Diplopia and Loss of Accommodation due to Chloroquine

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Impaired visual accommodation is a frequently occurring complication of chloroquine therapy. The present report describes a patient whose ocular function was assessed serially during chloroquine administration. Impaired convergence and loss of accommodative amplitude developed several weeks after beginning chloroquine treatment; the magnitude of these alterations in ocular function was dose related. Chloroquine-induced changes persisted during therapy, but ocular function returned to pretreatment limits 1 week after discontinuing the drug.

Among the ocular abnormalities induced by chloroquine, loss of accommodation and extraocular muscle weakness, although mentioned in the literature, are only sketchily described. When one attempts to analyze descriptions of patient complaints from written reports, it is difficult to evaluate the symptom, "blurring of vision." Corneal opacities (deposits), retinal changes, classical maculopathy, or even optic nerve injury are as likely to cause "blurring" as accommodative weakness and unrecognized minimal diplopia.

The reported incidence of the latter problems in patients being treated with chloroquine varies according to the diligence of the examiner. In Percival and Meanock's series,[1] 32 of 46 patients noticed blurred vision when reading soon after beginning treatment at double the regular dose. These authors attributed the symptom to a transient increase in presbyopia, ie, a transient loss of accommodation. Three of their patients also noted diplopia, which disappeared when the drug was discontinued. Diplopia in these patients was due variously to (1) an isolated, superior oblique muscle palsy (2) a latent internal strabismus which became manifest and (3) an exacerbation of a prior superior rectus muscle weakness. Henkind and Rothfield[2] reported their observations of 56 patients who had received chloroquine. Only in 2 was "occasional diplopia" noted, but there was frequent mention of "difficulty with close work, particularly reading." The true incidence of impaired accommodation could not be ascertained since refraction was not done and pretreatment measurements were not available. When treating patients with hepatic amebiasis, both Patel[3] and Conan[4] noted accommodation problems in an occasional patient whose dose of chloroquine

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had been abruptly increased from 500 mg/day to 1 g/day[3] or from 300 to 600 mg/day.[4] Karlsbeck[5] described an instance of bilateral paralysis of the abducens nerve with diplopia after using chloroquine. Whisnant *et al*[6] reported 4 patients with chloroquine-induced neuromyopathy, one of whom had blurring of vision with intermittent diplopia while receiving 500 mg/day.

In none of the reports of patients receiving chloroquine could we find actual documentation of the time-course and the extent of accommodation loss. The present report comprises observations of a patient who had dramatic accommodative loss and diplopia as dose-related sequelae of chloroquine administration.

CASE REPORT

F.L., a 50-year-old white woman, was found to have an enlarged spleen in 1958; in 1963, hypercalcemia was detected. Because of persistent anemia, a tremendously enlarged spleen was removed in 1965, and this operation revealed extensive sarcoidosis involving the spleen, mesenteric lymph nodes and liver. The anemia was corrected by the splenectomy. and the persisting hypercalcemia was subsequently controlled by continuous corticosteroid administration.

The patient was first seen by us in 1967 to determine if agents other than corticosteroids would be effective in correcting the hypercalcemia. The physical examination was unremarkable except for dry, atrophic skin, scattered subcutaneous ecchymoses and a firm, slightly enlarged liver. Serum analyses revealed a CO_2 of 24 mEq/liter, chloride 103 mEq/liter, potassium 4.4 mEq/liter, proteins 7.9 g/100 ml with total globulins of 3.9 g/100 ml, uric acid 8.5 mg/100 ml, creatinine repeatedly 1.7 to 2.1 mg/100 ml, calcium 12.3 to 12.5 mg/100 ml, inorganic phosphorus 3.0 to 3.6 mg/100 ml and alkaline phosphatase 54 to 63 KA units. The hematocrit was 40 vol %. The bromsulphthalein retention was 10%. Urinary calcium varied from 440 to 560 mg/24 hr while the patient was receiving a dairy product-free diet. Roentgenograms revealed calculi in one kidney.

