A STUDY OF
THE PHARMACOLOGY AND TOXICOLOGY OF
VISION IN THE SOLDIER

1. Chloroquine and Hydroxychloroquine

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FOREWORD

This is a technical report prepared for the Life Sciences Division, Army Research Office, Office of The Chief of Research and Development, Department of the Army, by the Staff of the Life Sciences Research Office, Office of Biomedical Studies, Federation of American Societies for Experimental Biology, with the consultative assistance of Wilbur M. Benson, M.D., Ph.D., in accordance with the provisions of United States Army Contract No. DA-HC19-68-C-0001.
I. SUMMARY

A critical evaluation of reports on the toxic effects of chloroquine and hydroxychloroquine on vision has revealed a relationship between the dosage and the hazards of these drugs for man. Chronic high doses, with a total dosage of 500 g or more administered over a period of months or years, may lead to ocular toxicity of a serious nature in some individuals. Relatively low total dosage of 100 g or less rarely results in visual pathology. The risk presented by intermediate dosage may be minimized by monitoring visual function at periodic intervals employing adequate tests to determine incipient injury. The detection of premacularopathy will permit the early cessation of drug therapy and reversal of pathologic changes in most patients.

Prolonged antimalarial chemoprophylaxis with chloroquine in the recommended doses for the military over a period of two years includes a total dose of approximately 60 g. The potential for retinal damage is so low at this dose that the use of chloroquine is not contraindicated. Caution must be exercised in administering higher doses because the retinopathy that may be produced in the rarely susceptible individual is serious and sometimes irreversible.

Research investigations on the biochemical transformation of melanin, and chloroquine binding to melanin in various tissues, revealed a possible explanation of the retinal toxicity of chloroquine and hydroxychloroquine. This phenomenon merits future study because reactions of this character appear to be closely associated with the oculocutaneous hyperpigmentation induced by a number of drugs.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreword</td>
<td>3</td>
</tr>
<tr>
<td>I. Summary</td>
<td>5</td>
</tr>
<tr>
<td>II. Introduction</td>
<td>9</td>
</tr>
<tr>
<td>III. Antimalarial Chemotherapy with the 4-Aminoquinolines</td>
<td>11</td>
</tr>
<tr>
<td>IV. The Pharmacology of Chloroquine and Hydroxychloroquine</td>
<td>13</td>
</tr>
<tr>
<td>A. Absorption, Distribution, and Excretion</td>
<td>14</td>
</tr>
<tr>
<td>B. Antimalarial Dosage of Chloroquine</td>
<td>15</td>
</tr>
<tr>
<td>C. Dosage of Chloroquine in Other Diseases</td>
<td>16</td>
</tr>
<tr>
<td>D. Antimalarial Dosage of Hydroxychloroquine Sulfate</td>
<td>16</td>
</tr>
<tr>
<td>E. Dosage of Hydroxychloroquine Sulfate in Other Diseases</td>
<td>17</td>
</tr>
<tr>
<td>V. Toxicology of Chloroquine</td>
<td>19</td>
</tr>
<tr>
<td>A. Antimalarial Chemoprophylaxis and Therapy</td>
<td>19</td>
</tr>
<tr>
<td>B. Chloroquine in Other Diseases</td>
<td>20</td>
</tr>
<tr>
<td>C. Corneal Deposits</td>
<td>20</td>
</tr>
<tr>
<td>D. Retinal Changes</td>
<td>23</td>
</tr>
<tr>
<td>E. Amount of Ingested Chloroquine in Retinopathy</td>
<td>24</td>
</tr>
<tr>
<td>F. Reversibility of Retinal Changes</td>
<td>27</td>
</tr>
<tr>
<td>G. Importance of Early Detection of Retinopathy</td>
<td>27</td>
</tr>
<tr>
<td>H. Histopathological Studies</td>
<td>28</td>
</tr>
</tbody>
</table>
I. Visual Changes of Possible Advantageous Nature

J. Attempts at Detoxification of Chloroquine

K. Chloroquine Ocular Pathology in Animals

VI. Toxicology of Hydroxychloroquine

VII. Diagnosis and Detection of Chloroquine or Hydroxychloroquine Retinal Pathology
   A. Individual Variation
   B. Degrees of Retinal Pathology
   C. Diagnostic Procedures for Retinopathy

VIII. Biochemical Transformation of Melanin and Chloroquine Binding to Melanin

IX. Conclusions

X. Suggestions for Future Studies

XI. Bibliography
   A. References Cited
   Author Index for References Cited (XI.A)
   B. References Reviewed but Not Cited
   C. Additional Clinical References Not Cited
II. INTRODUCTION

This report was initiated as a continuation of "A Study of Vision as Related to Dark Adaptation and Night Vision in the Soldier" (1). The objective of the study was to develop guidelines for future research useful in understanding the fundamental mechanisms of dark adaptation and night vision. The recognition of the adverse effect of drugs on vision prompted the specific review of the pharmacology and toxicology of vision as a separate report. The most urgent concern was the influence of the chemoprophylactic antimalarials on the vision of man. For this reason, the first report is related to the 4-aminoquinoline drugs; chloroquine and hydroxychloroquine.

Numerous drugs that are used in medical practice produce visual side effects. Some drugs are employed specifically for their actions on the eye. Adverse visual reactions may arise from the therapeutic misuse of drugs, or undesirable effects may occur from injudicious dosage. However, the majority of the reports of toxic visual drug effects are related to drugs prescribed in proper dosage for acceptable therapeutic requirements.

Emphasis in the broad study of the pharmacology and toxicology of vision will be placed on drugs prescribed for soldiers on active duty status, i.e., soldiers who are not hospitalized or relieved from duty for medical reasons. The chemical warfare agents will not be included even though the actions of these agents affect visual mechanisms. However, certain toxic military environmental substances, e.g., oxides of nitrogen, warrant specific mention and it is planned to include this topic in the scope of future reviews.

Pharmacologic parameters that determine whether a particular tissue of the body will be affected by a drug include: route of administration and dosage; metabolism at the specific tissue site; chemical interactions between responsive cells and the agent or its metabolic products; and the recipient's genetic makeup. Consideration is given to these aspects of the pharmacology and toxicology of drugs.

Environmental toxic substances in the air may act directly on the exposed eye, or they may be absorbed through the external integument, and act systemically on a target organ such as the eye. The constituents of respired air also may have effects both locally and systemically. Substances that impinge upon the body in these ways may produce visual effects that are not obviously related to the toxic agent, or they may enhance the toxicity of drugs such as the antimalarials.
Adverse visual drug effects include blurred vision, disturbances in color vision, scotomata, pigmentary degeneration of the retinal tissues, and morphologic tissue changes in the cornea, retina, and optic nerve. Visual disturbances produced as a side effect of certain drugs prescribed for therapeutic reasons may be anticipated, especially after high doses or prolonged therapy. However, in some instances, the ocular complications may be the result of unexpected individual reactions to a particular drug.

Pharmacotherapy with chloroquine and hydroxychloroquine embraces several dosage regimens. The dosage, duration of medication, and the therapeutic goals in malaria chemoprophylaxis, for example, are fundamentally different from those in rheumatoid arthritis or amebiasis. For this reason it was necessary to critically evaluate reports on the toxic effects of these drugs as they have been employed in different diseases.

Emphasis has been placed on reports of drug-induced corneal opacities, retinal changes, and the retinopathies including clinical observations on the nature of the retinal pathology. The review emphasizes dose-effect relationships, the pre-medication examination of the patient's vision, follow-up studies, and attempts to detoxify the drugs or reverse the pathologic changes. Animal studies designed to produce experimental ocular pathology with chloroquine, hydroxychloroquine, and other drugs that elicit similar toxic effects on vision, have been included in the review.

