. The fields were always full to* 1/1000 *mm. white. An EOG drop from* 200 *per cent. light rise in September*, 1964, *to* 160 *per cent. in September*, 1966, *could have predicted this premaculopathy state. Uncorrected visual acuity* 6/4 *each eye. Foveal reflexes absent and colloid bodies present at the maculae before start of trial*

Of the 100 matched control subjects, six had relative paracentral red scotomata. These defects were presumed to be physiological and possibly due to a slight variation of the configuration of the cones near the macula. The incidence of irreversible red scotomata in patients on chloroquine was only 3·5 per cent. compared with 6 per cent. in the control subjects; it is therefore reasonable to suppose that these were also physiological and that the true chloroquine red scotomata were all reversible.

Binocular examination

It was hoped that examination of the macula using a slit lamp and contact lens would clarify the significance of early pigmentary mottling but this technique showed that very fine mottling occurred in many subjects with normal foveal reflexes. However, when the appearance of the macular pigment was graded as I uniform, II stippled or granular, and III mottled or finely clumped, some correlation was found between grade III and the presence of red central field defects. Red-free light from the slit lamp provided no additional information.

Table III expresses the results in the 138 patients on continuous chloroquine whose fundi appeared ophthalmoscopically normal, of whom 79 had normal central fields and 59 had premaculopathy. It will be seen that there is a tendency for increased granularity and mottling with age and this is more marked in patients with premaculopathy. Numbers with the foveal reflex still present are shown in brackets. It is also apparent that premaculopathy is more common in the older age groups, suggesting that its development is enhanced by age changes.

Table III *Correlation between macula pigment (seen with a slit lamp), premaculopathy, and age*

Age group (yrs)	20–39		40–49		50–59		60–80	
Macular pigment	N	P	N	P	N	P	N	P
I	5 (4)	1 (1)	13 (13)	0	7 (6)	1 (1)	0	0
II	4 (4)	3 (2)	12 (8)	10 (7)	22 (12)	11 (4)	9 (2)	6 (1)
III	1 (1)	1 (1)	0	2 (0)	2 (1)	12 (2)	4 (0)	12 (1)
Totals	10 (9)	5 (4)	25 (21)	12 (7)	31 (19)	24 (7)	13 (2)	18 (2)

Macular pigment grading as described in text
79 patients with no field defect (Normal)
59 patients with reversible red field defects (Premaculopathy)
Presence of foveal reflex shown in parentheses

Patients in Grade II showed no particular correlation with either premaculopathy (39 per cent.) or with absent foveal reflexes (48 per cent.). But those in Grade III were associated with premaculopathy (79 per cent.) and an absent foveal reflex (82 per cent.). The Grade III changes however were present in only 46 per cent. of all premaculopathy cases. For this reason and because of the confusion in the borderline between pigmentary stippling and pigment clumping, especially between different observers, this test is probably not of sufficient value for routine use.

Electro-oculogram

EOG recordings were made on 31 patients before therapy had been started, and on 161 patients with healthy maculae after more than 100 g. total dose had been taken; four of these later developed maculopathy. EOG recordings were made on three others showing maculopathy at the time of diagnosis, and in eleven such patients more than 4 months after therapy had been discontinued. EOG readings are given as percentage of light rise/dark trough and examples are shown in Fig. 2 (overleaf).

Of the 157 patients whose maculae remained ophthalmoscopically normal, 84 underwent serial recordings: there was a total of 133 patients recorded during 1964/5 and 108 during 1966/7. When more than one recording was made in the period under consideration an average was taken. Results (Table IV, overleaf) show a general reduction in EOG reading

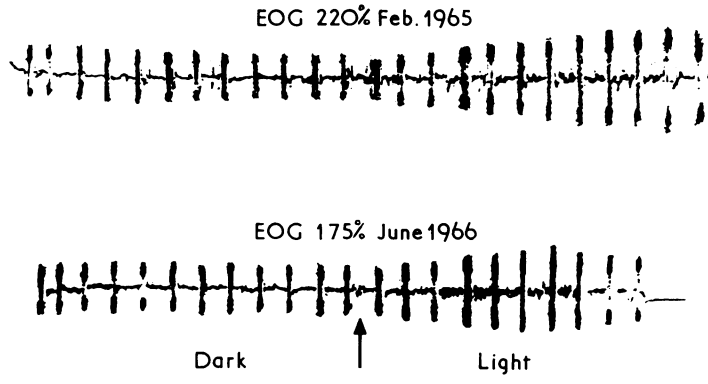

FIG. 2 *Serial EOG recording in a man aged 50 who developed premaculopathy. He had received 510 g. hydroxychloroquine over 5 years. The EOG was 220 per cent. in February, 1965, and 175 per cent. in June, 1966. Premaculopathy was diagnosed in October, 1966 and the therapy was discontinued. Field full in March, 1967. Foveal reflexes were absent throughout the trial.*