Because of previous observations about the efficacy of chloroquine in correcting hypercalcemia associated with sarcoidosis,[7] this form of therapy was instituted. Pretreatment ocular examination revealed no abnormalities; vision was 20/20 with a +1.75 D spherical correction. Although she wore a +2.0 bifocal add, the accommodative near point was determined without these lenses and was found to be 50 cm, indicating an accommodative amplitude of approximately 2 diopters (D). Color vision on the H-R-R test was normal, and visual fields were unrestricted. Full extraocular muscle rotations were present, but a 10 prism D esophoria (a latent tendency of the eyes to turn inward) was observed at both distance and near, and a near point of convergence of 3 cm was present.

After receiving chloroquine 500 mg/day for 2 weeks, the patient noted occasional diplopia and persistent, blurred near vision. The near point of accommodation had receded to approximately 1 meter. After 4 weeks of therapy, the dose was increased to 1000 mg/day. Within 2 days, diplopia became severe, especially by late afternoon, requiring reduction of the dose to the previous level. Within 3 days, exacerbation of visual symptoms had subsided.

Detailed ocular examinations after 7 weeks of treatment revealed orthophoria (the eyes remain perfectly aligned when there is no stimulus for fusion) for distance. The convergence near point had receded to 15 cm, and the accommodative amplitude was 1 D in each eye with an exophoria (a latent tendency of the eyes to turn outward) of 16 to 20 prism D for near vision. At this time, the dose was again increased to 1000 mg/day. By the second day, the amplitude of accommodation had decreased to 0.25 D; the exophoria at near remained at approximately 20 prism D; at distance, there was exophoria of 3 D. The patient's fusional amplitude was markedly reduced, and diplopia was almost constantly present. Symptoms and findings remained unchanged during an additional 5 days of chloroquine at 1 g/day. The drug was then discontinued. Forty-eight hours later, diplopia had largely disappeared; the accommodative amplitude had increased to 1 D; the exophoria at near decreased to 9 D. The patient was noted to have 4 prism D esophoria for distance. One week after cessation of chloroquine, the accommodative amplitude had improved to 1.5 D, and both near and distance phoria had returned to pretreatment position of 10 prism D esophoria.

During the 8 weeks of chloroquine therapy, serum calcium decreased slightly from pretreatment values of 12.3–12.5 mg/100 ml to 11.5–11.7 mg/100 ml; urinary calcium decreased to approximately 360 mg/24 hr.

DISCUSSION

The mean accommodative amplitude for a 50-year-old subject is 2.1 D (range of 1.0 to 3.2 D).[8] The amplitude of accommodation in patient F.L. was 1.5 to 2.0 D. The observed effects of chloroquine on her ocular function were: (1) to decrease the accommodative amplitude to 0.25 D and (2) to change extraocular muscle balance so that pretreatment esophoria was converted to marked exophoria of 20 prism D for near. In other words, the basic (resting) eye posture tended to be directed in an overconverged position for near, but during chloroquine therapy it became markedly under-converged, as if either the medial recti muscles or the central convergence center had been affected. The medial recti, however, were found to function well in both binocular and monocular rotations Thus, it appears that chloroquine affected the convergence center of the midbrain rather than the medial recti muscles or their nerve supply. The changes in accommodative amplitude might also be accounted for by a central effect of the chloroquine, since the neural centers for convergence and accommodation are closely approximated. Unfortunately, we did not use a peripheral accommodative stimulus, such as pilocarpine, to determine whether a peripheral effect was present. Thus, interference with peripheral accommodative mechanisms by the chloroquine remains a possibility.

The impairment of accommodation and convergence induced in this patient with chloroquine was more severe than in most of the previously cited reports.[1-5] It is possible that reduced hepatic and renal function sufficiently impaired chloroquine degradation and excretion to cause unusually high concentrations in various tissues. Nonetheless, there was a limited effect on the patient's hypercalcemia and hypercalciuria. Although certain manifestations of sarcoidosis frequently respond to chloroquine administration, there have been too few reported studies on chloroquine modification of the deranged calcium metabolism to assess how often this derangement may be modified or corrected by such therapy.[7, 9, 10]

In this patient, the effects of chloroquine on ocular functions persisted during therapy, but subsided within a few days after withdrawal of the drug. The rapidity of ocular change with variation in dosage may provide help in identifying the means by which chloroquine alters convergence and accommodation. High tissue concentrations and continued urinary excretion are known to persist long after chloroquine ingestion.[11] This retention of chloroquine has been attributed to its interaction with nucleic acid-containing compounds as well as with melanin. In addition to inhibiting the release or action of a number of lysosomal enzymes, chloroquine has been demonstrated to inhibit responses to acetylcholine, histamine and serotonin.[12] Interference with the action of such chemical mediators is possibly the means by which chloroquine induces the changes described. The site of action may be entirely central. More information is required, however, before the specific effects of chloroquine on the accommodation and convergence responses can be delineated.