The relationship of the biochemical transformations of the pigment melanin to the visual toxicity of chloroquine or hydroxychloroquine is unknown. However, melanin has been demonstrated to have a strong affinity for chloroquine and the complex formed presumably has toxicologic and possibly therapeutic significance. The nature of these unusual biochemical intermediates, although intensively studied, remains one of the fundamental questions for future research in this field. Because this subject has a number of military medical interests the studies on animals and man on the basic mechanisms of melanin-drug complexing have been reviewed.

The literature reviewed includes the effects of drugs on human subjects and animals with special reference to the visual processes of the eye. Reports of drug effects on central nervous system pathways or the visual cortex were excluded from the study.
III. ANTIMALARIAL CHEMOTHERAPY WITH THE 4-AMINOQUINOLINES

The 4-aminoquinolines were investigated during World War II in the search for suppressive antimalarial drugs superior to quinacrine (Table 1). As a result, chloroquine and amodiaquine were discovered. Later, hydroxychloroquine was introduced into medicine as a less toxic antimalarial than chloroquine.

Chloroquine is highly effective against the asexual erythrocytic forms of *Plasmodium vivax*, sensitive strains of *P. falciparum*, and the gametocytes of *P. vivax*. It exerts no significant activity against the exo-erythrocytic tissue stages of plasmodia, even when given in massive doses. Thus, the drug is not a casual prophylactic agent and does not prevent the establishment of infection. In the acute malarial attack, it rapidly controls parasitemia and clinical symptoms. Under chloroquine therapy most patients become afebrile within 24 to 48 hours and thick smears of peripheral blood are generally negative by 48 to 72 hours. Chloroquine completely controls falciparum malaria caused by sensitive strains; however, chloroquine-resistant falciparum malaria has developed in Southeast Asia and some other regions of the world in recent years.

Hydroxychloroquine is an effective antimalarial drug used in a manner similar to chloroquine. It is a suppressive agent for vivax malaria and will cure *P. falciparum* infections caused by susceptible strains.

Amodiaquine is a suppressive drug for vivax malaria and cures infections of sensitive strains of falciparum malaria when administered in adequate, single doses. The single dose regimen for amodiaquine has been cited as an advantage in treating tropical native populations. In general, it compares favorably with chloroquine as an antimalarial. It is not recommended in the treatment of other diseases where the 4-aminoquinolines may be indicated because it is toxic in the prolonged high doses required for therapy.
TABLE 1
ANTIMALARIAL DRUGS*

Acridine derivative:
Quinacrine dihydrochloride - Atabrine®, Mepacrine®

4-Aminoquinoline derivatives:
Chloroquine sulfate - Nivaquine®
Chloroquine diphosphate - Aralen®, Avloclor®, Imagon®, Resochin®, Tresochin®
Hydroxychloroquine sulfate - Plaquinil®, Ercoquin®
Amodiaquine dihydrochloride - Camoquin®

8-Aminoquinoline derivatives:
Pamaquine naphthoate - Plasmochin®
Primaquine diphosphate

Triquin® is a combination of 65 mg of chloroquine diphosphate, 50 mg of hydroxychloroquine sulfate, and 25 mg of quinacrine dihydrochloride.

* The trade names and generic names of these drugs are used interchangeably in the pharmacological and clinical medical literature. The diphosphate and dihydrochloride salts are termed phosphate or hydrochloride respectively.
IV. THE PHARMACOLOGY OF CHLOROQUINE AND HYDROXYCHLOROQUINE

Chloroquine is 7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline, and hydroxychloroquine is 7-chloro-4-[4-(N-ethyl-N-β-hydroxyethylamino)-1-methylbutylamino]quinoline (Figure 1). Chloroquine is available as the diphosphate and sulfate salts. Hydroxychloroquine also forms a diphosphate but the sulfate salt is the form used in therapy.

FIGURE 1

![Chemical structures of Chloroquine and Hydroxychloroquine](image)

Chloroquine  Hydroxychloroquine

In antimalarial doses, chloroquine and hydroxychloroquine essentially are without marked pharmacodynamic actions. Because they elicit "anti-inflammatory" effects these drugs are used in the treatment of the collagen diseases. They have been used also in "photoallergic reactions." The mechanisms of action in producing therapeutic benefits in these conditions are obscure, and much larger doses are required than used in prophylaxis and treatment of malaria. Chloroquine is administered for extraintestinal amebiasis and has been therapeutically successful in giardiasis, although quinacrine is the drug of choice in the latter disease. Chloroquine and hydroxychloroquine will terminate experimental atrial fibrillation in dogs and have been suggested as substitutes for quinidine in the treatment of cardiac arrhythmias.
Hydroxychloroquine was introduced into medical practice as a less toxic antimalarial than chloroquine but evidence for this proposed lower toxicity is not convincing. Perhaps its outstanding uses have been in the treatment of rheumatoid arthritis, chronic discoid lupus erythematosus, and light sensitivity eruptions. The use of this drug in the treatment of various vascular diseases as a "desludging" agent is of interest.

A. ABSORPTION, DISTRIBUTION, AND EXCRETION

In general, the absorption, fate, and excretion of chloroquine and related 4-aminoquinolines are similar. Chloroquine is almost completely absorbed from the gastrointestinal tract of man; small amounts are found in the stools. Approximately 55% of the drug in the plasma is bound to non-diffusible plasma constituents. Excretion is quite slow and only 10 to 20% is found unchanged in the urine under normal conditions (2, 3). Excretion is increased by acidifying the urine.

Chloroquine and related 4-aminoquinolines undergo metabolic degradation by sequential removal of the alkyl side chain residue. The major urinary metabolite of chloroquine is the monoethyl derivative that also has antimalarial activity. Glucuronic acid conjugation occurs, but the exact nature of the conjugates is unknown (4).

Chloroquine is deposited in the tissues including the formed cells of the blood in considerable amounts. In animals, 200 to 700 times the plasma concentration may be found in the liver, spleen, kidney, and lung. The brain and spinal cord, in contrast, contain only 10 to 30 times the amount present in plasma (5). The melanin binding of chloroquine in melanin-rich tissues is of special interest (Section VIII, p 37).

Because of the affinity of the tissues for chloroquine, a loading or priming dose has been considered essential if effective therapeutic plasma levels are to be reached quickly. When the drug is discontinued it slowly disappears from the tissues over a period of months. With a dose of 0.5 g of the phosphate once weekly, the peak plasma level varies between 150 to 250 \( \mu \text{g} \) per liter. Just prior to the succeeding dose, the range is 20 to 40 \( \mu \text{g} \) per liter.

Hydroxychloroquine is absorbed, distributed, and excreted in a manner similar to chloroquine. There are minor differences. In human volunteers, hydroxychloroquine produced higher peak plasma
levels than chloroquine in comparable antimalarial doses (2). When administered on a weekly suppressive dose schedule (0.62 g base in the first week and 0.31 g every 7th day thereafter) hydroxychloroquine provided plasma levels equivalent to chloroquine. Although man excretes less hydroxychloroquine than chloroquine in the urine, and the former drug may have a somewhat greater persistence in the blood, there does not appear to be a significant metabolic difference in the two compounds.

B. ANTIMALARIAL DOSAGE OF CHLOROQUINE

In chemoprophylaxis, the recommended military dosage for combined chloroquine-primaquine is "one weekly tablet of 0.5 g of chloroquine phosphate and 0.079 g of primaquine phosphate taken on the same day of each week*." Dosage is started at least one day prior to entering an endemic area and continued after leaving on a weekly basis for a minimum of 6 weeks, and preferably for 8 weeks (6).

In the treatment of the clinical disease, an initial dose of two chloroquine phosphate tablets (1.0 g) is administered. This is followed in six hours by one tablet (0.5 g) of chloroquine phosphate. Subsequently, one 0.5 g tablet is administered daily for the next two days. Thus, four doses are given over a period of 3 days for a total of 2.5 g of chloroquine phosphate (6).

