FURTHER OBSERVATIONS ON THE USE OF 4-AMINOQUINOLINE COMPOUNDS IN PATIENTS WITH RHEUMATOID ARTHRITIS OR RELATED DISEASES

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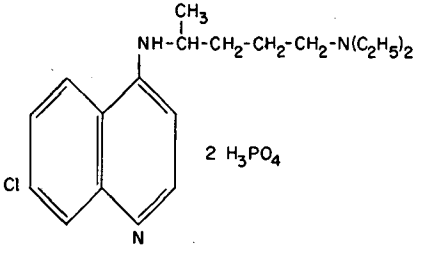
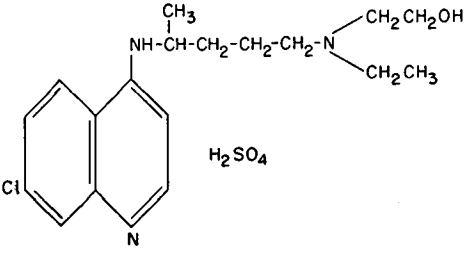
A NUMBER of investigators[1-11] have reported that in patients with rheumatoid arthritis and allied diseases, clinical improvement occurs after administration of the 4-aminoquinoline compounds, chloroquine phosphate and hydroxychloroquine sulfate.** In a previous report[11] the effect of hydroxychloroquine sulfate was compared with that of chloroquine phosphate in patients with rheumatoid arthritis. It was concluded that hydroxychloroquine sulfate in equal dosage caused fewer drug reactions than did chloroquine phosphate; however, in such dosage, hydroxychloroquine sulfate was less effective as an anti-inflammatory agent. The purpose of this report is to describe the results that were observed during the past three years in the administration of these compounds, alone or in combination with other agents, to 805 patients with rheumatoid arthritis or related diseases.

Drugs Used

Chloroquine phosphate is 7-chloro-4 (4-diethylamino-1-methylbutylamino) quinoline diphosphate. Hydroxychloroquine sulfate is 7-chloro-4-[4-(N-ethyl-N-β-hydroxyethylamino)-1-methylbutylamino] quinoline sulfate. The structural formulas are:



Chloroquine phosphate



Hydroxychloroquine sulfate

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**Chloroquine phosphate (Aralen), and hydroxychloroquine sulfate (Plaquenil), used in this study were supplied through the courtesy of Winthrop Laboratories, New York, New York.*

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Hydroxychloroquine sulfate is similar to chloroquine phosphate except that a hydroxyethyl group has been substituted for an ethyl group on the tertiary amino nitrogen. Both drugs are almost completely absorbed from the gastrointestinal tract, although hydroxychloroquine sulfate apparently is absorbed more rapidly than is chloroquine phosphate. Considerable amounts of the drugs are found in the liver, spleen, kidneys, lungs, skin, and leukocytes, while the lowest concentration is in the central nervous system. Approximately 25 per cent of the oral daily dose is excreted in the urine, and after administration has been discontinued, the remainder of the drugs slowly undergoes metabolic degradation.

Selection of Patients

Of 805 patients treated with one of the 4-aminoquinoline compounds, 716 patients had arthritis of the rheumatoid type, of which 627 had typical rheumatoid arthritis, 53 had arthritis of the rheumatoid type with a positive test for lupus erythematosus, 23 had rheumatoid arthritis with psoriasis, and 13 had juvenile rheumatoid arthritis. Eighty-nine patients had other disorders of the connective tissue, including arteritis, dermatomyositis, progressive systemic sclerosis (scleroderma), Reiter's syndrome, and systemic lupus erythematosus.

The results of treatment in these patients will be reported later, but the incidence and the variety of drug reactions that occurred from the use of chloroquine phosphate and hydroxychloroquine sulfate in the total group of 805 patients are included in this report. Of the 716 patients, 487 were treated for periods of from one to three years. Because of the characteristic instability of the course of rheumatoid arthritis, results of treatment include data from only those patients who were treated longer than one year.

Dosages and Administration of Drugs

Chloroquine phosphate is available in tablets of 125 mg. and of 250 mg. Originally an initial dose of 500 mg. daily was administered, which was reduced to 250 mg. as improvement was noted. Gastrointestinal reactions occurred in about 30 per cent of the first patients treated, and it was found that by reducing the initial dose the incidence of gastrointestinal reactions decreased. About 12 per cent of the patients did not tolerate an initial dose of 250 mg. of chloroquine phosphate daily; they were given 125 mg., and after two months an attempt was made to increase this to 250 mg. daily. At the present time we are recommending that the maximum daily dose of chloroquine phosphate be 250 mg. daily.

