Principles and Practice of Clinical Electrophysiology of Vision

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Retinal Toxicity With the Use of Chloroquine or Hydroxychloroquine

Gerald A. Fishman

The 4-aminoquinoline derivative chloroquine was first used in humans on a large scale during World War II as a treatment of malaria. At much higher doses, this drug was used in 1950 for the treatment of rheumatoid arthritis and in the following year for the treatment of patients with systemic lupus erythematosus. Hydroxychloroquine, which has been used since 1955, is also a 4-aminoquinoline derivative and is similar to chloroquine except that a hydroxyethyl group has been substituted for an ethyl group. It is marketed as a sulfate compound (Plaquenil). Both compounds are water soluble and well absorbed in the gastrointestinal tract after oral administration.

Patients receiving high dosages of chloroquine diphosphate (Aralen, Resochin) or chloroquine sulfate (Nivaquine) for extended periods can experience any of the following: tinnitus and imbalance on rapid head movements; cutaneous hyperpigmentation; whitening of the scalp hair, eyebrows, and eyelashes; temporary diplopia from extraocular muscle palsies affecting particularly the sixth cranial nerve; reduction in the amplitude of accommodation; decreased corneal sensitivity; intraepithelial corneal deposits; and retinal changes.

CORNEAL TOXICITY

The use of chloroquine and hydroxychloroquine can be associated with intraepithelial deposits in a whirl-like configuration, mainly in the lower third of the cornea. These deposits have some phenotypic similarities to those seen in carriers of Fabry's disease as well as those seen with the use of, among other drugs, amiodarone and certain aminoglycoside antibiotics. No relation has been demonstrated between the development of these corneal deposits and retinopathy. Although some reports in the literature indicate that as high as 30% to 45% of patients receiving long-term chloroquine therapy will develop these corneal changes, a more realistic expectation is closer to 10%. The development of these changes does not generally appear to be related to total drug dosage. Their occurrence is not a contraindication to continued treatment since they are gradually reversible when medication is withdrawn. In most instances, the corneal changes do not affect visual acuity, although perhaps as many as 50% of patients with corneal involvement will complain of seeing halos around lights, manifest some degree of photoaversion, and show a decrease in corneal sensation. Corneal deposits may appear as early as 2 to 3 weeks after antimalarial therapy is begun.

RETINAL TOXICITY

Retinal toxicity associated with the use of chloroquine was first clearly recognized by Hobbs and coworkers[21] in 1959. The clinical characteristics consist initially of a subtle parafoveal and, to a lesser degree, foveal granularity as the result of hypopigmentation and mottling of the retinal pigment epithe-

lium. A reduction in the foveal light reflex may be apparent. These changes can be difficult to identify with certainty unless patients have been examined prior to therapy. At this early stage, the patient is frequently symptom free since central visual acuity is often entirely normal. However, testing of parafoveal function with static perimetry will not infrequently detect a decrease in sensitivity in the parafoveal region of each eye. As retinal toxicity progresses, a bull's-eye–like pattern of hypopigmentation of the parafoveal retinal pigment epithelium becomes apparent by ophthalmoscopy. Its presence and pattern can be more apparent on fluorescein angiography as a regionalized hyperfluorescence. In addition to elevations of threshold (decrease in sensitivity) on static perimetry, a pericentral or paracentral scotoma can often be detected within 2 to 3 degrees of fixation by kinetic perimetry. At this stage, patients are frequently aware of visual disturbance, particularly while reading, that are associated with the parafoveal or perifoveal scotomas or with a reduction in central acuity.