A soldier maintained on the recommended prophylactic dosage would receive a total dose of 30 g of chloroquine phosphate according to the following calculation:

\[
\begin{align*}
52 \text{ weeks of endemic prophylaxis} & \\
+ 8 \text{ weeks of post-endemic prophylaxis} & \\
60 \text{ weeks} & \\
\times 0.5 \text{ g chloroquine phosphate per week} & \\
30.0 \text{ g for total dosage regimen} & 
\end{align*}
\]

During a two-year tour of duty a soldier would not usually receive more than 60 g of chloroquine phosphate. By calculation, 30 g of chloroquine phosphate is equivalent to 18 g of base.

* 0.5 g chloroquine phosphate is equivalent to 0.3 g of chloroquine base; 0.079 g of primaquine phosphate is equivalent to 0.045 g of primaquine base. The dose for these drugs is frequently expressed in terms of the base.
Chloroquine phosphate is administered in tablet form by the oral route either before or after meals. The hydrochloride of chloroquine may be employed for parenteral (intramuscular) injection if necessary. If parenteral therapy is required during coma in the treatment of falciparum malaria, the equivalent of 0.2 g of chloroquine base may be administered intramuscularly. This may be repeated at intervals of 6 hours, but the total dose for the first 24 hours should never exceed the equivalent of 0.9 g of base (equivalent to 1,125 g of chloroquine hydrochloride). Parenteral administration should be terminated as soon as the drug can be taken orally.

C. DOSAGE OF CHLOROQUINE IN OTHER DISEASES

The administration of chloroquine in the long-term treatment of diseases other than malaria may involve the administration of 0.25 to 0.75 g of the phosphate daily for many months or even years. Consequently, the incidence of side effects and degree of toxicity may be greater following such high dose, long-term therapy. To equate these high dosage schedules with antimalarial therapy the following calculations have been made:

0.25 g chloroquine phosphate per day = 91.25 g per year
0.50 g chloroquine phosphate per day = 182.50 g per year
0.75 g chloroquine phosphate per day = 273.75 g per year.

In the treatment of extra-intestinal amebiasis, the usual adult dosage of chloroquine phosphate is 1.0 g daily for two days followed by 0.5 g daily for at least two or three weeks. The maximum dose by this regimen would be 12.5 g.

D. ANTIMALARIAL DOSAGE OF HYDROXYCHLOROQUINE SULFATE

In chemoprophylaxis a dose of 0.4 g weekly has been used to prevent recurrent attacks of vivax malaria.

In the treatment of the clinical attack a 0.8 g dose is given initially, followed by 0.4 g in 6 to 8 hours, and 0.4 g on each of two successive days. A single 0.8 g dose has been used to control \textit{P. falciparum} infections caused by sensitive strains.
E. DOSAGE OF HYDROXYCHLOROQUINE SULFATE IN OTHER DISEASES

In discoid lupus erythematosus and polymorphous light eruptions, an initial adult dose of 0.4 g is administered once or twice daily for several weeks or until a favorable or a toxic response is obtained. Maintenance therapy usually may require a dose of 0.2 to 0.4 g daily.

In rheumatoid arthritis an initial daily dose of 0.4 to 0.6 g is continued for 4 to 12 weeks before the maximal beneficial effects may be obtained. When the desirable clinical response has been achieved, the dosage may be reduced to 0.2 to 0.4 g daily. This dosage may be continued for several years in some patients, thus a total yearly dose may be calculated:

\[
\begin{align*}
0.2^* \text{ g hydroxychloroquine sulfate per day} &= 73 \text{ g per year} \\
0.4 \text{ g hydroxychloroquine sulfate per day} &= 146 \text{ g per year}.
\end{align*}
\]

* 0.2 g hydroxychloroquine sulfate is equivalent to 0.155 g of hydroxychloroquine base.
V. TOXICOLOGY OF CHLOROQUINE

A. ANTIMALARIAL CHEMOPROPHYLAXIS AND THERAPY

Dosage of chloroquine for therapy of the acute malarial attack may cause mild and transient headache, gastrointestinal complaints (anorexia, nausea, vomiting, diarrhea, abdominal cramps), pruritus, or psychic stimulation. Prolonged chronic medication for suppressive purposes causes few significant untoward effects, and only rarely must the drug be discontinued because of intolerance.

A comprehensive study of the long-term toxicity of chloroquine to healthy volunteers was reported in 1948 (7). Two groups of 20 men each were given chloroquine orally for one year in doses greater than those required for antimalarial suppression or therapy. One group took 0.3 g (base) daily for 77 days (total 23.1 g) and then 0.5 g (base) once weekly for the remainder of the year (total dose 43.6 g for the year). Group 2 received 0.5 g (base) weekly throughout the period of one year (total 26 g). The authors note that high daily dosage caused visual disturbances, headache, bleaching of the hair, electrocardiographic changes, and slight weight loss. These changes diminished or disappeared when the dosage was decreased. The visual symptoms consisted of a difficulty in changing focus quickly from a near to a far object. Tests for visual acuity, accommodation, and diplopia failed to demonstrate any abnormality. The visual symptoms disappeared when the dosage was lowered to 0.5 g weekly. The electrocardiogram changes (T-wave depression) were considered to be without clinical significance. The bleaching of the hair gradually disappeared after the dosage was reduced. The toxicity was reduced in subjects on the weekly dosage regimen and difficulty in accommodation was observed rarely. Skin eruptions developed in two individuals, were mild, and similar to those reported during therapy with quinacrine. Headache and loss of body weight were considered to be without significance. This early report and similar studies on related 4-aminoquinolines (8) demonstrated the relative safety of these drugs in the recommended antimalarial dose range. In the intervening 20 years chloroquine has had world-wide use as a safe and effective drug in the treatment of malaria.
B. CHLOROQUINE IN OTHER DISEASES

Chloroquine has been used extensively in long-term therapy of rheumatoid arthritis (9, 10, 11, 12, 13), discoid lupus erythematosus (14, 15), systemic lupus erythematosus (16, 17), and light sensitivity eruptions (18). The benefits that occur in most patients with discoid lupus erythematosus have led to the rather general acceptance of chloroquine or hydroxychloroquine in the treatment of this disease. The benefits in rheumatoid arthritis have been less notable and the use of these drugs in systemic lupus erythematosus or polymorphous light eruptions is controversial.

The reports on toxicity selected from the clinical literature are related to the use of chloroquine or hydroxychloroquine in prolonged, high doses in diseases other than malaria or amebiasis. An excellent current summary of the side effects of these drugs appeared in 1968 (19).

In addition to the untoward effects on vision, other infrequent but reversible side effects of chloroquine noted in the manufacturer's brochure (20) are: "pleomorphic skin eruptions, erythema annulare centrifugum, pigmentary changes, leukopenia with normal differential count, thrombocytopenia, aplastic anemia, agranulocytosis, neuropsychiatric disturbances (nervousness, vertigo, tinnitus, irritability, emotional change, nightmares, psychotic episodes, and convulsions), and slight weight loss. A few cases of a nerve type of deafness have been reported after prolonged therapy, usually in high doses." There are reports of skeletal muscle weakness in some patients, noted during prolonged therapy with chloroquine. The muscle strength usually began to improve within a few weeks when the drug was discontinued. The principal toxicity of chloroquine and hydroxychloroquine is injury to the cornea and the retina (19).

C. CORNEAL DEPOSITS

According to Nylander (21) deposits of "chloroquine" in the cornea of patients receiving this drug were described in 1958. Similar reports followed and numerous clinical observations on "keratopathy" in patients on long-term chloroquine or hydroxychloroquine therapy are recorded in the literature.

The corneal changes have been described in various terms but the descriptions of Schindel (19) and Nylander (21) provide an
accurate summary. The first detectable change is the appearance of dot-shaped, granulated opacities, scattered over the entire cornea. These deposits are arranged in indistinct lines corresponding to the Hudson-Stühli lines (pigmented lines in eyes of elderly patients, just below the center of the cornea). The deposits are curved or have central spiral formations with horizontal arms—like radiation lines in a magnetic field—progressing to irregular, buckled, crowded, opaque lines, often slightly pigmented. Some reports note that in the late stages the deposits lay more deeply in the parenchyma, and form greenish-yellow, thicker lines. The changes are always bilateral.