Hydroxychloroquine sulfate is available in coated tablets of 200 mg. In equal dosages we have found hydroxychloroquine sulfate to be approximately from one half to two thirds as potent as chloroquine phosphate (600 mg. of hydroxychloroquine sulfate is approximately as effective as 250 mg. of chloroquine phosphate), while the incidence of drug reactions is approximately one half that of chloroquine phosphate. Originally we administered up to 1.0 gm. daily in divided doses with or after meals, but the larger doses did not hasten initial improvement.

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Although the incidence of drug reactions was less than that occurring from chloroquine phosphate, the reactions still remain a problem. Consequently, the initial dosage of hydroxychloroquine sulfate was reduced to 600 mg. daily, administered in divided doses with or after meals. After major improvement (grade I or grade II response*) had been maintained for at least one year, the dosage of hydroxychloroquine sulfate was reduced to 400 mg. daily in divided doses taken with or after meals.

Sixteen children have been included in this study. For those who weighed approximately 15 kg. the usual daily dose was 125 mg. of chloroquine phosphate, or 200 mg. of hydroxychloroquine sulfate. Two children who weighed 10 kg. and 12 kg., respectively, received 125 mg. of chloroquine phosphate on alternate days. With one exception all of the children have continued to receive maintenance doses of one of the drugs after from one to three years of treatment. One child with active rheumatoid arthritis of one year's duration was given chloroquine phosphate (125 mg. daily) for one year, at which time a remission occurred. Chloroquine phosphate was continued for six more months and then was discontinued. The child's disease has remained in remission for two years since chloroquine phosphate therapy was stopped.

Clinical Response to Therapy

Previously the results of therapy were reported with 4-aminoquinoline compounds in 51 adult patients who were observed for 18 months.[11] Of 26 patients who received hydroxychloroquine sulfate, 23 tolerated the drug and 15 of those obtained major improvement. Of 25 patients who received chloroquine phosphate, 19 tolerated the drug and 12 obtained major improvement. There was no direct correlation between the response to therapy and the stage or the duration of the disease, or the patient's functional capacity.

Since the previous report, an additional 63 patients have been treated with an antimalarial compound as the sole therapeutic agent. Eight patients from our original group have been lost to follow-up study; 60 patients are receiving hydroxychloroquine sulfate and 46 are receiving chloroquine phosphate (Table 1).

Response to therapy in this group resembles that in our original group. Of those patients who received hydroxychloroquine sulfate, 60 per cent had grade I or grade II response; of those who received chloroquine phosphate, 62 per cent had a similar response. Again it was observed that little or no correlation existed between response to therapy and stage of disease, functional capacity of the patient, or duration of the disease. We have found a better correlation between response to therapy and the serum polysaccharide-protein ratio[13] as a measure of disease activity than we have with any other test now available. The majority of patients who obtained major improvement had serum polysaccharide-protein ratios of 2.55 or less. No patient with a serum polysaccharide-protein ratio of 2.80, or greater, obtained major improvement while receiving one of the 4-aminoquinoline compounds as the sole therapeutic agent. Nonarticular features

**A.R.A. classification*[12].

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of the disease, including weakness, emotional instability, loss in weight, and vasomotor reactions, usually were not severe.

We believe that it is important to emphasize the subtle manner in which clinical improvement often occurred, since it did not become obvious in many patients until they had been treated for one year or longer.

Table 1.—*Results of hydroxychloroquine sulfate and chloroquine phosphate therapy for rheumatoid arthritis in 106 patients*

Drug	Number of patients	Stage* of disease	Class** of functional capacity: Number of patients I	II	III	IV	Duration of disease at onset of therapy	Grade+ of response after from 1 to 3 yrs. of therapy: Number of patients I	II	III	IV
Hydroxychloroquine sulfate	14 (17-3++)	I	1	3	7	3	3 mos. to 26 mos.	4	7	2	1
	20 (22-2++)	II	0	8	10	2	16 mos. to 4 yrs.	5	5	8	2
	16	III	0	3	8	5	2 yrs. to 12 yrs.	3	6	7	0
	10	IV	0	2	6	2	3 yrs. to 18 yrs.	1	5	3	1
Total	60 (65-5++)		1	16	31	12		13	23	20	4
Chloroquine phosphate	13 (14-1++)	I	0	5	6	2	5 mos. to 3 yrs.	6	7	1	0
	11 (13-2++)	II	0	4	6	1	11 mos. to 8 yrs.	3	4	2	2
	12	III	1	5	5	1	2 yrs. to 16 yrs.	1	4	6	1
	10	IV	0	3	5	2	3 yrs. to 26 yrs.	1	3	4	1
Total	46 (49-3++)		1	17	22	6		11	18	13	4
Total	106		2	33	53	18		24	41	33	8

A.R.A. Classification.[12]

**Stage:* I—*Joint swelling, no joint destruction;* II—*minimal cartilage or bone destruction;* III—*subluxation;* IV—*ankylosis.*