Subsequently, the foveal lesion can become more extensive, with loss of its bull's-eye pattern (Fig 77–1). Additionally, the retinal periphery may subsequently show initial pigmentary changes in the form of nonspecific granular hyperpigmentation, followed by areas of retinal pigment epithelial cell hypopigmentation with anterior pigment migration and clumping in the form of bone spicule–like changes. In the more advanced stages, the peripheral pigmentary changes can become extensive and associated with narrowing of retinal arterioles, pallor of the optic disc, and peripheral visual field restriction (Fig 77–2). Infrequently, peripheral field restriction, peripheral pigmentary changes, and attenuated retinal vessels can be noted before the appearance of an atrophic or bull's-eye–appearing change within the fovea.[29]

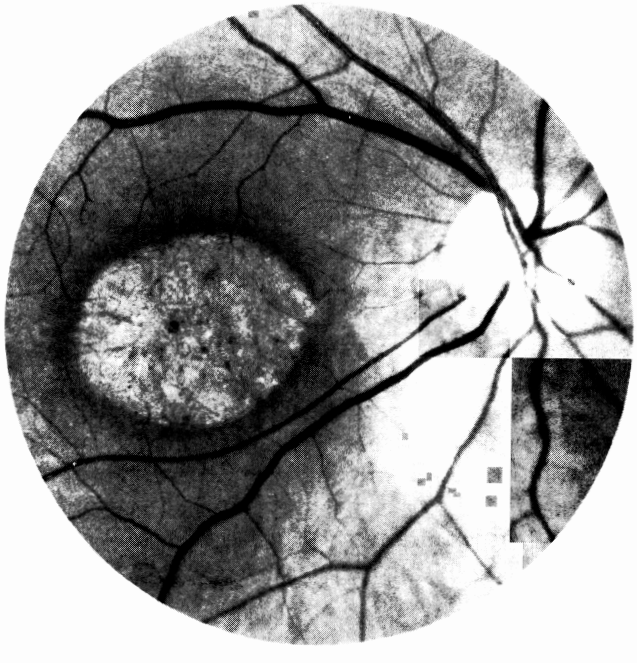

FIG 77–1.
Atrophic-appearing foveal lesion in the right eye from a patient with retinal toxicity associated with the use of chloroquine.

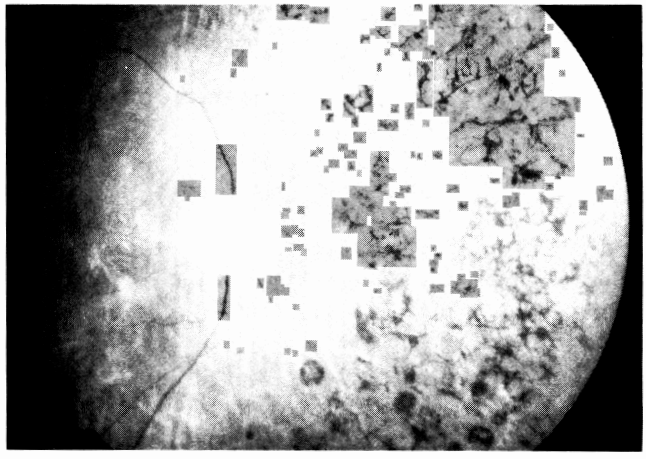

FIG 77–2.
Extensive pigmentary degeneration of the retina including large areas of hypopigmentation and bone spicule–like pigment clumping. Also note the attenuated retinal vessels and optic nerve pallor.

In the absence of clinically apparent retinopathy, mild degrees of foveal functional impairment may be reversed when drug therapy is discontinued. When retinopathy is recognized, even reasonably early, and chloroquine or hydroxychloroquine therapy is discontinued, in most instances the vision that has been impaired is not recovered, and the appearance of foveal pigmentary changes remains stable.[7, 10, 35] In a small proportion of cases, however, there may be improvement or total recovery of normal visual function and disappearance of the foveal abnormalities.[10] In a small but unfortunate number of cases, loss of vision and progressive pigmentary changes occur despite discontinuation of the drugs.[10, 34, 35] In rare instances, chloroquine-induced retinopathy can first develop after chloroquine therapy has been discontinued.[8] Generally, it seems that the more advanced the fundus changes are at the time of cessation of therapy, the greater is the likelihood of

progressive deterioration of visual function, and the greater is the likelihood of progressive retinopathy.