It is not known if the corneal deposits are chloroquine or a colored compound formed as a result of a photochemical reaction of chloroquine with some intracellular substance, such as melanin (Section VIII, p 37).

There is disagreement regarding the effect of these corneal deposits on the vision of the subject. Some authors report that the corneal changes do not usually influence visual acuity and patients do not complain of visual difficulties. Some patients describe a flickering experience, a photophobia, and colored rings or halos around lights. These complaints decrease on continued drug treatment in most patients, and disappear within a few weeks after the drug is discontinued (22, 23, 24, 25, 26, 27, 28). For these reasons, the majority of authors have expressed the view that chloroquine treatment need not be discontinued because corneal deposits are detected or because the patient experiences the mild visual symptoms.

The relationships between duration of drug therapy, total dose and the incidence of corneal deposits or keratopathy are uncertain. An incidence of 31 to 48% has been reported by different authors. The degree of deposition of opacities varies from mild corneal edema to "fairly strong marked lines of greenish-yellow pigmentation." Nylander (21) included all these changes as "corneal deposits" in his data on duration of chloroquine therapy (Table 2). Unfortunately, the total dosage for these patients is not recorded. Not all physicians would agree with this definition of corneal deposits. It is difficult to determine the criteria used by different clinicians to classify the corneal changes, the prior elimination of patients with corneal deposits before drug therapy, the dosage, and duration of therapy.

The detection of pigmented corneal deposits after prolonged, high dosage of chloroquine or hydroxychloroquine may be an expression of the accumulation of the drugs in the body tissues. Animal experiments support this view (Section V, p 29). Exposure of
TABLE 2


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<th>Duration of therapy, years</th>
<th>Total number of cases</th>
<th>Corneal deposits</th>
</tr>
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<tbody>
<tr>
<td>½ - 1</td>
<td>26</td>
<td>9 (34%)</td>
</tr>
<tr>
<td>1 - 2</td>
<td>44</td>
<td>14 (32%)</td>
</tr>
<tr>
<td>2 - 3</td>
<td>49</td>
<td>19 (38%)</td>
</tr>
<tr>
<td>3 - 8</td>
<td>120</td>
<td>57 (46%)</td>
</tr>
<tr>
<td>½ - 8</td>
<td>239</td>
<td>99 (41%)</td>
</tr>
</tbody>
</table>

(Ref. 21).
the eye to light intensifies pigment formation; in addition, corneal deposits are readily observed. However, there seems to be no relationship between the occurrence of corneal deposits and chloroquine-induced retinopathy (21, 29).

D. RETINAL CHANGES

Patients administered daily chloroquine doses for several months or years for lupus erythematosus or rheumatoid arthritis have exhibited retinal changes including: narrowing of arterioles, optic disc pallor, optic atrophy, and patchy retinal pigmentation. In addition, macular lesions have been reported consisting of loss of foveal reflex, areas of edema, atrophy, and abnormal pigmentation. These descriptions have been given by various authors to describe the "retinopathies" observed in patients. Unfortunately, standard criteria for terminology are not used and it is impossible to accurately correlate the degree of visual pathology in the different reports (Section VII, p 33). Studies of control groups of patients of the same age and with the same disease are seldom reported. The absence of pre-drug eye examinations and careful post-drug examinations makes the determination of drug causal relationships uncertain. Nevertheless, it is generally agreed that these retinal changes are serious, are usually related to prolonged administration of high daily doses of chloroquine or hydroxychloroquine, and emphasize the importance of careful ophthalmoscopic examination to detect early symptoms reversible upon discontinuing the drug.

These retinal changes, in addition to the field defects of paracentral or pericentral ring type scotomata, and typically, temporal scotomata, apparently account for the nyctalopia, difficulty in reading, blurred distant vision, "floaters," flashes of light, photophobia, misty vision, and defective color vision reported by patients.

The fundus changes seen in advanced chloroquine retinopathy are characteristic, with a dark spot in the center of the macula surrounded by a broad zone of granular pigmentation—a feature described as a "bullseye" lesion. Nylander (21) cites 11 references reporting this characteristic retinal change. These changes were considered largely irreversible (22, 25) but not progressive if drug administration was stopped. Other reports suggest that the lesion is neither progressive nor regressive (30).

The comprehensive report of Percival and Meanock (13) noted the characteristic ring or bullseye lesion with a diagnosis of
"chloroquine maculopathy" in 11 of 272 patients on high doses of the drug. Careful examination revealed early manifestations of maculopathy in an additional 5 patients on the basis of pigment irregularity and loss of the foveal reflex in maculae previously normal. The authors comment that fine macular pigment mottling and loss of the foveal reflex are well-known age changes in the normal eye. They illustrated the correlation of red-field threshold changes with age and with chloroquine-induced red-field defects (Figure 2). It is necessary to differentiate clinically unimportant symptomatic eye changes from serious pathologic changes. This is obviously difficult. Some reviews have stressed the significance of the ocular manifestations of the collagen diseases and the need to avoid confusing these signs with retinopathy from chloroquine therapy.

E. AMOUNT OF INGESTED CHLOROQUINE IN RETINOLOGY

A review of the literature indicates that this type of ocular toxicity is, in general, related to excessive dosage. Only a small number of retinopathy cases have been reported in which the daily dose was consistently moderate, and those patients showing retinotoxic effects on lower dosages may metabolize the drug in some unusual manner or may have a true idiosyncracy to chloroquine. Several studies have shown a daily dosage of chloroquine greater than 0.25 g produced visible retinal abnormalities (31, 32). Scherbel et al. (28) studied 408 patients receiving no more than 0.25 g chloroquine or related medication daily for prolonged periods of time, and found little evidence of fundic change typical of chloroquine retinopathy. In terms of total dosage of chloroquine, one study (17) indicated that in those patients manifesting retinopathy the total mean dose was 785 g. In patients on a comparable regimen but without retinopathy, the total mean dose was 368 g. Potts in 1966 (33) indicated that the total dose for retinopathy is above 100 g of drug. Nylander confirmed this view if the duration of chloroquine treatment is less than one year and the total dose less than 100 g (21). Voipio (34) reported only 4 cases of chloroquine retinopathy in a total of 121 patients treated for less than a year (Table 3).

Some reports stress that chloroquine retinopathy is not the result of an individual idiosyncracy but occurs in all patients ingesting a critical daily amount of chloroquine. There is evidence that ophthalmoscopically visible chloroquine retinal toxicity usually occurs only when a daily dosage rate greater than 0.25 g is administered when the total exceeds 400 g. In contrast, there is evidence obtained by retinal threshold testing that all patients receiving a total dose of only 100 g and a daily dose greater than 0.2 g show evidence of "disturbed" retinal function (16, 35).
Disappearance of the foveal reflex with age. White columns give the incidence of absent foveal reflex in different age groups of 138 patients with normal maculae and no red field defects. Black columns give the incidence in 59 patients on chloroquine with red field defects which disappeared on discontinuation of treatment (Ref. 13).
TABLE 3

CHLOROQUINE RETINOPATHIES. DURATION OF THERAPY AND TOTAL DOSE

<table>
<thead>
<tr>
<th></th>
<th>up to 1 yr</th>
<th>1-2 yrs</th>
<th>2-3 yrs</th>
<th>3-5 yrs</th>
<th>over 5 yrs</th>
<th>Unknown Duration</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>up to 100 g</td>
<td>2</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>101 - 200 g</td>
<td>2</td>
<td>10</td>
<td>3</td>
<td>-</td>
<td>3</td>
<td>-</td>
<td>18</td>
</tr>
<tr>
<td>201 - 300 g</td>
<td>-</td>
<td>4</td>
<td>7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>11</td>
</tr>
<tr>
<td>301 - 500 g</td>
<td>-</td>
<td>-</td>
<td>12</td>
<td>12</td>
<td>-</td>
<td>-</td>
<td>24</td>
</tr>
<tr>
<td>over 500 g</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>18</td>
<td>24</td>
<td>-</td>
<td>42</td>
</tr>
<tr>
<td>Unknown dose</td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td><strong>Total</strong></td>
<td><strong>16</strong></td>
<td><strong>24</strong></td>
<td><strong>32</strong></td>
<td><strong>29</strong></td>
<td><strong>16</strong></td>
<td><strong>121</strong></td>
</tr>
</tbody>
</table>

