V. CHEMOTHERAPY IN RHEUMATOID ARTHRITIS: A CONCEPT

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RHEUMATOID ARTHRITIS is a variable and unstable disease that disappears spontaneously or responds quickly to nonspecific measures in approximately half of the patients seeking medical care.[46] In the patients in whom the disease does not respond satisfactorily to simple measures, treatment becomes difficult, and in approximately one third of those patients the disease may become so intractable as to defy almost any method of therapy.

To be completely efficacious in the treatment of rheumatoid arthritis, a therapeutic agent must be nontoxic and able quickly to suppress the acute phase of the disease, to elevate mood or to counteract emotional instability when present, to prevent relapses, and constantly to suppress chronically active disease associated with persistent inflammatory joint manifestations, while permitting the maintenance of useful activity. Unfortunately, no single therapeutic agent, or, heretofore, any combination of agents has been capable of fulfilling all of these criteria. We believe that our present therapeutic program comes closer to the ideal than any therapy that we have used previously. Inasmuch as each of the drugs that have been used possesses a different pharmacologic action, it appeared logical that results could be improved and the danger of toxicity could be reduced by administering a combination of drugs each in a dose smaller than that which ordinarily would be used if the drug were employed alone. An exception was the antimalarial agents (hydroxychloroquine sulfate and chloroquine phosphate), the dosage of which was not reduced since they rarely cause toxic reactions.

Our program of therapy for patients with rheumatoid arthritis begins with an analgesic and becomes increasingly complex as the disease increases in severity. Unless the disease is obviously progressive or a simple drug program previously has been unsuccessful, simple methods of therapy are instituted before resorting to the combined-drug programs.

Physiotherapy, which is not discussed in detail here, is considered essential in patients with musculoskeletal symptoms. It was used routinely when indicated, supplementing each chemotherapeutic program.

Analgesic and Tranquilizing Agents

Patients with early or nonprogressive disease who were able to maintain light-to-moderate activity were initially given sodium salicylate, from 4 to 8 gm. daily. The salicylate was administered primarily for its analgesic effect, rather than for its anti-inflammatory effect which we consider insignificant in comparison to that of certain nonsteroid drugs now available. Subjective and objective responses to treatment were evaluated at from six- to eight-week intervals for from three to six months. When mild alteration in the patient's affect or in his emotional stability accompanied the arthritis, one of the tranquilizing and muscle-relaxing agents was given in addition to the salicylate. The most effective agent available at present is meprobamate*, administered orally in doses of 400 mg. three or four times daily. Recently phenaglycodol** has been used in doses of 200 mg. three times daily, but we have not completely evaluated its effect at this time. Depressed states may occur from overdosage. Usually these drugs can be discontinued as anxiety states subside and confidence is restored.

Anti-Inflammatory Agents

Hydroxychloroquine sulfate or chloroquine phosphate. The antimalarial drugs were administered to those patients who did not respond satisfactorily to salicylate, to those patients who had more active or deep-seated disease, to those patients who had associated diseases contraindicating the use of corticosteroids, such as diabetes mellitus, tuberculosis, peptic ulcer, and to certain patients with hypertension. The usual dosage of hydroxychloroquine sulfate ranged from 400 mg. to 600 mg. daily, although in some patients improvement was delayed for a matter of weeks or remained incomplete even when the daily dose was increased to 1.0 gm. The usual dosage of chloroquine phosphate initially was 500 mg. daily, which for most patients was decreased to 250 mg. daily after improvement had occurred. Gastrointestinal side effects often prevented the administration of a larger initial dose of chloroquine phosphate, but with hydroxychloroquine sulfate these effects were not so frequent.

Decrease in joint swelling with lessening of pain in joints and muscles usually was the first manifestation of improvement. Patients often stated that their joints "felt looser" before there was an apparent decrease in joint size. In patients with moderately severe rheumatoid arthritis the improvement frequently was incomplete, especially during the first three months and up to six months of treatment. In some cases salicylate, from 4 to 8 gm. daily, or prednisone, 3 mg. daily, also was administered, while in others more resistant to therapy a combination of drugs was utilized (page 107).

ACTH. When antimalarial therapy was supplemented by prednisone for more than a few weeks, ACTH gel, 10 units, was given intramuscularly at

**Equanil, Wyeth Laboratories; Miltown, Wallace Laboratories.*
***Ultran, Eli Lilly and Company.*

weekly intervals. We have observed repeatedly that patients receiving maintenance antimalarial therapy and from 3 to 6 mg. of prednisone or a related steroid, maintain more satisfactory improvement and have fewer fluctuations in disease activity if they also receive a small amount of ACTH. The dose is too small to produce hyperfunction of the adrenal cortex which will result in a measurable increase of plasma hydrocortisone, although it may cause minimal stimulation of the entire adrenal cortex and result in a mild subclinical state of hypercorticalism that is clinically desirable in patients with rheumatoid arthritis. No significant degree of anterior hypopituitarism is believed to result from the administration of this amount of ACTH. Wilson[47] has observed apparent steroid abnormalities in the urine of two male patients with rheumatoid arthritis as compared with that of normal males. He believed that the administration of ACTH diminished the abnormal steroid metabolites, which were replaced with the metabolite pattern found in the normal males. Holley[48] states that the diurnal steroid excretion pattern observed by Hill and Warren may not reflect variations in intermediary metabolism or in excretion of adrenocortical steroids, but a change in the "pituitary-adrenal or hypothalamic-pituitary-adrenal" secretory mechanism.