***Class:* I—*asymptomatic, full activity;* II—*minor symptoms, adequate activity;* III—*moderate-to-severe symptoms, limited activity;* IV—*severe symptoms, near or complete incapacitation.*

+*Grade:* I—*complete remission;* II—*major improvement;* III—*minor improvement;* IV—*no improvement, or progression of disease.*

++*Patients lost to follow-up.*

Initial response. The onset of clinical improvement usually was delayed for from six weeks to three months, when it began slowly and progressed irregularly over a period of from six to 12 months. Rarely was maximum improvement delayed beyond 12 months. After the first month of therapy only 22 patients

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(21 per cent) of the 106 had attained grade I or grade II response; after three months 50 patients (47 per cent) were similarly improved. After six months, 57 patients (54 per cent), and after one year 65 patients (62 per cent) were asymptomatic. Thirty-three patients (30 per cent of the group) had grade III response to therapy, and eight patients (8 per cent) had grade IV response (Table 1).

Persistence of disease fluctuations. One of the most characteristic features of rheumatoid arthritis is fluctuating disease activity. This feature of the disease persisted and was modified but was not eliminated by the administration of 4-aminoquinoline compounds. Exacerbations became less severe and of shorter duration in those patients who eventually attained major improvement, while periods of relative freedom from most musculoskeletal manifestations increased in duration. Eventually the exacerbations were manifested only by periods of weakness or of exhaustion which lasted one or two days and usually followed increased activity, stress situations, or infections. Minor, self-limiting flare-ups occurred just before the menses in about one half of the menstruant women.

Variation in maximum response. There was wide variation in response to therapy. About 25 per cent of the patients obtained complete relief of joint manifestations within a few months after the onset of therapy, while in 37 per cent the same degree of improvement did not appear for from six to 12 months. In 38 per cent of the patients some improvement occurred, but remained incomplete; this group was considered to have an insignificant response (grade III or grade IV) (Table 1).

It was observed repeatedly that an initial twofold or threefold increase in dosage of the medication did not hasten the onset of clinical improvement, although the number and the severity of the reactions to the drug were increased.

Response to therapy was unsatisfactory in patients who had relapsed while receiving corticosteroids for prolonged periods of time. It never was possible to substitute either chloroquine phosphate or hydroxychloroquine sulfate for one of the corticosteroids in patients with chronic hypercortisonism without a period of hospitalization and supplementation with other chemotherapeutic agents.[14]

4-Aminoquinoline—Corticosteroid Therapy

Because maximum improvement from therapy with chloroquine phosphate or hydroxychloroquine sulfate usually did not occur before three months of therapy and frequently was delayed longer, prednisone or prednisolone, 3.0 to 7.5 mg. daily, supplemented the 4-aminoquinoline compound during the initial phase of therapy of 187 patients. Limitation of functional capacity usually was the determining factor in deciding whether one of the corticosteroids was to be added to the therapeutic program. Again, it was noted that the stage and the duration of the disease, and the functional capacity of the patient had no direct correlation with response to therapy.

Initial improvement seemed to appear more rapidly when a small dose of a corticosteroid was simultaneously administered with a 4-aminoquinoline com-

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pound, but eventual over-all improvement after one year was not significantly better than it was in those patients who received only 4-aminoquinoline compounds. In this group, major improvement occurred in 54 per cent of the patients after the first month of therapy and in 61 per cent after six months. Major improvement (grade I or grade II response) was obtained in 67 per cent of the patients in this group after one year, during which time corticosteroid dosage was reduced by one half or administration of the drug was stopped in 47 per cent. In addition to oral medication, 11 per cent of the patients in this group received initial intraarticular injections during the first three months of therapy because joint swelling had been persistent.[15]

We believe that corticosteroids should be considered only as temporary supplemental adjuncts in the treatment of rheumatoid arthritis. They should be administered in small doses equivalent to from 3 to 7.5 mg. of prednisone per day, and should be reduced or should be stopped as improvement appears. Under no circumstances should they be given without a definite, organized plan for reduction in dosage and for withdrawal. Side effects and complications associated with steroid therapy usually were not apparent when the corticosteroids were administered in this manner. We observed two duodenal and one gastric ulcer in three patients who were receiving 3 mg. of prednisone or less per day for periods ranging between 16 and 21 months. The incidence of peptic ulcer in this group was 1.5 per cent (3 of 187 patients). Since none of the patients had symptoms of peptic ulcer prior to the onset of treatment for arthritis, it is likely that the medication was an aggravating factor. No other complications related to steroid therapy were apparent in this group. Patients with diabetes mellitus usually were not given oral steroid therapy.