REFERENCES

1. PERCIVAL, S. P. B., and MEANOCK, I. Chloroquine: Ophthalmological safety and clinical assessment in rheumatoid arthritis. *Brit Med J* 579, 1968.

2. HENKIND, P., and ROTHFIELD, N. F. Ocular abnormalities in patients treated with synthetic antimalarial drugs. *New Eng J Med 269*:433, 1963.

3. PATEL, J. C. Chloroquine therapy for hepatic amebiasis. *Brit Med J 1*:811, 1963.

4. CONAN, N. J. The treatment of hepatic amebiasis with chloroquine. *Amer J Med 6*:309, 1949.

5. KARLSBECK, F. Bilateral paralysis of abducent nerve as a cause of diplopia after use of chloroquine. *Nederl T Geneesk 104*:1414, 1960.

6. WHISNANT, J. P., ESPINOSA, R. E., KIERLAND, R. R., and LAMBERT, E. H. Chloroquine neuromyopathy. *Proc Mayo Clin 38*:501, 1963.

7. HUNT, B. J., and YENDT, E. R. The response of hypercalcemia in sarcoidosis to chloroquine. *Ann Intern Med 59*:554, 1963.

8. SLOANE, A. E. *Manual of Refraction*. Little, Boston, 1961, p 15.

9. HENDRIX, J. Z. Sarcoidosis and bone mineral metabolism. *Clin Research 12*:457, 1964.

10. MORSE, S. I., COHN, Z. A., HIRSCH, J. G., and SCHAEDLER, R. W. The treatment of sarcoidosis with chloroquine. *Amer J Med 30*:779, 1961.

11. VON SALLMANN, L., and BERNSTEIN, H. N. Adverse effects of chloroquine and related antimalarial drugs on ocular structures. *Bull Rheum Dis 14*:327, 1963.

12. SAMS, W. M., JR. Chloroquine: Mechanism of action. *Proc Mayo Clinic 42*:300, 1967.

Discussion

Chloroquine, as Drs. Rubin and Thomas document, exerts toxic effects not only on the retina (especially the retinal pigment epithelium), but also on the extraocular function. Although this patient clearly suffered nonretinal damage by chloroquine, the site of chloroquine action was not exactly localized. The drug interacts with a considerable variety of biological structures including melanosomes, DNA and lysosomes. It is difficult to be certain which of these targets in the cells was most vitally affected. But since lysosomes and their membranes constitute a model for structures bounded by biomembranes (including myelin), perhaps a brief review of the effects of chloroquine on lysosomes would be of interest.

Many studies have documented the capacity of steroids and chloroquine to influence lysosomes both in vivo and in vitro, yet frequently it is not possible to decide whether such effects are causally related. The establishment of causal relationships between the effects of agents upon isolated systems and their action on the whole organism constitutes a major task for both pharmacology and physiology. Studies of lysosomes may provide general clues to the mechanism of action of steroids and drugs. Since the functions of lysosomes are varied, a given pharmacologic agent can effect the lysosomal system in many ways.[1] For example, an agent can act to regulate the escape of enzymes from, or the access of substrate to, any of the subgroups of lysosomes (eg, cortisol, chloroquine, polyene antibiotics). It is also possible that substances may be taken up selectively and sequestered within primary or secondary lysosomes, reaching such high concentrations that the enzymes contained within these organelles are affected directly (eg, inorganic gold salts, trypan blue). It is also possible that an agent can prevent the proper merger of primary with secondary lysosomes, or of the phagosome with hydrolase-rich particles (eg, colchicine). A drug may also be converted to its active form by lysosomal hydrolases (eg, aniline mustard). Finally, it is possible for drugs or hormones to affect the formation of primary lysosomes from the Golgi apparatus or to induce the formation of autophagic vacuoles (eg, glucagon, cyclophosphamide).