RISK OF RETINAL TOXICITY

There has been considerable debate as to whether the total cumulative dose of chloroquine and/or hydroxychloroquine is more relevant to the development of retinopathy than are the maximal daily doses. Initially, it was observed that the majority of cases of retinal toxicity associated with the use of these antimalarial drugs occurred after at least 2 or 3 years of treatment. This led some investigators[9, 41, 52] to emphasize careful assessment of those patients who had ingested a total cumulative dose of 100 g or more of chloroquine. Subsequently, Nylander[34] emphasized that enhanced vigilance was warranted primarily after patients had exceeded a total cumulative dose of 300 g. He observed that 79% of his patients with chloroquine retinopathy had been treated for a period of 3 years with a mean total dose of 300 g. However, other investigators[4, 16, 26, 31, 32, 36, 46, 49, 51, 53] emphasized the importance of the maximal daily dose rather than the total cumulative dose or duration of therapy as being the critical factor in antimalarial retinopathy. Johnson and Vine[24] emphasized that patients receiving daily doses of 400 mg/day (or less) or 6.5 mg/kg of body weight per day (whichever is less) may tolerate large cumulative doses (ranging from approximately 1,000 to nearly 4,000 g) of hydroxychloroquine without developing retinopathy. Similarly, they emphasized that the incidence of retinopathy with visual loss was negligible in patients ingesting 250 mg or less of chloroquine per day.

Nevertheless, Bernstein[5] showed that in a review of 65 cases from the literature in which antimalarial retinal toxicity occurred, 7 patients had not ingested more than 250 mg/day of chloroquine or 200 mg/day of hydroxychloroquine. More recently, Easterbrook[13] noted 35 patients with bilateral irreversible chloroquine retinopathy who had received 250 mg or less of chloroquine per day. Easterbrook suggested that the recommended maximal daily dose of chloroquine should be adjusted downward. Thus, it would appear as if both the total accumulative drug dose as well as maximal daily doses are both likely to be risk factors for the development of retinal toxicity.

The incidence of chloroquine-induced retinal toxicity has varied in different series from less than 1% to 22%, depending on the definition of retinopathy and the methods used for its detection.[52] From a realistic assessment of the literature, one would conclude that the incidence currently is from less than 1% to 6%,[4, 15] particularly if adherence to currently recommended daily dosages are maintained. Overall, there has been a considerably higher prevalence of retinal toxicity with the use of chloroquine as compared with hydroxychloroquine.[15] There is reasonable speculation that the higher prevalence with the use of chloroquine may relate to the higher dosages of the drug that were employed during its initial use. Prospective, appropriately controlled investigations are necessary to convincingly resolve this issue. It would seem prudent to exercise due caution with the use of each of these drugs.

MONITORING PATIENTS FOR RETINAL TOXICITY

There are a number of opinions in the literature on how to best monitor patients receiving chloroquine for signs of retinal toxicity. Ideally, any surveillance methods should catch signs of toxicity before there is irreversible damage. Some suggested methods of monitoring such as electroretinography (ERG) and fluorescein angiography do not meet the goal of catching toxicity at a point when it can be reversed. The method of monitoring recommended by the author is serial static perimetry. Because of the short-term variability in threshold measurements, it is vital to obtain baseline static threshold fields on all patients before or shortly after the beginning of drug therapy. This is also important for kinetic field measurements, particularly if red test targets are implemented since up to 6% of a normal population has been noted to have small scotomas with the use of this chromatic target as well as scotomas due to other pathology.[37] Therefore, during the first year of drug ingestion, in addition to obtaining a best-corrected visual acuity, it is recommended that two static perimetry examinations evaluating the central 5 to 10 degrees be performed approximately 6 to 9 months apart. If kinetic perimetry methods are to be used, at least one and preferably two baseline studies would be of merit. Color fundus photographs of the disc, macula, and periphery are warranted. If foveal changes are present at baseline, a fluorescein angiogram would likely be indicated.