Combined-Drug Therapy

Of the 487 patients with progressive and persistent disease, 94 patients (40 per cent) were treated with the combination of drugs that we have found to be most effective.[16] This group consisted of 194 patients in whom various forms of therapy had been tried, often with unsatisfactory results. Corticosteroids previously were administered to 133 patients (68 per cent), of which 24 patients (18 per cent) had severe chronic hypercortisonism. Serum polysaccharide-protein ratios[13] were 2.85 or greater. Central nervous system manifestations characteristic of rheumatoid arthritis, including emotional instability, weakness, depression, vasomotor reactions, paresthesias, and altered deep tendon reflexes, were more apparent in this group than in those groups described previously.

The same principles of therapy were instituted as described previously, consisting of the administration of a 4-aminoquinoline compound for long-term maintenance therapy, and a small dose of prednisone or prednisolone from 3.0 to 7.5 mg. daily. In order to suppress inflammation initially, intravenous therapy[17] was administered to all patients and intraarticular injections were given to 76 per cent of the patients in this group.[15] Iproniazid, an inhibitor of monoamine oxidase, was a supplement to the therapeutic program in all

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patients of this group. The pharmacologic action, dosage, and rationale for administering this drug have been described.[14,18,19]

Despite greater difficulty in treating these patients because of the administration and adjustment of dosage of several medications, and the need for patient co-operation as well as persistence and patience on the part of the physician, major improvement (grade I or grade II response) eventually occurred in 83 per cent of this group in an irregular and slowly progressive manner.

Side Reactions to Therapy

Drug reactions. Reactions that occur after the use of chloroquine phosphate and hydroxychloroquine sulfate are frequent, but fortunately the majority are transient and insignificant. It is likely that some of the pharmacologic actions responsible for these reactions are also responsible for clinical improvement that occurs in patients with rheumatoid arthritis.

Some type of reaction that involved either the neurovascular system, gastrointestinal tract, skin, or endocrine system occurred in 440 (approximately 55 per cent) of our patients. However, the reactions were transient and disappeared spontaneously in 67 per cent. After the dose of medication was reduced or administration of the drug was temporarily stopped, reactions disappeared in another 26 per cent. Seven per cent of reactions was severe enough to preclude further use of these agents.

In 805 patients who received one of the 4-aminoquinoline compounds there was no evidence of leukopenia, thrombocytopenia, methemoglobinemia, hepatic disease, or psychosis, after treatment was started. In 32 patients (4 per cent) the peripheral leukocyte count was less than 3,000 per cu. mm. before treatment was started. In 21 patients it increased during the period of drug therapy. We believe that the peripheral leukocyte count may fluctuate because of factors related to the disease, rather than because of any serious effect these drugs might have on the bone marrow.

Neurovascular reactions. Of 440 reactions, 49 per cent involved both the nervous and vascular systems; they usually were transient and disappeared spontaneously in 80 per cent of the patients in this group. In all except six of the patients, symptoms subsided when the dosage was reduced temporarily for one or two months. Neurovascular reactions of these patients included: difficulty in visual accommodation, vascular headaches with or without visual aura, vestibular dysfunction, tinnitus, nervousness, insomnia, and mental confusion.

Difficulty in visual accommodation and headaches were the most common reactions in this group. Blurring of vision disappeared within a few weeks and never was a cause for withdrawal of the drug. One third of the patients had throbbing, unilateral headaches. Occasionally a visual aura appeared in patients who never had experienced migraine headaches. Patients susceptible to migraine usually had more frequent and more severe headaches during the first few months of therapy. In most instances the headaches subsided spontaneously within a few weeks after the onset of therapy.

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Vestibular dysfunction was manifested by a sensation of imbalance or of light-headedness, but usually not by a true vertigo. Symptoms occurred when the head was turned quickly, and persisted for only a few seconds. Usually this reaction subsided spontaneously within a few weeks without reduction in dosage of medication.

Tinnitus occurred in 11 patients and disappeared spontaneously in eight while medication was continued without reduction in dosage. In three patients, tinnitus disappeared when the dose of medication was reduced. In no patient did it persist beyond a few weeks.

Insomnia and increased nervousness, which occurred in 13 patients of this group, were controlled with sedation. One 58-year-old woman experienced temporary mental confusion that lasted about 36 hours after medication was started; it subsided spontaneously while medication was continued.

Gastrointestinal reactions. Of 805 patients, 17 per cent had gastrointestinal reactions that included: nausea, anorexia, vomiting, bloating, abdominal cramps, heartburn, diarrhea, and loss in weight. Thirty-one per cent of all reactions involved the gastrointestinal tract. They were of greater significance than the neurovascular reactions because they were not so well tolerated and in some instances they did not subside spontaneously, especially when larger doses of the drugs were administered initially.