Because of the possibility that the anti-inflammatory actions of cortisone and its analogues were due to an effect upon lysosomes, chloroquine was also examined, since it, too, is useful in chronic inflammatory diseases. It was found that this agent stabilized lysosomes against simple thermal activation; indeed, chloroquine retarded the release of hydrolytic enzymes from rabbit liver granules induced by streptolysin S, lysolecithin, etiocholanolone, or progesterone.[2] Tests of related compounds showed that although the diamine side chain itself was capable of stabilizing the organelles, both amine groups were necessary.[3] Furthermore, the presence of chlorine in position 7 was required, since deschloroquine had little effect upon lysosomes. A series of other antimalarial compounds, differing from chloroquine both in ring structure and side-chain configuration, defined the parameters necessary for membrane activity. Miller and Smith[4] also found that chloroquine stabilized the membranes of rat liver lysosomes in vitro. Each of these studies employed concentrations of chloroquine above 10^{-5} M, a concentration that might be expected to be reached in cells which take up chloroquine avidly, ie, liver, skin, and retina. Indeed, Allison and Young[5] have found that chloroquine is taken up selectively and concentrated in lysosomes of cultured cells.

Considerable evidence exists that lysosomes or other parts of the vacuolar system are affected by the administration of chloroquine. Observing abnormal granules in polymorphs and lymphocytes from patients given chloroquine, Fedorko[6] found many abnormal myelin figures, autophagic vacuoles, and multivesicular bodies in leukocytes and pan-

creatic cells of rats treated with the drug.[7] Abraham *et al*[8] found that the lysosomes of heart muscle became enlarged and abnormal following chloroquine treatment and also encountered these changes in hypoxic liver. Further evidence that chloroquine affects vacuolar systems was obtained by Macomber *et al*,[9] and Warhurst and Hockley,[10] who, by light and electron microscopy observed malarial parasites, *Plasmodium berghei*, treated with the drug. The parasites, living within erythrocytes, apparently endocytose hemoglobin in cytoplasmic vacuoles. Following chloroquine treatment, the phagocytic vacuoles enlarged to a tremendous diameter; myelin figures appeared; and cell death ensued. It is possible that the engorged parasite, filled with phagosomes which could not receive hydrolases from primary lysosomes, became starved of nutriment and died. Allison,[11] however, has suggested another interpretation of these results.

Do the effects of chloroquine upon the vacuolar system reduce tissue changes brought about by agents which impair the integrity of lysosomes in living cells? Allison[12] found that chloroquine reduced the toxicity of oxygen excess to cultured cells and also retarded lysosomal damage. Abraham *et al*[8] found that chloroquine inhibited the histochemical dissolution of lysosomes after anoxic insults to liver, and Lotke[13] was able to reduce the effects of hypothermia on the viability of kidney slices by bathing these in a medium containing chloroquine. Moreover, we have been able to attenuate the effect of hypervitaminosis A upon the larvae of *Xenopus laevis* by exposing larvae to chloroquine together with the vitamin.[2] It has also been observed that the marked proliferation of acid hydrolase-rich organelles which follows stimulation of human lymphocytes by phytohemagglutinin could be diminished if the cells were incubated with a short course of chloroquine. Finally, transformation and subsequent mitosis (which has been related to redistribution of acid hydrolases) was inhibited by the presence of chloroquine.[14]

Each of the above studies is quite circumstantial and does not conclusively prove that a primary effect of chloroquine upon lysosomes is responsible for the protection of tissues against excess or lack of oxygen, hypothermia, excess vitamin A, etc. Indeed, chloroquine has been shown to react with other cellular constituents, especially with DNA, the template capacity of which for RNA polymerase is diminished by the drug.[15] However, when the in vitro stabilizing effects of chloroquine upon lysosomes and membrane models are correlated with the protective effects described above, it seems reasonable to suggest that the interaction of chloroquine with lysosomes and other parts of the vacuolar apparatus accounts for some of the pharmacologic actions of this drug.