Table IV *EOG results in 157 patients on chloroquine with normal fundi*

EOG (per cent. light rise)	1964/5	1966/7
Over 200	90	51
185–200	17	16
Less than 185	26	41

between 1964/5 and 1966/7. All patients had received continuous chloroquine therapy. Of the 108 patients recorded during 1966/7, premaculopathy was diagnosed in 47 at the time of the final recording. The incidence of readings below 185 (per cent. light rise) in patients with premaculopathy and maculopathy compared with the incidence in normal patients and those who had not yet started chloroquine is shown in Table V. There is an obvious tendency for the response to be reduced in patients with overt maculopathy. It will also be seen that in patients with maculopathy the EOG tends to return to normal after discontinuation of the drug.

Table V *Suppression of EOG by chloroquine*

Description		*No. of patients*	*EOG average (per cent. light rise)*	*EOG readings less than 185*	
				No.	*Per cent.*
Before chloroquine started		31	225	6	19
During therapy	Normal maculae	61	213	17	28
	Premaculopathy	47	197	25	53
	Maculopathy	7	175	6	86
Maculopathy over 4 months after discontinuation		11	218	2	18

Because there is a proportion of normal patients who have EOGs below the normal range for no apparent reason, the most reliable results are obtained from serial recordings excluding all patients who have an EOG below 185 (per cent. light rise) before the drug is started. The pathological EOG or positive result may then be defined as one which falls by more than 15 units to a level below 185.

Using these criteria seventeen patients were excluded from the 84 serially recorded and the results of the rest are shown in Table VI. It will be seen that a significant drop in the average EOG reading occurred in patients with premaculopathy, and that a positive result was obtained in nearly half. An example of the positive result is shown in Fig. 2. In all three patients with irreversible red field defects (physiological) who had undergone serial recordings, the EOG remained normal. However, it is concluded that because of the individual variability of the EOG and because of the incidence of false positive results (11 per cent.), EOG recordings even when serial are not sufficiently reliable for general use in the screening of toxicity.

Table VI *2-year follow-up of EOG initially greater than* 185 *(per cent. light rise)*

Description	*No. of patients*	*EOG average*		*No. of positive results*
		1964/5	1966/7	
Maculae remained normal	37	229	221	4 (11%)
Premaculopathy developed	30	229	198	14 (47%)

Corneal sensation

Anaesthesiometry was performed on 177 patients in order to investigate the local anaesthetic action of chloroquine. Impaired corneal sensation was found in 49 per cent. of the 94 patients receiving chloroquine (Table II) and in 27 per cent. of 83 who had had the drug discontinued for more than four months. There was no significant correlation, however, with the presence of visible deposits.

Visual symptoms

62 of all patients originally referred complained of ocular symptoms. 32 of them noticed a blur when reading soon after commencement of therapy, often when receiving double the standard dose; it is considered to be due to a transient increase in presbyopia. Seventeen other patients complained of blurring or distortion of images: in nine the symptoms were attributed to maculopathy, in three to retinal vascular lesions, and in five to other causes. In two of the maculopathy patients visual symptoms progressed following discontinuation, but there were no cases of delayed retinopathy. Two patients complained of haloes due to keratopathy and which quickly disappeared on cessation of therapy.

There were three instances of diplopia which in each case disappeared every time the drug was discontinued. The first was due to an isolated superior oblique palsy in which serial Hess charts proved a functional return to normal after discontinuation. The second was due to a latent convergent squint which became manifest during therapy. The third was due to superior rectus weakness, probably congenital, and although the diplopia cleared each time the drug was stopped, the Hess chart remained unaltered.

Twelve patients felt a gritty sensation. In nine of them this was due to conjunctivitis sicca and in two to marginal keratitis, both disorders being associated with rheumatoid arthritis.