There was a significant difference between the incidence of gastrointestinal reactions related to hydroxychloroquine sulfate (11 per cent) and those related to chloroquine phosphate (19 per cent). In 60 per cent of the patients who had gastrointestinal reactions, nausea and anorexia occurred soon after medication was started. The most serious gastrointestinal reactions were: anorexia with loss in weight (41 patients), diarrhea (11 patients), and persistent vomiting (4 patients). In the group of 106 patients receiving one of the 4-aminoquinoline compounds as the sole therapeutic agent, only one patient had a duodenal ulcer.

Dermatologic reactions. Skin reactions from chloroquine phosphate and from hydroxychloroquine sulfate were about equally frequent. These were the most distressing as well as the most serious of all of the drug reactions. The skin lesions varied greatly in character and extent and accounted for 12 per cent of all drug reactions; about one half of these were considered serious.

The types of skin reactions included: dryness of the skin, itching, urticaria, morbilliform eruptions, maculopapular eruptions, desquamating lesions, exfoliating lesions, increased pigmentation, alopecia, and graying or bleaching of the hair. Pre-existing psoriatic lesions and those involved with necrotizing arteritis were susceptible to exacerbations. In 76 per cent of the patients in whom there was a skin reaction other than increased pigmentation, alopecia, or color changes of the hair, the reaction appeared within the first month of treatment. The less serious skin reactions consisted of dryness, itching and urticarial reactions. Maculopapular or morbilliform eruptions usually were followed by generalized desquamation that began over the face and shoulders and slowly spread down over the upper extremities, the trunk, and finally the lower extremities. The entire reaction evolved in from five days to two weeks. When the

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reaction was mild, the medication was stopped and one of the antihistaminic agents was administered. For more severe reactions, prednisone was administered in doses of 5 mg. three times daily and, more recently, triamcinolone* (2 to 4 mg. three times daily) has been a more effective agent in hastening the reversal of the skin reactions.

Patients with psoriasis appeared to be more susceptible to severe skin reactions than were other patients. We have treated 23 patients with psoriasis and rheumatoid arthritis, 16 of whom improved satisfactorily with disappearance or some lessening of the skin lesions. Severe maculopapular eruptions appeared in five patients, two of whom later had generalized exfoliating lesions that persisted for weeks after the 4-aminoquinoline therapy had been discontinued. One of these patients had a severe exacerbation of psoriasis one week after the exfoliating lesions disappeared. The psoriasis at that time was more severe than it had ever been and was unaffected by the administration of prednisone in doses of 5 mg. four times daily. Triamcinolone was administered (4 mg. three times daily), which resulted in partial improvement of the psoriatic skin lesions. Another patient with psoriasis and arthritis had improvement in joint manifestations but not in skin lesions while receiving chloroquine phosphate. He was admitted to the hospital for Goeckerman (tar and ultraviolet) treatment, but failed to respond until chloroquine phosphate therapy was stopped. A patient with severe psoriasis and mild rheumatoid arthritis was given 250 mg. of chloroquine phosphate daily. After two weeks an extensive urticarial reaction occurred and an exacerbation of the psoriasis, which responded slowly and incompletely to triamcinolone.

Bleaching or graying of the hair occurred in four patients. Chloroquine phosphate was administered to three of these patients in excessive amounts varying between 750 mg. and 2.0 gm. per day for three months or longer. The fourth patient received 600 mg. of hydroxychloroquine sulfate daily for two months, when the hair began to lighten in color. Goldman and Preston[20] reported one case in which bleaching of the hair was followed by the return to the normal color despite continuance of the drug.

Four women had partial alopecia while they were receiving one of the 4-aminoquinoline compounds. Patches of alopecia appeared in two patients who were receiving hydroxychloroquine sulfate in doses of 600 mg. daily for three and six months respectively. In another patient mild alopecia occurred at the onset of her arthritis, subsided during treatment with chloroquine phosphate, 250 mg. daily, and returned six months later while she was still receiving therapy. In the fourth patient, after eight months of 250 mg. daily of chloroquine phosphate, alopecia and graying of the hair developed simultaneously; both conditions subsided when the medication was stopped.

Excessive pigmentation of the exposed areas of the skin occurred routinely in most patients during the summer with the use of either drug. It disappeared slowly and incompletely during the winter (Fig. 1).

Aristocort was supplied through the courtesy of Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.