(Ref. 34).
F. REVERSIBILITY OF RETINAL CHANGES

The reversibility of retinal changes depends on a number of factors, but the principal one is the degree of pathology or "the extent of retinal involvement." If the obvious signs of retinal abnormalities can be detected by "standard ophthalmological techniques," probably the injury has advanced to a degree that is irreversible (16, 26). Early detection is regarded as essential if irreversible changes are to be avoided. However, such measures as electrophysiological tests and perimetric threshold to red light are required to detect these early changes that presumably elude standard testing procedures (16, 27). According to one report, even macular lesions may be reversible if observed before overt visual symptoms are noted (27).

Prior to prolonged chloroquine or hydroxychloroquine therapy with the high doses administered in rheumatoid arthritis or discoid lupus erythematosus, patients should have careful ophthalmoscopic examinations including slit-lamp, fundus, and visual field studies. Some authors suggest ocular examinations every three months to detect retinopathy at the earliest possible time (16, 26, 28, 36). This is particularly important when one considers that retinopathy can be asymptomatic and reversible only in the early stages.

G. IMPORTANCE OF EARLY DETECTION OF RETINOPATHY

The accuracy and sensitivity of the ophthalmological examination are critical. If skillfully employed, then definitive measures may be instituted to prevent the development of retinopathy. Although a number of diagnostic procedures are used and periodic eye examinations may be carried out, there is a need for increased use of sensitive screening techniques. In addition to funduscopic and general visual field tests, other measures of detection of early changes have been employed: dark adaptometry (25, 37), campimetry and Amslar charts (25), electroretinogram (ERG) (37), and the electro-oculogram (EOG) (27). However, the ERG and EOG are not always abnormal in cases of chloroquine retinopathy (16).

A determination of the red visual threshold for a small area of the retina can be more sensitive than the ERG or EOG (16). Perimetric light threshold tests (retinal profiles) are most sensitive in determining retinal dysfunction caused by chloroquine. Elevation of the retinal threshold after a total dosage exceeding 100 g is an initial sign of retinal degeneration, especially in the macular and paramacular areas. Unfortunately, these reports of
early detection of retinal pathology in patients receiving chloroquine or hydroxychloroquine would not identify those cases of retinopathy that appear after a long delay (38).

H. HISTOPATHOLOGICAL STUDIES

Wetterholm and Winter (39) reported histopathological examination on a patient receiving high doses of chloroquine who subsequently died of acute cardiac arrest. Previously, the subject had reported constricted peripheral vision and a pericentral ring scotoma was evident. Histopathological examination of retinal sections revealed normal retinal vascularity, choroid, ganglion cells, and inner nuclear layer. However, rod and cone processes of the receptor layer were severely reduced. Both inner and outer segments of the receptors were affected. Autopsy studies by Bernstein et al. (40) revealed pigment aggregation in the inner nuclear layer as well as destruction of rods and cones following chloroquine therapy. Histopathologic study of the eye is not usually included in postmortem examinations. This explains the paucity of records on ocular and retinal pathology related to the antimalarial drugs.

I. VISUAL CHANGES OF POSSIBLE ADVANTAGEOUS NATURE

Although most visual changes reported have been of an adverse nature, one is of interest because it indicates a possible beneficial side effect of antimalarial medication (41). While taking chloroquine and primaquine (post-endemic prophylaxis) a physician, returned from Vietnam, personally experienced a decrease "to almost zero" of his dark adaptation time. It was possible for him to perform fluoroscopy within one or two minutes in the darkened examining room. The ability to dark adapt decreased over a period of time. This phenomenon should be studied in other subjects receiving antimalarial medication.

J. ATTEMPTS AT DETOXIFICATION OF CHLOROQUINE

Chloroquine excretion is enhanced by acidification of the urine. Jaller et al. (42) determined the influence of orally administered NaHCO₃ or NH₄Cl on the renal excretion of chloroquine. In 5 patients receiving 0.2 to 0.4 g of chloroquine daily, the urinary excretion varied from 15 to 50% of the ingested dose during
control periods. This was reduced to 7 to 20% following alkalinization with NaHCO₃ and was increased to 20 to 90% after acidification by ingestion of NH₄Cl.

Although Perez et al. (43) were unable to demonstrate a removal of chloroquine from the choroid or iris of rabbits by the administration of NH₄Cl or the heavy metal antidote dimercaprol (BAL), pretreatment with ascorbic acid sharply decreased chloroquine binding. They explained the effects on the basis of increasing acidity in the tissues as causing a decrease in chloroquine adsorption.

Animal data indicate chlorpromazine pretreatment interferes with the ocular deposition of chloroquine. Potts (44) showed that chlorpromazine and other phenothiazines are concentrated in ocular tissues and their uptake may be inhibited by prior treatment with substances competing for melanin binding. The effect of ascorbic acid on chloroquine tissue distribution in guinea pigs profoundly affected the overall metabolism of chloroquine (45). However, it did not significantly affect the ocular concentration of the drug.

K. CHLOROQUINE OCULAR PATHOLOGY IN ANIMALS

Experimental keratopathy was produced in albino rats by the intramuscular administration of high, repeated doses of chloroquine sulfate for 3 to 7 months (46). The keratopathy was characterized by epithelial edema, epithelial and superficial stromal deposits of yellow or reddish-brown color, and newly formed capillaries in the subepithelial stroma. An orange-red fluorescence of the peripheral two-thirds of the cornea was observable with ultraviolet irradiation. Other workers have produced corneal changes in pigmented rats (47).

The development of experimental chloroquine retinopathy in animals has been more difficult. Zvaifler et al. (47) analyzed ocular tissues of pigmented rats fed 0,25 g of chloroquine weekly for 6 months. High concentrations of the drug and its metabolites were found in the cornea, iris, retina, and sclera. Bernstein et al. (40) observed storage of chloroquine in the iris and choroid of pigmented rabbits and rats in concentrations significantly greater than in other tissues.

Chronic exposure of pigmented-rat eyes to high concentrations of chloroquine or hydroxychloroquine and their degradation products did not produce any detectable ocular histopathology. Administration of these drugs to both albino and pigmented rats in daily doses of 40 mg/kg, produced a rapid rise in tissue concentration during the
first month of medication, but comparatively little additional increase when the medications were continued for 2 more months (48). The mean tissue concentration of chloroquine at 1 month was about 100 mg/kg compared to about 30 mg/kg for hydroxychloroquine. However, rats degrade the latter drug more extensively. The order of increasing tissue concentration for both drugs was: muscle, eye, heart, kidney, liver, lung, and spleen.

Albino and pigmented rabbits fed chloroquine phosphate for 11 months with approximately 10 or 20 times the usual human body weight daily dose, were studied for retinopathy (49). Microscopic ocular examination of the pigmented rabbits revealed characteristic pigmented deposits involving the choroid, pigment epithelium, iris, and ciliary body. The albino rabbits showed no abnormality in these structures.