During the second year of drug ingestion, recommended follow-up would include repeated visual acuity and static perimetry examination within the central 5 to 10 degrees 9 months after the last examination. If there is a change of 0.3 log units or less from previous thresholds, the findings should be considered unchanged. If a change greater than 0.3

log units is apparent, particularly 0.5 log units or greater, the examination should be repeated within 2 weeks. If a similar change is noted from the two baseline examinations, serious consideration should be given to termination of the drug therapy or at least to careful and frequent monitoring. It is reasonable to obtain color photographs. A fluorescein angiogram is probably not necessary unless baseline changes are being monitored since it is unlikely that retinopathy will be detected by fluorescein photography before the development of functional foveal defects discernible by static or even careful kinetic perimetry. Although some authors advocate the use of an Amsler grid test for patients,[13] this examination is also not likely to be either as sensitive or more sensitive than static perimetry testing. Nevertheless, isolated exceptions to this sentiment have been noted.[14] If patients are requested to monitor themselves with an Amsler grid at home, it should be emphasized that this self-assessment procedure does not replace careful follow-up examination by an ophthalmologist.

During the third year of drug ingestion, static perimetry as well as visual acuity assessment should be repeated 9 months after the last examination. Color photographs and kinetic perimetry are also reasonable to repeat at this time. Some authors advocate the use of a photostress test. Although abnormalities in recovery of visual function after light exposure can be apparent in patients with retinal toxicity caused by antimalarial drugs, there is no evidence that this procedure is more sensitive than static perimetry testing. Furthermore, results must be carefully interpreted by comparisons with age-similar controls.

In subsequent examinations, visual acuity and static perimetry testing should be performed. The frequency of the testing cannot be determined with precise accuracy, although evaluations every 9 to 12 months are probably reasonable since the examinations are noninvasive and not particularly time-consuming. Although some authors advocate protecting the eyes by tinted lenses for patients receiving antimalarial drugs,[31] there are no hard data to support the benefits of this suggestion. Since approximately 40% of hydroxychloroquine and chloroquine is renally excreted in an unchanged form,[31] properly functioning kidneys would likely be a factor to avoid unnecessarily elevated drug levels and an increased risk of retinal toxicity. Similarly, since up to 50% of each drug is biotransformed and broken down, probably mainly in the liver,[31] it is conceivable that patients with liver disease might be at greater risk for the development of drug toxicity. Thus, patients with renal or liver disease might warrant closer monitoring. Similarly, the frequency of monitoring for retinal toxicity might also be related to a patient's age since there is speculation that the development of toxicity may at least partially be age related.[31, 49]

It is further relevant to note that since these agents can cross the placenta and have been associated with birth defects, their use during pregnancy is probably contraindicated. Congenital defects such as deafness, mental retardation, and convulsions have occurred in the newborns of women who received chloroquine during pregnancy.[19, 28]

OTHER TESTS TO MONITOR TOXICITY

Although in the past, ERG,[50] electro-oculography (EOG),[3, 11, 23, 25] and color vision testing have all been advocated as meaningful measurements of retinal function for patients receiving antimalarial drugs, my experience suggests that static perimetry more reliably detects the early stage of retinopathy. Thus, ERG and color vision test plates are not likely to ascertain functional impairment of the retina in patients at risk for developing retinopathy at a sufficiently early stage to warrant their use in monitoring these patients.[1, 8, 12, 20, 30, 31, 33, 47, 48]

Infante and associates[23] demonstrated in a group of patients receiving chronic hydroxychloroquine that a few patients developed abnormal EOG light-to-dark ratios and abnormal values on the Farnsworth 100-hue test that reverted to normal values on withdrawing the medication. A few patients restarted after a period not receiving medication again developed abnormal EOG values that reverted to normal after drug withdrawal. No patients in their test group developed maculopathy, so it is not known whether any of their patients with abnormal values would have developed retinal damage.

Pinckers and Broekhuyse[38] note that even in the presence of a bull's-eye–appearing foveal lesion resulting from the use of chloroquine or hydroxychloroquine, only 37% of such cases have a reduced EOG ratio. These same authors caution that consideration needs to be given the possible effect that the underlying disorder for which antimalarials are being administered might have on EOG recordings. For example, in their experience, 20% of untreated rheumatoid arthritis patients were found to have subnormal EOG ratios. Further, the intraindividual variability in EOG ratios was found by Graniewski-Wijnands and coworkers[18] to be greater for patients

with rheumatoid arthritis than for a control population, and this resulted in more liberal criteria for change and less reliability in the monitoring of patients receiving antimalarial treatment.