The visual acuity of the 198 patients (Table II) was always 6/6 or better except in a few with lesions unconnected with chloroquine, but there were two patients whose vision dropped from 6/5 to 6/6 as a result of early maculopathy.

7-year follow-up

76 patients had started therapy during 1960 or before at a time when there were no regular eye follow-ups. Thirteen of these developed maculopathy. 54 of the others underwent full examination 7 years later. All were found to have ophthalmoscopically normal maculae although some of those still taking the drug had developed the reversible pre-maculopathy. There was no evidence of delayed toxicity.

Discussion

Chloroquine is bound to desoxyribonucleic acid and concentrated in the pigmented tissues in the eye. It interferes with metabolism in the ellipsoids of the rods and cones by inhibiting the enzyme diphosphopyridine nucleotide diaphorase (Yanoff and Tsou, 1965). Where there is maculopathy there is destruction of rods and cones and dispersal of retinal pigment. This stage appears to be irreversible and it is essential to diagnose toxicity before it is reached. The term *premaculopathy* has been introduced to indicate a state of interference at the metabolic level which is reversible. Clinical evidence for the existence of this is provided by the reversibility of red field scotomata in patients with normal appearance of the fundus oculi. Further, EOG changes suggest metabolic involvement of the pigment epithelium as a whole, and reversibility of the EOG changes provides evidence that interference at the metabolic level in the peripheral retina is reversible.

Progression of maculopathy after discontinuation of treatment has been noticed by Penner and Somers (1962) and by Okun, Gouras, Bernstein, and von Sallmann (1963). It is also known that chloroquine may be present in plasma, red blood cells, and urine 5 years after cessation of therapy. Burns (1966) concluded that retinopathy could be delayed for some years following discontinuation before becoming manifest. His cases had not, however, been examined with respect to toxicity at the time of discontinuation, and are very likely to have been examples of progressive retinopathy but not delayed retinopathy. Experience from the present survey suggests that it is now always possible to prevent the occurrence of progressive retinopathy, and that the occurrence of delayed retinopathy is extremely unlikely.

For the diagnosis of premaculopathy although there is good correlation between the red central field defect and loss of the foveal reflex or suppression of the EOG, it is felt that the changes in the red field are the most reliable. The foveal reflex tends to become lost and the macular pigment irregular with advancing age; all patients should therefore undergo serial charting of the central field to a red target and serial foveal examination under mydriasis, the initial examination being before therapy has been commenced. A scheme has been detailed by Percival and Meanock (1968). The testing of retinal thresholds to red light in dark adapted subjects has also been shown to demonstrate early effects of chloroquine toxicity (Carr, Gouras, and Gunkel, 1966; Gunkel, 1967); fundus fluorescein photography shows clearly a defect in overt maculopathy, but has not yet been evaluated in cases of early toxicity. These tests, however, are not available at every ophthalmic outpatient department.

Electroretinography and dark adaptation studies have been shown to be unreliable (Okun and others, 1963; Carr and others, 1966); and the testing of colour vision, Amsler charting, perimetry, central field charting to white objects, and serial photography are of no value in screening patients for ocular toxicity (Percival and Meanock, 1968). If a patient has physiological red field defects at the commencement of therapy or is unreliable

for this type of testing or is colour blind, extreme caution is necessary, but serial EOG recordings and examination with a slit lamp and contact lens may be found useful.

The value of antimalarial drugs in discoid lupus and other skin disorders is undoubted (Kennedy, O'Quinn, Henington, and Perret, 1963; Rees and Maibach, 1963), and there have been several reports of benefit in rheumatoid arthritis (Freedman and Steinberg, 1960; Percival and Meanock, 1968), particularly when gold or steroids are contraindicated (Kersley, 1966). It may also be useful in the treatment of nephrotic syndromes and in systemic lupus erythematosus. But without an ophthalmological supervision which can be proved to be safe, the drug must be rejected from all forms of long term therapy.

Summary

An ophthalmic assessment was made serially on 198 patients whose fundi were normal and who were undergoing long-term chloroquine therapy. The difficulty in differentiating early signs of macular toxicity from normal age changes and the necessity for initial examinations to take place before therapy commenced were emphasized. By the serial recording of the central fields to red targets it was possible to diagnose a state of premaculopathy the effects of which were considered reversible after discontinuation of therapy. Serial electro-oculography and binocular examination of the macula with a slit lamp were both found to be of value in nearly half the patients with premaculopathy but were not considered sufficiently reliable for routine use.

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