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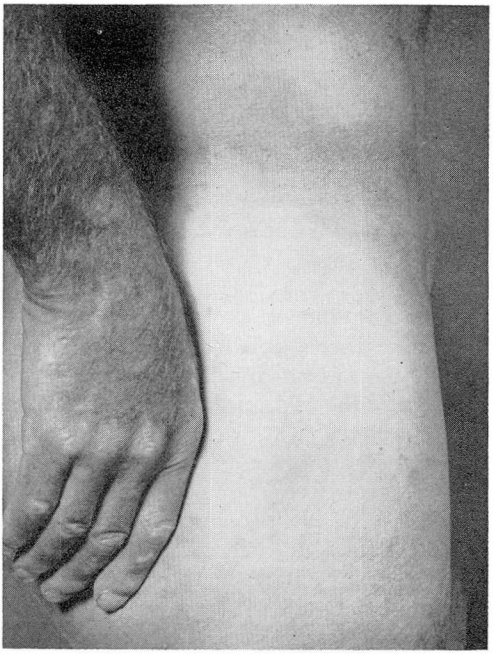

Fig. 1. Photo showing excessive pigmentation on hand and forearm exposed to sunlight.

Endocrine dysfunction. During therapy, alteration in menstrual periods occurred in 11 per cent of menstruant women. Usually these patients had intermenstrual spotting or excessive menstrual flow. Dilatation and curettage was performed in six patients. Microscopic study of endometrial tissue disclosed hypertrophic endometrium.

Theories of Pharmacologic Action

The mechanism of pharmacologic action of the 4-aminoquinoline compounds responsible for clinical improvement in patients with active rheumatoid arthritis is not known. The pharmacologic adage that "no drug has a single action" should be emphasized, as it is likely that these 4-aminoquinoline compounds have a wide spectrum of stimulating and inhibiting actions, both in the central nervous system and in the peripheral tissues.

Previously we postulated that two major biochemic alterations might be related to the disease manifestations characteristic of rheumatoid arthritis.[14] A central nervous system defect manifested by decreased neurohormonal activity was suggested as a factor responsible for nonarticular manifestations, including generalized weakness, emotional instability, depression, fatigability, autonomic imbalance, paresthesias, vasomotor reactions, some instances of muscle atrophy, and altered tendon reflexes.

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We have reported that the nonarticular manifestations are alleviated by the administration of iproniazid, an inhibitor of monoamine oxidase.[14] Brodie and Shore[21] have postulated that serotonin, rather than acetylcholine, is the chemical transmitter of nerve impulses in the central parasympathetic system, and that norepinephrine is the chemical transmitter in the central sympathetic system. If this concept is correct, we can assume that improvement in central nervous system manifestations following the administration of iproniazid may result from delayed inactivation of certain neurohormones, namely serotonin and norepinephrine.

Inhibition of cholinesterase in plasma, and in erythrocytes, resulting from the administration of chloroquine phosphate has been reported.[22] It is likely that inhibition of cholinesterase would result in delayed destruction of acetylcholine, thus further enhancing the transmission of nerve impulses through cholinergic nerve fibers. However, the initial improvement that occurs in central nervous system manifestations after the administration of 4-aminoquinoline compounds is less significant than that after iproniazid.

Neither chloroquine phosphate nor hydroxychloroquine sulfate are potent inhibitors of amine oxidase, inasmuch as their inhibitory effect on amine oxidase activity of isolated mitochondria of rat liver is approximately two hundredths as active as that of iproniazid.[23] It is entirely possible that, although the mechanism of action is different, increased neurohormonal activity occurs from the administration both of iproniazid and of chloroquine phosphate or hydroxychloroquine sulfate.

Decreased cholinesterase has been reported[24] as occurring during pregnancy, but it is not known whether a relationship exists between the low cholinesterase and the spontaneous improvement that frequently occurs in pregnant women who have rheumatoid arthritis. It is interesting that neurologic manifestations occurred in a woman who, in the fifth month of pregnancy, accidentally took an overdose of chloroquine phosphate (from 1.5 to 3.5 gm.).[25] One hour later she experienced double vision and severe nausea, and suddenly fainted. Other symptoms included vomiting, depressed respiration, difficulty in swallowing, paresthesia, and anesthesia. She recovered completely within 36 hours with no adverse effect on the pregnancy.[25] Perhaps those symptoms resulted from inhibition of cholinesterase that already was depressed as a result of pregnancy.

Decreased cholinesterase has been noted in normal persons,[26] and the theoretical possibility that persons with pre-existing low concentrations are more susceptible to certain drug reactions that accompany the administration of 4-aminoquinoline compounds is under investigation.

In addition to a biochemic alteration within the central nervous system, we have postulated a peripheral biochemic defect within the mesenchymal tissues manifested by increased activity of tissue catecholamines and increased formation of mucopolysaccharides in patients with active rheumatoid arthritis.

We are investigating the possibility that increased activity of certain catecholamines or other irritating substances may cause both proliferation of fibrous tissue and the inflammatory reaction characteristic of rheumatoid arthritis. We have reported elsewhere[19] that either free serotonin or histamine in minute

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amounts is capable of producing an acute inflammatory reaction when injected into noninvolved joint tissue of patients with active rheumatoid arthritis; this reaction is less severe in nonrheumatoid persons.