In one report, investigators suggest that a supranormal EOG ratio may represent evidence of a pretoxic state in patients receiving hydroxychloroquine therapy.[23] This preliminary finding awaits confirmation and verification by other investigators in addition to long-term follow-up on such patients.

Preliminary studies on two patients with chloroquine retinopathy suggest that reductions in the ERG c-wave amplitude can be apparent while a- and b-wave amplitudes as well as EOG ratios remain normal.[43]

Although fluorescein angiography may be helpful in monitoring the progression of retinopathy once it has developed, its sensitivity in detecting the earliest drug-related foveal changes does not appear to parallel that afforded by static perimetry within the central 5 to 10 degrees.

PATHOGENESIS OF DRUG TOXICITY

Although the exact mechanism(s) by which these antimalarial drugs affect photoreceptor cell and retinal pigment epithelial cell function remains uncertain, it is of interest that chloroquine is known to heavily adsorb to uveal melanin.[30] This drug has a special affinity for melanin granules and will bind to melanin in the skin and hair as well as the pigmented tissues of the eye. Bernstein and coworkers[6] emphasize that chloroquine accumulates in the retina in concentrations 80 times that in the liver. Lawwill and coworkers[27] noted that chloroquine accumulates in the human choroid in an amount related to the dose and duration of drug ingestion. It has been speculated that chloroquine affects retinal cell function by inducing an inhibition of protein synthesis within retinal pigment epithelial cells.[17, 45] Alternatively, chloroquine is known to bind to DNA and thus may block DNA and RNA synthesis.[2] There is speculation as to the role of antimalarial drugs in affecting subcellular organelles such as lysosomes and smooth endoplasmic reticulum since lamellar membranous cytoplasmic bodies have been observed to occur in retinal cell neurons, particularly ganglion cells, with the use of these drugs.[22, 40, 42]

Once evidence of chloroquine toxicity has developed, patients should be monitored even after drug treatment has been terminated. A percentage of patients will continue to experience additional retinal degeneration. In this regard, it has been noted that metabolites of chloroquine have been detected in plasma, red blood cells, and urine for as long as 5 years after treatment with the drug has been discontinued.[44] The overall incidence of antimalarial drug retinal toxicity is fortunately quite low, but in view of the number of patients being treated with these drugs, it seems wise to not entirely relax vigilance in monitoring these patients since the consequence of not detecting retinal toxicity during its earliest stages is great in terms of loss in visual function. The management course outlined in this discussion seems prudent since it balances the low risk of developing retinal toxicity with the potentially dire consequences. The majority of ophthalmic practitioners are likely to have reasonably ready access to a device for static perimetry testing. The application of this test in the context of a regular ophthalmic examination every 9 to 12 months would seem justified in an attempt to prevent the development or progression of retinal toxicity with the use of antimalarial drugs. Although, as noted, the relative importance of daily dose vs. accumulative dose remains unresolved, it is likely that a majority of patients who receive dosages of chloroquine not exceeding 250 mg/day or hydroxychloroquine not exceeding 400 mg/day will be relatively safe but not immune to the development of retinal toxicity. With a total accumulative dose of 300 g, it is best to monitor patients with static perimetry assessment on at least an annual basis.