Meier-Ruge (50) demonstrated abnormal retinal pigmentation in cats by chronic administration of subtoxic doses (1.5 to 6.0 mg chloroquine per kg body weight daily) by examining paraffin and histochemically treated sections. The primary "toxic action" of chloroquine in the cat involved enlargement of the pigment epithelium followed by a decrease in mucopolysaccharidase activity. This change progressed to a reduced enzyme activity in the ellipsoids of rods and cones. Eventually, a focal detachment of the retina and desquamation of pigment epithelium was observed. Finally, atrophy of the rods and cones ensued. Chloroquine retinopathy in cats appeared 4 to 7 weeks after starting treatment. Initially there was a light pigmentation of the whole fundus. The retinal disturbance began with an opaqueness of the fundus, resembling edema, followed by a pigmentation with small grey-black and white spots. After 7 to 8 weeks the retinopathy was completely developed. Pigmentation appeared to diminish after 20 weeks.
VI. TOXICOLOGY OF HYDROXYCHLOROQUINE

Hydroxychloroquine is reported to be better tolerated in large doses than chloroquine in most patients, although there is marked variation of individual patient tolerance to both drugs. The incidence of side effects is lower with hydroxychloroquine therapy than with chloroquine therapy, but the reactions are similar and may be equally severe (51, 52, 53). In one report hydroxychloroquine produced an incidence of corneal deposits of 21% as compared to 38% in patients treated with chloroquine (54). However, most authors neither comment on, nor compare, the clinical effectiveness of relative toxicity of the two drugs.
VII. DIAGNOSIS AND DETECTION OF CHLOROQUINE OR HYDROXYCHLOROQUINE RETINAL PATHOLOGY

A. INDIVIDUAL VARIATION

Chronic ingestion of chloroquine or hydroxychloroquine in the dosage used for the treatment of rheumatoid arthritis and discoid lupus erythematosus may lead to retinal pathology in some patients. This dosage and the chronicity of administration greatly exceeds the dosage used for malarial suppression or therapy. No reports were found in this review of the literature of documented retinal pathology caused by antimalarial medication with these two drugs. Nevertheless, it must be recognized, because of the broad range of individual variation, that some sensitive individuals may develop ocular pathology to a moderately low dosage. It is not known if the retinal injury produced by these drugs could be related to allergic hypersensitivity.

B. DEGREES OF RETINAL PATHOLOGY

No exact definition of the term chloroquine retinopathy is found in the literature (21). To better correlate the degree of pathology with the dosage of ingested chloroquine or hydroxychloroquine, the following outline is an attempt to describe, by degree, the nature of retinal involvement. These descriptions are modified from previous suggestions (13, 35).

Degree 1 - Premacularopathy. The earliest indication of retinopathy has been referred to by Percival and Meanock (13) as "premaculopathy." The maculae appear to be normal yet either develop paracentral red scotomata or lose the foveal reflex during therapy.

Degree 2 - Macular Mottling. The first visible sign of retinopathy may occur in the macular region where a deep mottling occurs, usually accompanied by loss of the foveal reflex and a perimacular sheen.

Degree 3 - Macular Bullseye. The pigment disturbance increases and a so-called macular bullseye occurs in which there is a central pigmented area surrounded by an atrophic region of the retina. The rest of the retina appears
normal. The patient may be asymptomatic up to, and occasionally including, this latter stage. Generally, there is no detectable vascular change in the sense of arteriolar narrowing in the early stages.

Degree 4 - Marked Pigment Disturbance. As the retinopathy progresses, a marked pigment disturbance resembling a tapeto-retinal degeneration may be noted over the entire retina.

C. DIAGNOSTIC PROCEDURES FOR RETINOPATHY

Evidence is abundantly clear that retinopathy may occur with chloroquine and hydroxychloroquine after administration of large doses over a long time. For this reason, periodic ophthalmologic examination is indicated. While corneal deposits disappear with discontinuation of the drugs, once established, the advanced retinal changes appear to be irreversible. Certainly any patient on large doses of these drugs presenting visual symptoms should be evaluated promptly. Both electrophysiologic and psychophysical tests have been used in the attempt to determine retinal damage at an early stage. Visual field examination and tests of color vision have limited value except in more advanced cases of retinopathy. Dark adaptometry and perimetric threshold determinations have been useful (16). Chronic stages of retinopathy resemble natural pigmentary degeneration supporting the view that both aging or drug administration may produce a primary lesion in the pigment epithelium.

In chloroquine retinopathy the ERG and EOG may present striking abnormalities even though visual sensitivity and the visual fields are not necessarily affected (55). The ERG is a measure of retinal potentials after stimulation of the eye by light. On the other hand, the EOG is a measure of the resting, unstimulated, ocular potential. The latter is more difficult to record and interpret. Of importance is the discovery that after chloroquine therapy the ERG exhibits enlarged c-waves. Although commonly found in the rabbit eye, any c-wave in the human eye is considered pathological. Noell (56) proposed that the c-wave is generated in the pigment epithelium. The finding of large c-waves in the affected human retina is, therefore, very compelling evidence as to the site of action of the drug (55).

In the "photostress test" (macular dazzle test) of Severin et al. (57) chloroquine increased the mean time of visual acuity recovery (Table 4).
TABLE 4

EFFECT OF CHLOROQUINE ON RECOVERY OF VISUAL ACUITY BY MACULAR DAZZLE TEST

<table>
<thead>
<tr>
<th>Controls</th>
<th>Chloroquine</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 26</td>
<td>N = 32</td>
</tr>
<tr>
<td>Range = 12-35 Sec</td>
<td>Range = 40-180 Sec</td>
</tr>
<tr>
<td>Mean = 24.5 Sec</td>
<td>Mean = 93.5 Sec</td>
</tr>
</tbody>
</table>

(Ref. 35).

In a study of central field assessment, Percival and Meanock (13) found that of 144 subjects receiving chloroquine, 65 had red scotomata while 79 had no scotomata. In the control group of 100 subjects, 6 had red scotomata while 94 had none. The defects in the control group were presumed to be physiological and possibly due to a slight variation of cone configuration near the macula. Although in this study there was little relationship of red field defect to dose, the red field defect was reported to correlate well with the loss of foveal reflex, and was a much earlier measurable feature in the development of maculopathy.
VIII. BIOCHEMICAL TRANSFORMATION OF MELANIN AND CHLOROQUINE BINDING TO MELANIN

Melanin production usually involves the formation of dihydroxyphenylalanine (DOPA) from the amino acid tyrosine. This process is an oxidation mediated by the enzyme, tyrosinase, producing the quinone of DOPA. The oxidation is followed by spontaneous ring closure and polymerization to melanin (58). The entire process is autocatalytic as the production of DOPA stimulates both tyrosine oxidation as well as tyrosinase activity. Tyrosinase is both a monophenol and a polyphenol oxidase, oxidizing DOPA to DOPA quinone and the latter to polymerized precursors of melanin.

When the polyphenolase activity of the tyrosinase system is blocked, accumulation of DOPA and its quinone may occur. It has been suggested that DOPA accumulation could affect melanin binding with various drugs. Chloroquine-type compounds are known to induce depigmentation of the skin and hair, as well as pigment changes in the eye. In addition, melanin, in the pigment epithelium, does bind chloroquine. Thus, alteration of melanin metabolism is probably accompanied by impaired permeability and chloroquine binding, but the mechanisms are poorly understood. Because chloroquine is a good electron donor and melanin a good electron acceptor, it has been suggested that the binding involves π-complexing (59).

Chloroquine is known to interact with melanin and other metabolic intermediates. Chloroquine binds to deoxyribonucleic acid, stabilizes lysosomes, blocks the sulfhydryl-disulfide interchange reactions, and interferes with the action of several other enzymes. Furthermore, chloroquine can cause bleaching of the hair (7, 24, 60, 61, 62).

It is possible that chloroquine binding of melanin interferes with the normal metabolism of the pigment epithelium, resulting in disruption of the visual cycle. The pigment epithelium is known to have a role in supplying and regulating certain precursors of the rod visual pigment, rhodopsin. In primary pigmentary degeneration of the retina, the dark adaptation threshold may be elevated. Thus, when chloroquine binding occurs the result could be diminution of night vision capability and ultimately blindness. Further studies of the relation between chloroquine metabolism in the retina and the visual cycle are required.