The possibility of a cause-and-effect relationship between serotonin and the proliferation of fibrous tissue needs further investigation before significance can be attached to the numerous descriptions of fibrotic right-sided valvular cardiac lesions and masses of fibrous tissue surrounding pelvic organs and lower abdominal arteries in patients with metastatic carcinoid tumors associated with increased concentration of serotonin in the blood. Although we have observed normal concentrations of serotonin in the blood of patients who have active rheumatoid arthritis, this does not imply that a biochemic alteration within the tissues may not exist.

Many investigators are of the opinion that the mast cell is an important functional component of connective tissue. It is well known that mast cells are rich in polysaccharides and histamine.[27] Recently, on direct analysis, mast cells isolated from rat peritoneum contained serotonin.[28] Histamine liberation has been reported after the administration of chloroquine phosphate in the rat.[29] In many instances histamine liberators are capable of damaging mast cells. However, it must be emphasized that the liberation of histamine does not necessarily imply that is was released from mast cells and, perhaps most important, it is well known that since there is marked species difference in pharmacologic response, a reaction that occurs in the rat cannot be assumed to occur in the human. We are currently investigating the possibility that 4-aminoquinoline compounds are antimetabolites that decrease activity of mast cells in patients with active rheumatoid arthritis.

Clinically the 4-aminoquinoline compounds seem to affect primarily the peripheral or mesenchymal manifestations of the disease, and secondarily the central nervous system manifestations, in contrast to iproniazid, which affects primarily the nonarticular or clinical features related to the central nervous system, and has little effect peripherally on mesenchymal tissue in the small dosages that we use.

Discussion

It is well known that rheumatoid arthritis is a complicated disease, of unknown etiology, which involves many systems of the body, and that no specific therapy is available. Consequently, current treatment is directed toward control of the numerous disease manifestations which vary greatly.

There is complete agreement among investigators that no single agent is capable of controlling all disease manifestations indefinitely without relapse or drug reactions. The desirable and undesirable features of the 4-aminoquinoline compounds are becoming apparent, although we believe that more experience and time are necessary before final conclusions can be made as to their true value as therapeutic agents for rheumatoid arthritis and related diseases.

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Desirable features. An important desirable feature of these compounds is the low incidence of *serious* drug reactions during long-term maintenance therapy. It should be kept in mind that certain drug reactions occur frequently and are of temporary duration; therefore, administration of the drug need not be stopped. All drug reactions that were considered serious were completely reversible when the drug therapy was discontinued.

There is a low incidence in major relapse after the attainment of maximum improvement. However, minor fluctuations manifested by transient aching, stiffness or mild joint swelling, frequently follow physical overactivity and emotional stress.

The 4-aminoquinoline compounds can be administered orally and simultaneously with other therapeutic agents[14,16] to patients whose response to therapy previously has been unsatisfactory and, after improvement occurs, the use of therapeutic agents other than the 4-aminoquinoline compound can be stopped.

There are no apparent contraindications to the use of these compounds in cases of pregnancy, peptic ulcer, pulmonary tuberculosis, diabetes mellitus, or hypertension.

Undesirable features. One of the most undesirable features of the 4-aminoquinoline compounds is that the patient responds slowly to therapy, and maximum improvement may be delayed for from six months to one year.

In about one third of the patients there are joint manifestations that do not subside completely, and the central nervous system manifestations characteristic of rheumatoid arthritis initially are not significantly improved with the administration of these drugs.

Cystic changes and demineralization of bone may develop in spite of the disappearance of joint pain and swelling during chloroquine therapy. A 16-year-old girl had rheumatoid arthritis with involvement of both wrists and knees. The joints were moderately swollen and painful on motion. Six months after the onset of joint manifestations, chloroquine phosphate (250 mg. daily) was started. Roentgenograms of the joints taken before medication was started revealed normal structure. Although joint swelling and tenderness disappeared after three months of therapy, medication was continued. One year after the onset of therapy, roentgenograms showed a generalized demineralization of the bones in the hand and the wrist and a cystic change in the navicular bone (Fig. 2).

The most serious reactions involve the skin, and patients with psoriasis are highly susceptible to a variety of skin reactions, including an exacerbation of their psoriatic lesions. We believe that it is best to avoid the use of these compounds when psoriasis is present.