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REFERENCES

1. Adlakha D, Crews SJ, Shearer ACJ, Tonks EL: Electrodiagnosis in drug induced disorders of the eye. *Trans Ophthalmol Soc U K* 1967; 87:267–284.
2. Allison JL, O'Brien RL, Hahn FE: DNA: Reaction with chloroquine. *Science* 1965; 149:1111–1113.
3. Arden GB, Friedman A, Kolb H: Anticipation of chloroquine retinopathy. *Lancet* 1962; 1:1164–1165.
4. Bernstein HN: Chloroquine ocular toxicity. *Surv Ophthalmol* 1967; 12:415–442.
5. Bernstein HN: Ophthalmologic considerations and testing in patients receiving long-term antimalarial therapy. *Am J Med* 1983; 75(suppl):25–34.
6. Bernstein HN, Zvaifler N, Rubin M, Mansour AM: The ocular deposition of chloroquine. *Invest Ophthalmol* 1963; 2:384–392.
7. Brinkley Jr J, DuBois EL, Ryan SJ: Long-term course of chloroquine retinopathy after cessation of medication. *Am J Ophthalmol* 1979; 88:1–11.
8. Burns RP: Delayed onset of chloroquine retinopathy. *N Engl J Med* 1966; 275:693–696.
9. Carr RE, Gouras P, Gunkel RD: Chloroquine retinopathy: Early detection by retinal threshold test. *Arch Ophthalmol* 1966; 75:171–178.
10. Carr RE, Henkind P, Rothfield N, Siegel IM: Ocular