Hague (63) suggested that drug-induced pigment changes in the eye may not be drug effects directly upon the eye but that the
retino-hypothalamo-hypophyseal mechanism may play an intermediate role. Little is known about this system in mammals and if neuronal mechanisms acting through the pineal gland affect retinal pigmentation. Currently there is considerable interest and research in this area.

In studies with pigmented rats and rabbits, Bernstein et al. (40) found that chloroquine is stored in the iris and choroid in concentrations significantly greater than in other tissues of the body. The high levels of chloroquine in the melanin granules of the choroid and pigment epithelium strongly suggests that the initial pathologic alterations leading to the development of chloroquine retinopathy originate in one or both of these areas. The drug first appears in these tissues of the rabbit between 6 and 12 hours after administration when it can no longer be detected in plasma. There is a rapid buildup to maximum levels within 24 hours for the choroid and 48 hours for the iris. The drug levels then gradually decrease; at 28 days, when there are no longer detectable quantities in the liver or any of the other organs studied, the concentration in the choroid remains exceedingly high. Even 63 days after a single intramuscular injection, the drug was still found in high concentrations in the choroid. The concentration of the drug in the iris of the pigmented rat was over 80 times the concentration found in the liver. However, chloroquine was not detected in the iris or choroid of the albino rat. Sams (59) indicated the presence or absence of white light does not influence the amount of chloroquine bound to ocular melanin in guinea pigs.

The characteristic deposits in the eyes of pigmented rabbits involving the choroid, pigment epithelium, iris, and ciliary body after prolonged oral administration of chloroquine is especially noteworthy. Treated albino rabbits showed no abnormality of these structures (49).

These studies emphasize the striking affinity of chloroquine for the melanin-containing tissues of the eye — the iris, choroid, and pigment epithelium and the possible relationship of this unusual biochemical characteristic to the development of the retinopathy. The extensive tissue accumulation and the prolonged retention in the tissues after drug administration are of importance. These facts explain, in part, the low level of urinary excretion of chloroquine for at least 10 days following the administration of a single dose. In patients on long-term chloroquine therapy, traces of the drug have been found in the blood and urine several years after cessation of therapy.
IX. CONCLUSIONS

Chronic high dosage of chloroquine or hydroxychloroquine, totaling 500 g or more, may be associated with ocular toxicity of a serious nature. However, low dosage, totaling no more than 100 g, rarely, if ever, results in retinopathy. With intermediate dosage, retinopathy can occur and the degree of risk involved in pursuing a course of therapy is related to the daily dose, the accumulated dose, and the sensitivity of the patient. The risk may be minimized by monitoring visual function prior to therapy, at regularly scheduled time intervals during therapy, and immediately if visual difficulties are experienced.

The potential for retinal damage in antimalarial suppressive dosage of chloroquine does not contraindicate its use. However, the seriousness of potential visual injury requires caution in the administration of the drug for prolonged periods. If chloroquine or hydroxychloroquine is administered for the treatment of collagen diseases for prolonged periods of time, dosage should be kept at the lowest possible level consistent with the chemotherapy.

No reports were found in the literature on careful eye examinations of subjects receiving antimalarial chemoprophylaxis of chloroquine or hydroxychloroquine for periods of one to two years. To resolve this question, a controlled study should be made. This information would be extremely useful in understanding the degree or nature of any visual changes experienced in military personnel as a result of long-term administration of these drugs.
X. SUGGESTIONS FOR FUTURE STUDIES

No published reports have been found on the study of the vision of subjects receiving long-term suppressive antimalarial therapy with chloroquine or hydroxychloroquine. The vision of these subjects should be evaluated by the improved diagnostic techniques now available for the early detection of retinal involvement. A comprehensive clinical and laboratory evaluation, including appropriate vision tests, might be made pre-drug, at monthly intervals, immediately after discontinuing the drug, and several months later to determine the character of any visual changes. These determinations, including dark adaptation thresholds and paracentral red scotomata on a small number of men of different ages, would reveal the degree of visual changes, if any, induced by these drugs. The continued use of chloroquine as an antimalarial warrants the study of the effects of this drug in antimalarial doses on all aspects of vision. It would be valuable to have documented, reliable clinical and laboratory data on the absence of untoward visual effects of chloroquine or hydroxychloroquine when administered in antimalarial doses.

More information is needed on the toxic mechanisms of chloroquine and hydroxychloroquine in high doses that produce retinopathy. Histopathologic studies by electron microscopy would be most useful in understanding the nature of the pathologic lesions. Improved funduscopic visualization techniques and retinal photography may be helpful in screening large numbers of individuals and in providing better analyses of individual cases.

The significance of chloroquine binding to the melanin pigments of the body is not understood. The biological half-life of melanin-bound chloroquine is not known. Chloroquine effects on the retina may be correlated with the persistent binding of the drug to melanin; but until the role and significance of the melanins in different tissues are better understood it will not be possible to explain these relationships. Not all the melanin in the body has the same chemical characteristics and it is possible that the melanin in the eye is unique in its binding ability for numerous drugs, including chloroquine or hydroxychloroquine. Analytical techniques to determine the type and degree of tissue and melanin-chloroquine binding would be useful. Postmortem ocular tissues should be examined histologically and histochemically to study these drug-tissue interactions. The latent visual effects of chloroquine or hydroxychloroquine may be explained by the persistent melanin binding if the analytical data supported this concept.
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Retinopathy.

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to Quinine.
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Complications.

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of the Retina.

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of Visual Cells and Pigment Epithelium.

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Appel, B.
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and Chloroquine Diphosphate (Aralen).

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Bleaching of Hair by Chloroquine.

63. Hague, E.B.
Opening Remarks.
### AUTHOR INDEX FOR REFERENCES CITED (XI.A)

- **A**-

<table>
<thead>
<tr>
<th>Author</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alving, A.S.</td>
<td>7</td>
</tr>
<tr>
<td>Appel, B.</td>
<td>61</td>
</tr>
<tr>
<td>Arden, G.B.</td>
<td>55</td>
</tr>
<tr>
<td>Atjijian, M.</td>
<td>28</td>
</tr>
<tr>
<td><strong>-G-</strong></td>
<td></td>
</tr>
<tr>
<td>Couras, P.</td>
<td>16, 37</td>
</tr>
<tr>
<td>Gunkel, R.D.</td>
<td>16</td>
</tr>
</tbody>
</table>

- **B**-

<table>
<thead>
<tr>
<th>Author</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baldwin, E.</td>
<td>58</td>
</tr>
<tr>
<td>Bater, G.R.</td>
<td>61</td>
</tr>
<tr>
<td>Banks, W.F.</td>
<td>2, 45, 48</td>
</tr>
<tr>
<td>Bernstein, H.</td>
<td>37, 40, 47</td>
</tr>
<tr>
<td>Blanchard, K.C.</td>
<td>8</td>
</tr>
<tr>
<td>Bricknell, P.P.</td>
<td>52</td>
</tr>
<tr>
<td>Burns, R.P.</td>
<td>38</td>
</tr>
<tr>
<td><strong>-H-</strong></td>
<td></td>
</tr>
<tr>
<td>Hague, E.B.</td>
<td>63</td>
</tr>
<tr>
<td>Harper, J.Y.</td>
<td>57</td>
</tr>
<tr>
<td>Haydu, G.G.</td>
<td>9</td>
</tr>
<tr>
<td>Heidensleben, E.</td>
<td>29</td>
</tr>
<tr>
<td>Henkind, P.</td>
<td>17, 26</td>
</tr>
<tr>
<td>Hobbs, H.E.</td>
<td>15, 25</td>
</tr>
<tr>
<td>Hollingsworth, A.</td>
<td>52</td>
</tr>
<tr>
<td>Hughes, Hettie B.</td>
<td>5</td>
</tr>
</tbody>
</table>