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REFERENCES

1. DE DUVE, C. In *The Interaction of Drugs and Subcellular Components in Animal Cells.* Campbell, P. N., Ed. Churchill, London, 1968, p 155.

2. WEISSMANN, G. *Fed Proc 23:*1038, 1964.

3. WEISSMANN, G. *Topics Pharmaceutical Sci 1:*125, 1968.

4. MILLER, W. S., and SMITH, J. G. *Proc Soc Exp Biol Med 122:*634, 1966.

5. ALLISON, A. C., and YOUNG, M. R. *Life Sci 3:*1407, 1964.

6. FEDORKO, M. E. *J Clin Invest 46:*1932, 1967.

7. FEDORKO, M. E. *Lab Invest 18:*27, 1968.

8. ABRAHAM, R., GOLDBERG, L., and GRASSO, P. *Nature (London) 215:*194, 1967.

9. MACOMBER, P. B., SPRINZ, H., and TOUSIMIS, A. J. *Nature (London) 214:*937, 1967.

10. WARHURST, D. C., and HOCKLEY, D. J. *Nature (London) 214:*935, 1967.

11. ALLISON, A. C. In *The Interaction of Drugs and Subcellular Components in Animal Cells.* Campbell, P. N., Ed. Churchill, London, 1968, p 218.

12. ALLISON, A. C. *Nature (London) 205:*141, 1965.

13. LOTKE, P. A. *Nature (London) 212:*512, 1966.

14. HIRSCHHORN, R., HIRSCHHORN, K., and WEISSMANN, G. *Blood 30:*84, 1967.

15. COHEN, S. N., and YIELDING, K. L. *Proc Nat Acad Sci US 54:*521, 1965.

This is a very interesting article in which the authors call to our attention a frequently noted, but little understood, ocular complication of antimalarial therapy. The impairment in accommodation resulting from the use of large doses of chloroquine has been noted since the original descriptions of the pharmacology of the 4-amino-quinolines. Berliner and his associates reported ocular symptoms in 18 of 32 subjects receiving chloroquine,[1] pointing out that this was the most striking and frequent toxic effect noted. The complaints appeared soon after the dose was increased to 400 mgm base/day (approximately 750 mgm chloroquine diphosphate). However, until this report, there has been no attempt to explain the impairment in accommodation and convergence. This toxicity differs from the other ocular complications of chloroquine: it occurs soon after initiation of treatment and is quickly

reversible when the drug is discontinued. This pattern is in striking contrast to chloroquine retinopathy, which is, in part, dose related, but requires ingestion of the drug for many years and is not reversible unless detected at its first appearance. The authors suggest two possible mechanisms to explain the impairment in accommodation and convergence: a peripheral effect on the ocular muscles or a direct effect on the neural centers controlling conversion and accommodation. They present evidence that suggests that the latter possibility is more likely. Support for this comes from the known toxicology of chloroquine and the other 4-aminoquinolines. Peripheral myopathy and/or neuromyopathy have been reported following the use of chloroquine, but like retinal toxicity, these conditions usually develop only after prolonged use of the drug. In addition, they are reversible lesions, but require several months before they clear. In acute chloroquine poisoning, the predominant symptoms are in the CNS, with marked depression of vasomotor and respiratory functions, convulsions and, finally, cardiac arrest. This usually occurs 1–3 hr after ingestion of large doses of the drug.[2] Poisoning in adults is accompanied by other neurologic symptoms, including double vision, dizziness, difficulty in swallowing and speaking, and occasionally, convulsions. In those instances where the patient has survived from overdoses of chloroquine, the CNS effects of the drug were abolished in 24–48 hr. The rapid appearance and clearing of the diplopia and loss of accommodation, plus the relationship to large doses of chloroquine, support the authors contention that this toxic effect of the drug is mediated through the CNS.

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REFERENCES

1. BERLINER, R. W., *et al.* Studies on the chemotherapy of the human malarias. VI. The physiologic disposition, antimalarial activity and toxicity of several derivatives of 4-aminoquinoline. *J Clin Inv 27*:98, 1948.