The use of 4-aminoquinoline compounds in rheumatoid arthritis. In patients with rheumatoid arthritis the clinical response to 4-aminoquinoline compounds in many ways resembles that of patients with chronic gouty arthritis who are treated solely with probenecid. In each disease there usually is a delay in clinical improvement. If the dosage of medication is increased, there is little or no significant immediate effect on the course of either disease, except occasionally

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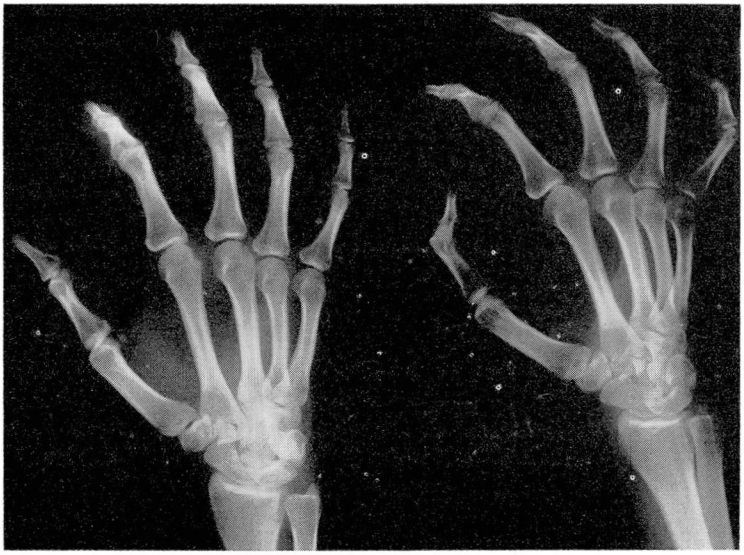
when transient exacerbations appear shortly after the onset of therapy. After periods from six months to one year, patients with chronic gouty arthritis are less susceptible to acute exacerbations, but mild flare-ups still may occur. This also is characteristic of most patients with rheumatoid arthritis treated with one of the 4-aminoquinoline compounds. In both diseases, long-term administration of these drugs usually results in maintenance of clinical improvement.



A B

Fig. 2. (A) Roentgenogram taken before the patient was given chloroquine phosphate therapy. (B) One year after beginning chloroquine phosphate therapy; note generalized demineralization of the bones in the hand and the wrist, and a cystic change in the navicular bone.

Combined-drug therapy has been advocated and used with increased effectiveness in chronic gouty arthritis. Acute exacerbations are treated separately with drugs that quickly suppress the acute attack, while probenecid is given to maintain the improved state and to prevent future exacerbations. Because of the characteristic response to 4-aminoquinoline compounds we have applied the same principle of therapy to patients with progressive and persistently active rheumatoid arthritis. One of the 4-aminoquinoline compounds is administered primarily to maintain long-term suppression of connective-tissue inflammation. Small doses of oral corticosteroids and/or intravenous corticotropin with or without nitrogen mustard may be used temporarily at the onset of therapy to suppress inflammation rapidly. During the first few months of therapy, central nervous system manifestations are treated with iproniazid. Thus, an individualized program of therapy can be instituted for each patient depending upon the disease manifestations present at the time treatment is started. As improvement

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occurs, the drugs can be withdrawn in orderly fashion, and maintenance therapy can be continued with a 4-aminoquinoline compound.

Summary

1. Chloroquine phosphate or hydroxychloroquine sulfate was administered to 805 patients with rheumatoid arthritis and allied diseases for periods ranging up to three years.

2. Of 106 patients with rheumatoid arthritis who were given only a 4-aminoquinoline drug, there was major improvement in 62 per cent. There was a wide variation in response: less than 25 per cent of patients obtained major improvement within the first three months; 37 per cent obtained similar improvement after 12 months; 38 per cent showed an insignificant response after 18 months.

3. Reactions related to the administration of 4-aminoquinoline compounds in 805 patients are grouped as neurovascular, gastrointestinal, dermatologic, and endocrine. Although 55 per cent of patients exhibited some reaction to the drugs, 67 per cent of these reactions cleared spontaneously while medication was continued. Seven per cent of toxic reactions was serious enough to require withdrawal of the 4-aminoquinoline compound.

4. The pharmacologic action of these compounds is not known, although biochemic alterations occur within the central nervous system and peripheral tissues.

5. The desirable features of therapy using 4-aminoquinoline compounds are the low incidence of serious drug reactions and of chronic toxicity, the ease of administration, the compatibility with other therapeutic agents, and the low incidence of relapse after maximum improvement has been obtained.

6. The undesirable features of 4-aminoquinoline compounds are the delayed onset of major improvement, the persistence of minor disease fluctuations and the lack of major improvement that is observed in one third or more of the patients, and sometimes an apparent susceptibility to skin reactions that may be serious although not necessarily frequent.

7. Those patients in whom slow onset in clinical improvement or incomplete response to therapy was anticipated, were given supplemental agents to induce further suppression of the disease. The 4-aminoquinoline drugs together with supplemental agents administered in nontoxic doses effectively maintained suppression of the disease in 83 per cent of 194 patients followed for 18 months. Emphasis is placed on a definite, orderly withdrawal of supplemental agents as improvement occurs.

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