toxicity of antimalarial drugs: Long-term follow-up. *Am J Ophthalmol* 1968; 66:738–744.
11. Copeman MPW, Cowell TK, Dallas NL: Screening test for chloroquine retinopathy. *Lancet* 1964; 1:1369–1370.
12. Dubois EL: Antimalarials in the management of discoid and systemic lupus erythematosus. *Semin Arthritis Rheum* 1978; 8:33–51.
13. Easterbrook M: Dose relationships in patients with early chloroquine retinopathy. *J Rheumatol* 1987; 14:472–475.
14. Easterbrook M: The sensitivity of Amsler grid testing in early chloroquine retinopathy. *Trans Ophthalmol Soc U K* 1985; 104:204–207.
15. Finbloom DS, Silver K, Newsome DA, Guakel R: Comparison of hydroxychloroquine and chloroquine use and the development of retinal toxicity. *J Rheumatol* 1985; 12:692–694.
16. Frisk-Holmberg M, Bergkvist Y, Domeij-Nyberg, Hellstrom L, Jansson F: Chloroquine serum concentration and side effects: Evidence for dose-dependent kinetics. *Clin Pharmacol Ther* 1979; 25:345–350.
17. Gonasun LM, Potts AM: In vivo inhibition of protein synthesis in the retinal pigment epithelium by chloroquine. *Invest Ophthalmol* 1974; 13:107–115.
18. Graniewski-Wijnands HS, Van Lith GHM, Vijfvinkel-Bruinenga S: Ophthalmological examinations of patients taking chloroquine. *Doc Ophthalmol* 1979; 48:231–234.
19. Hart CW, Naunton RF: The ototoxicity of chloroquine phosphate. *Arch Otolaryngol* 1964; 80:407–412.
20. Henkind P, Carr RE, Siegel IM: Early chloroquine retinopathy. Clinical and functional findings. *Arch Ophthalmol* 1964; 71:157–165.
21. Hobbs HE, Sorsky A, Freedman A: Retinopathy following chloroquine therapy. *Lancet* 1959; 2:478–480.
22. Hodgkinson B, Kolb H: A preliminary study of the effect of chloroquine on the rat retina. *Arch Ophthalmol* 1970; 84:509–515.
23. Infante R, Martin DA, Heckenlively JR: Hydroxychloroquine and retinal toxicity. *Doc Ophthalmol Proc Ser* 1983; 37:121–126.
24. Johnson MW, Vine AK: Hydroxychloroquine therapy in massive doses without retinal toxicity. *Am J Ophthalmol* 1987; 104:139–144.
25. Kolb H: Electro-oculogram findings in patients treated with antimalarial drugs. *Br J Ophthalmol* 1965; 49:573–590.
26. Laaksonen A, Koskiahde V, Juva K: Dosage of antimalarial drugs for children with juvenile rheumatoid arthritis and systemic lupus erythematosus. *Scand J Rheumatol* 1974; 3:103–108.
27. Lawwill T, Appleton B, Allstatt L: Chloroquine accumulation in human eyes. *Am J Ophthalmol* 1968; 65:530–532.
28. Lewis R, Laverson NH, Birnbaum S: Malaria associated with pregnancy. *Obstet Gynecol* 1973; 42:696–700.
29. Lowes M: Peripheral visual field restriction in chloroquine retinopathy: Report of a case. *Acta Ophthalmol* 1976; 54:819–826.
30. Mackenzie AH: Antimalarial drugs for rheumatoid arthritis. *Am J Med* 1983; 75:48–58.
31. Mackenzie AH: Dose requirements in long-term therapy of rheumatoid arthritis with antimalarials. *Am J Med* 1983; 75(suppl):40–45.
32. Marks JS: Chloroquine retinopathy: Is there a safe daily dose? *Ann Rheum Dis* 1982; 41:52–58.
33. Marks JS, Power BJ: Is chloroquine obsolete in treatment of rheumatic disease? *Lancet* 1979; 1:371–373.
34. Nylander V: Ocular damage in chloroquine therapy. *Acta Ophthalmol Suppl* 1967; 92:5–71.
35. Okun E, Gouras P, Bernstein H, Sallmann LV: Chloroquine retinopathy. *Arch Ophthalmol* 1963; 69:59–71.
36. Olansky AJ: Antimalarials and ophthalmologic safety. *J Am Acad Dermatol* 1982; 6:19–23.
37. Percival S, Behrman J: Ophthalmological safety of chloroquine. *Br J Ophthalmol* 1969; 53:101–109.
38. Pinckers A, Broekhuyse RM: The EOG in rheumatoid arthritis. *Acta Ophthalmol* 1983; 61:831–837.
39. Potts AM: Further studies concerning the accumulation of polycyclic compounds on uveal melanin. *Invest Ophthalmol* 1964; 3:399–404.
40. Ramsey M, Fine BS: Chloroquine toxicity in the human eye. *Am J Ophthalmol* 1972; 73:229–235.
41. Reed H, Campbell AA: Central scotomata following chloroquine therapy. *Can Med Assoc J* 1962; 86:176–178.
42. Rosenthal AR, Kolb H, Bergsma D, Huxsoll D, Hopkins JL: Chloroquine retinopathy in the rhesus monkey. *Invest Ophthalmol Vis Sci* 1978; 17:1158–1175.
43. Rover J, Bach M: Slow retinal potentials in diseases of the retinal pigment epithelium. *Dev Ophthalmol* 1984; 9:195–203.
44. Rubin M, Bernstein HN, Zvailles NJ: Studies on the pharmacology of chloroquine: Recommendations for the treatment of chloroquine retinopathy. *Arch Ophthalmol* 1963; 70:474–481.
45. Rubin M, Slonicki A: A mechanism for the toxicity of chloroquine. *Arthritis Rheum* 1966; 9:537.
46. Rynes RI: Antimalarial treatment of rheumatoid arthritis: 1985 status. *J Rheumatol* 1985; 12:657–659.
47. Rynes RI, Krohel G, Falbo A, Reinecke RD, Wolfe B, Bartholomew LE: Ophthalmologic safety of long-term hydroxychloroquine treatment. *Arthritis Rheum* 1979; 22:832–836.
48. Sassaman FW, Cassidy JT, Alpern M: Electroretinography in patients with connective tissue diseases treated with hydroxychloroquine. *Am J Ophthalmol* 1970; 70:515–523.
49. Scherbel AL, Mackenzie AH, Nousek JE, Atdjian M: Ocular lesions in rheumatoid arthritis and related disorders with particular reference to retinopathy: A study of 741 patients treated with and without chloroquine drugs. *N Engl J Med* 1965; 273:360–366.
50. Schmidt B, Muller LW: Electroretinographic examinations following the application of chloroquine. *Acta Ophthalmol Suppl* (Copenh) 1962; 70:245–251.
51. Tobin DR, Krohel GB, Rynes RL: Hydroxychloroquine: Seven-year experience. *Arch Ophthalmol* 1982; 100:81–83.
52. Voipio H: Incidence of chloroquine retinopathy. *Acta Ophthalmol* 1966; 44:349–354.
53. Young P, Ispey E, Briggs H, Brosnan DW: Chloroquine retinopathy: A preliminary report of a five year study. *Arthritis Rheum* 1966; 9:552.