2. CANN, H. M., and VERHULST, H. L. Fatal acute chloroquine poisoning in children. *Pediatrics 27*:95, 1961.

The mechanism or mechanisms of action for chloroquine and related drugs is a subject of considerable importance because of the widespread use of these compounds in parasitic as well as nonparasitic diseases. Careful study of the side effects of drug administration, such as that of Rubin and Thomas, may be particularly useful in explaining drug action and in furnishing clinical data even though toxic effects could well represent secondary drug effects unrelated to the primary therapeutic mechanism of action. In any event, it is of interest to consider the side effects of chloroquine in light of its known biochemical effects.

The binding of chloroquine to nucleic acids (both DNA and RNA), first reported about 20 yr ago,[1] has been studied in depth in recent years.[2–6] This binding process has been of particular interest because of its specificity (purines > pyrimidines and helical > coiled DNA), the resultant changes in the physical properties of DNA, and its inhibition of DNA-directed DNA synthesis. Because of the remarkably good correlation between antimalarial action and inhibition of DNA synthesis, and because of the report that chloroquine inhibited DNA synthesis in the intact parasite, it was proposed that this inhibition might account for the biological action of the drug.[7,8] Studies and speculations have now been extended to a variety of antimalarial drugs, including quinacrine,[9] quinine[10] and the 8-amino quinolines.[11] Interference with the function of nucleic acid in vivo has also been shown for bacteriophage replication in *E coli*[12] and for excision repair (nonconservative or "unscheduled synthesis") of DNA in *E coli* and in human lymphocytes.[13] Recently, this excision repair mechanism has been implicated in the resistance of certain tumors to the effects of x-ray and alkylating agents, and chloroquine has been used successfully in increasing the effectiveness of these antitumor agents in experimental tumors.[14]

Binding to melanin[15] and porphyrins[16] has also been reported for chloroquine. Thus, pigment-containing tissues bind large quantities of the drug with resulting local changes. Whether this accounts for the toxicity of chloroquine for the retina is a moot question. Porphyrin binding also occurs in vivo, as shown by alterations in porphyrin excretion[17] and by protection against hematoporphyrin-induced photosensitivity.[18] Porphyrin binding has also been suggested as a possible resistance mechanism for malarial parasites in view of their content of hemoglobin breakdown products.[16]

Chloroquine interferes with oxidative metabolism by inhibiting mitochondrial respiration,[19,20] a property that it shares with steroids and certain other anti-inflammatory agents as well as barbiturates and a variety of central nervous system depressant drugs. Whether this effect results from binding to one of the heme proteins in the respiratory chain has not been established, but is an interesting possibility in view of its porphyrin-binding capacity.

Most of the biochemical effects of chloroquine involve somewhat higher drug concentrations than would be expected in tissues during most treatment schedules for parasitic diseases. It is difficult, therefore, to be certain of the relationship of such effects to therapeutic action. However, prolonged administration of the drug, often at the high doses occurring in some disease situations. suggests that these

biochemical effects do relate to some of the toxic effects and some of the "secondary" therapeutic uses of the drug.

For example, as suggested by in vitro studies, chloroquine's toxic effects could interfere with a number of critical cellular functions involving nucleic acid expression and respiration. Both types of mechanisms are of interest for the eye signs reported by Rubin and Thomas. particularly since their studies suggest a central, rather than merely a peripheral effect of the drug. Oxidative metabolism has long been implicated in the central nervous system effects of a variety of drugs. Recently, there has been great interest in nucleic acids, for both their role in information storage and in the function of nerve cell receptor sites. This interest has been stimulated because of observations that LSD[20] and certain other CNS-active drugs and neuroeffectors[21] bind to nucleic acids. (The well-known occurrence of "quinacrine psychosis" should receive particular attention in this regard.) In any event, the proposal that chloroquine has a direct effect on the CNS in producing eye symptoms has considerable merit, particularly since this class of drugs, in general, readily crosses the blood-brain barrier.

Finally, it is interesting to speculate that chloroquine might have a particularly potent effect on such tissues as those of the brain, which are heavily dependent on mitochondria. The drug interferes with mitochondrial function (respiration) and potentially could interfere with mitochondrial biogenesis by virtue of its inhibition of DNA synthesis. Careful clinical evaluation of the toxic effects of drugs is a most important process in elucidating mechanisms of drug action.