- **C**-

<table>
<thead>
<tr>
<th>Author</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calkins, L.C.</td>
<td>24</td>
</tr>
<tr>
<td>Carr, R.E.</td>
<td>16, 17, 35</td>
</tr>
<tr>
<td>Collins, Sylvia F.</td>
<td>61</td>
</tr>
<tr>
<td>Craig, B.</td>
<td>7</td>
</tr>
<tr>
<td>Crews, S.J.</td>
<td>27</td>
</tr>
<tr>
<td>Culver, J.F.</td>
<td>57</td>
</tr>
<tr>
<td><strong>-J-</strong></td>
<td></td>
</tr>
<tr>
<td>Jacobson, C.</td>
<td>14</td>
</tr>
<tr>
<td>Jailer, J.W.</td>
<td>42</td>
</tr>
<tr>
<td>Jones, R.</td>
<td>7</td>
</tr>
</tbody>
</table>

- **D**-

<table>
<thead>
<tr>
<th>Author</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dale, A. J.D.</td>
<td>49</td>
</tr>
<tr>
<td>Dall, J.L.C.</td>
<td>60</td>
</tr>
<tr>
<td>Deering, D.</td>
<td>23</td>
</tr>
<tr>
<td>Dept. of the Army</td>
<td>6</td>
</tr>
<tr>
<td><strong>-K-</strong></td>
<td></td>
</tr>
<tr>
<td>Karo, T.</td>
<td>31</td>
</tr>
<tr>
<td>Keane, J.A.</td>
<td>60</td>
</tr>
<tr>
<td>Kersley, G.D.</td>
<td>53</td>
</tr>
<tr>
<td>Knox, J.M.</td>
<td>18, 32</td>
</tr>
<tr>
<td>Kuroda, K.</td>
<td>3</td>
</tr>
</tbody>
</table>

- **E**-

<table>
<thead>
<tr>
<th>Author</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eadie, S.P.</td>
<td>25</td>
</tr>
<tr>
<td>Egelius, N.</td>
<td>54</td>
</tr>
<tr>
<td>Eichelberger, L.</td>
<td>7</td>
</tr>
<tr>
<td>Elliott, J.H.</td>
<td>36</td>
</tr>
<tr>
<td>Ellsworth, R.J.</td>
<td>22</td>
</tr>
<tr>
<td>Evans, E.M.L.</td>
<td>52</td>
</tr>
<tr>
<td><strong>-L-</strong></td>
<td></td>
</tr>
<tr>
<td>Lamb, J.H.</td>
<td>18</td>
</tr>
<tr>
<td>Layton, D.D.</td>
<td>49</td>
</tr>
<tr>
<td>Life Sci. Res. Office</td>
<td>1</td>
</tr>
<tr>
<td>Lindstedt-Johnsson, E.</td>
<td>54</td>
</tr>
</tbody>
</table>

- **F**-

<table>
<thead>
<tr>
<th>Author</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fojas, M.R.</td>
<td>55</td>
</tr>
<tr>
<td><strong>-M-</strong></td>
<td></td>
</tr>
<tr>
<td>Mackenzie, A.H.</td>
<td>28</td>
</tr>
<tr>
<td>Madow, B.P.</td>
<td>51</td>
</tr>
</tbody>
</table>

- 49 -
<table>
<thead>
<tr>
<th>Name</th>
<th>Page(s)</th>
<th>Name</th>
<th>Page(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mansour, A.M.</td>
<td>40,43</td>
<td>Shannon, J.A.</td>
<td>42</td>
</tr>
<tr>
<td>Mantyjarvi, M.</td>
<td>31</td>
<td>Sharvill, D.E.</td>
<td>62</td>
</tr>
<tr>
<td>Maudgal, M.C.</td>
<td>46</td>
<td>Shelimire, B.</td>
<td>18</td>
</tr>
<tr>
<td>Mayer, W.</td>
<td>30</td>
<td>Sommerville, F.</td>
<td>25</td>
</tr>
<tr>
<td>McAuliff, J.P.</td>
<td>2</td>
<td>Sorsby, A.</td>
<td>15</td>
</tr>
<tr>
<td>McChesney, E.W.</td>
<td>2,45,48</td>
<td>Steinberg, V.L.</td>
<td>12</td>
</tr>
<tr>
<td>Meanock, I.</td>
<td>13</td>
<td>Sullivan, D.J.</td>
<td>48</td>
</tr>
<tr>
<td>Meier-Ruge, W.</td>
<td>50</td>
<td>Tye, M.J.</td>
<td>61</td>
</tr>
<tr>
<td>Middleton, H.G.</td>
<td>52</td>
<td>Voipio, H.</td>
<td>34</td>
</tr>
<tr>
<td>Mills, J.B.</td>
<td>36</td>
<td>von Sallmann, L.</td>
<td>37</td>
</tr>
<tr>
<td>Morgan, R.J.</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noell, W.K.</td>
<td>56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nousek, J.E.</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nylander, U.</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Okun, E.</td>
<td>37</td>
<td>Wetterholm, D.H.</td>
<td>39</td>
</tr>
<tr>
<td>Parkhill, E.M.</td>
<td>49</td>
<td>Whorton, M.</td>
<td>7</td>
</tr>
<tr>
<td>Percival, S.P.B.</td>
<td>13</td>
<td>Wiland, J.</td>
<td>45</td>
</tr>
<tr>
<td>Perez, R.</td>
<td>43</td>
<td>Williams, R.T.</td>
<td>4</td>
</tr>
<tr>
<td>Pillsbury, D.M.</td>
<td>14</td>
<td>Winter, F.C.</td>
<td>39</td>
</tr>
<tr>
<td>Potts, A.M.</td>
<td>33,44</td>
<td>Winthrop Laboratories</td>
<td>30</td>
</tr>
<tr>
<td>Pullman, T.N.</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rane, P.S.</td>
<td>41</td>
<td>Zeller, R.W.</td>
<td>22,23</td>
</tr>
<tr>
<td>Rinehart, R.E.</td>
<td>10</td>
<td>Zvaifler, N.J.</td>
<td>40,43,47</td>
</tr>
<tr>
<td>Rosenfeld, M.</td>
<td>42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rothfield, N.F.</td>
<td>17,26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rubin, M.</td>
<td>40,43,47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sams, W.M., Jr.</td>
<td>59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scherbel, A.L.</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schiff, B.L.</td>
<td>61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schindel, L.</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schmidt, Ida G.</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schmidt, L.H.</td>
<td>5,8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severin, S.L.</td>
<td>57</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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- 55 -
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- 56 -
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A STUDY OF THE PHARMACOLOGY AND TOXICOLOGY OF VISION IN THE SOLDIER

1. Chloroquine and Hydroxychloroquine

Technical Report

Staff Report, Life Sciences Research Office

July 1969

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Life Sciences Division, Army Research Office, OCRD, DA, Washington, D.C., 20310

A critical evaluation of reports on the toxic effects of chloroquine and hydroxychloroquine on vision has revealed a relationship between the dosage and the hazards of these drugs for man. Chronic high doses, with a total dosage of 500 g or more administered over a period of months or years, may lead to ocular toxicity of a serious nature in some individuals. Relatively low total dosage of 100 g or less rarely results in visual pathology. The risk presented by intermediate dosage may be minimized by monitoring visual function at periodic intervals employing adequate tests to determine incipient injury. The detection of premacularopathy will permit the early cessation of drug therapy and reversal of pathologic changes in most patients.

Prolonged antimalarial chemoprophylaxis with chloroquine in the recommended doses for the military over a period of two years includes a total dose of approximately 60 g. The potential for retinal damage is so low at this dose that the use of chloroquine is not contraindicated. Caution must be exercised in administering higher doses because the retinopathy that may be produced in the rarely susceptible individual is serious and sometimes irreversible.

Research investigations on the biochemical transformation of melanin, and chloroquine binding to melanin in various tissues, revealed a possible explanation of the retinal toxicity of chloroquine and hydroxychloroquine. This phenomenon merits future study because reactions of this character appear to be closely associated with the oculocutaneous hyperpigmentation induced by a number of drugs.
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