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REFERENCES

1. IRVIN, J. L., IRVIN, E. M., and PARKER, F. S. The interaction of antimalarials with nucleic acids. *Science 110:*476, 1949.

2. KURNICK, N. B., and RADCLIFFE, I. E. Reaction between DNA and quinacrine and other antimalarials. *J Lab Clin Med 60:*669, 1962.

3. STOLLAR, D., and LEVINE, L. Antibodies to denatured deoxyribonucleic acid in lupus erythematosus. V. Mechanism of DNA-Anti DNA inhibition by chloroquine. *Arch Biochem 101:*335, 1963.

4. COHEN, S. N., and YIELDING, K. L. Spectrophotometric studies of the interaction of chloroquine with deoxyribonucleic acid. *J Biol Chem 240:*3123, 1965.

5. BLODGETT, L. W., and YIELDING, K. L. Comparison of chloroquine binding to DNA, and polyadenylic and polyguanylic acids. *Biochem Biophys Acta 169:*451, 1968.

6. STERNGLANZ, H., YIELDING, K. L., and PRUITT, K. M. Nuclear magnetic resonance studies of the interaction of chloroquine diphosphate with adenosine 5-phosphate and other nucleotides. *Molec Pharmacol 5:*376, 1969.

7. COHEN, S. N., and YIELDING, K. L. Further studies on the mechanism of action of chloroquine: Inhibition of DNA and RNA polymerase reachons. *Arthritis Rheum 7:*302, 1964.

8. COHEN, S. N., and YIELDING, K. L. Inhibition of DNA and RNA polymerase reactions by chloroquine. *Proc Nat Acad Sci 54:*521, 1965.

9. O'BRIEN, R. L., OLENICK, J. G., and HAHN, F. E. Reactions of quinine, chloroquine, and quinacrine with DNA and their effects on the DNA and RNA polymerase reactions. *Proc Nat Acad Sci 55:*1511, 1965.

10. ESTENSEN, R. D., KREY, A. K., and HAHN, F. E. Studies on a deoxyribonucleic acid-quinine complex. *Molec Pharmacol 5:*532, 1969.

11. WHICHARD, L. P., MORRIS, C. R., SMITH, J. M., and HOLBROOK, D. J. The binding of primaquine, pentaquine, pamaquine, and plasmocid to deoxyribonucleic acid. *Molec Pharmacol 4:*630, 1968.

12. YIELDING, K. L. Inhibition of the replication of a bacterial DNA virus by chloroquine and other 4-aminoquinoline drugs. *Proc Soc Exp Biol Med 125:*780, 1967.

13. YIELDING, K. L., and GAUDIN, D. Unpublished data.

14. GAUDIN, D., and YIELDING, K. L. Response of a 'resistant' plasmacytoma to alkylating agents and X-ray in combination with the excision repair inhibitors caffeine and chloroquine. *Proc Soc Exp Biol Med 131:*1413, 1969.

15. BERNSTEIN, H., ZVIFLER, N., RUBIN, M., and MANSOUR, A. M. The ocular deposition of chloroquine. *Invest Ophthal 2:*384, 1969.

16. COHEN, S. N., PHIFER, K., and YIELDING, K. L. Complex formation between chloroquine and ferrihemic acid and its effect on antimalarial action of chloroquine. *Nature (London) 202:* 805, 1964.

17. SCHOLNICK, P., and MARVER, H. The molecular basis of chloroquine responsiveness in porphyria cutanea tarda. *Clin Res 16:*258, 1968.

18. YIELDING, K. L. Unpublished data.

19. MUSHINSKI, J. F., and YIELDING, K. L. A comparison of the *in vitro* effects of steroid hormones and certain antimalarial compounds. *Arthritis Rheum 5:*118, 1962.

20. YIELDING, K. L., and STERNGLANZ, H. Lysergic acid diethylamide (LSD) binding to deoxyribonucleic acid (DNA). *Proc Soc Exp Biol Med 128:*1096, 1968.

21. SMYTHIES, J. R., and ANTUN, F. Binding of tryptamine and allied compounds to nucleic acids. *Nature (London) 223:*1061, 1969.

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