At present we consider the administration of ACTH in the dosage described to be an integral part of the chemotherapeutic program for patients with severe active disease that requires maintenance corticosteroid therapy.

Combined-Drug Therapy

For those patients incapacitated by persistently active disease, or for those in relapse who have been resistant to all previous treatment, a program of therapy has been devised in which certain drugs are administered in various combinations. The drug combinations and routes of administration vary depending upon the severity of the disease, the extent of inflammatory and destructive joint manifestations, the emotional state of the patient, and the previous therapy. For this treatment patients are hospitalized for two weeks during which time they receive chemotherapy, physical therapy, instruction in home physical therapy and in maintenance of chemotherapy, and proper shoes or orthopedic appliances if indicated.

Pharmacologic action varied for each drug, and it appeared that a greater therapeutic effect with fewer side reactions was achieved with multiple drugs than was achieved with larger doses of any single agent.

Induction therapy. We believe that the intravenous administration of ACTH and HN_2 in the doses recommended is one of the quickest and safest methods of suppressing generalized activity of rheumatoid arthritis. Ten units of aqueous ACTH was diluted in 500 ml. of 5 per cent dextrose in water, andt he solution was infused over a period of four hours. To prevent nausea and vomit-

ing, 50 mg. of promazine hydrochloride was given at the beginning of the ACTH infusion. One-half hour later, 2 or 3 mg. of HN_2 diluted in 2 ml. of saline solution was injected directly into the intravenous tubing. When the gastrointestinal side effects were properly controlled with promazine hydrochloride, most patients welcomed this therapy because of the rapid relief of symptoms.

Intravenous therapy was continued daily for five days and then stopped for from one to three days in order to evaluate the immediate results. If symptoms rapidly returned on the first day, four or five more daily infusions were given; if minor symptoms persisted or returned, two or three more daily infusions were administered. If no symptoms appeared after three days, no further infusions were given.

This treatment was most effective in suppressing soft-tissue swelling, fever, constitutional symptoms, and acute or subacute inflammatory joint swelling. Joint involvement manifested by thick pannus formation and persistent effusion did not subside completely. The suppressive effect was of short duration and symptoms usually reappeared in from four weeks to three months. However, the temporary remission usually was of sufficient duration to allow the oral maintenance therapy to become effective enough to maintain the suppression of disease activity without large doses of corticosteroids.

Oral maintenance therapy. An antimalarial drug, preferably hydroxychloroquine sulfate, was used for oral maintenance therapy, begun simultaneously with the ACTH and HN_2 intravenous therapy. The average initial total daily dose was 600 mg., one 200-mg. tablet after each meal. Prednisone or prednisolone, 1 or 2 mg. three times daily, also was given. This combination of orally administered drugs was continued until the patient was practically symptom free, usually for from 3 to 12 months, and then the dose of corticosteroid was reduced to half. If the disease remained suppressed after a few months, the corticosteroid was stopped, as it was assumed that the patient was experiencing a remission. Whether the remission was spontaneous or drug-induced is not known and is not important; rather, it is important to realize that alteration in the diseased state had occurred and permitted a modification of the drug schedule whereby the corticosteroid could be decreased in dosage or could be stopped. The remission sometimes persisted, but if an exacerbation occurred the corticosteroid again was added to the program of oral maintenance therapy. Exacerbations usually were infrequent after the first year of maintenance therapy in patients receiving one of the antimalarial drugs. Patients who were asymptomatic but in whom the disease remained active on the basis of laboratory studies were maintained on a reduced dose of an antimalarial, 250 mg. of chloroquine phosphate or 200 mg. of hydroxychloroquine sulfate. If all symptoms subsided and laboratory tests, including serum protein fractionation as determined by electrophoresis, erythrocyte sedimentation rate, and serum polysaccharide-protein ratio, returned to normal for three months the antimalarial drug was stopped.

ACTH administered intramuscularly. ACTH was used routinely in this program of therapy as described previously on page 106. The rationale for its use

has been discussed. The routine dosage was 10 units of long-acting ACTH injected intramuscularly once weekly. The patient or a close relative of his was instructed in the technic of administration. If during the first month or two of therapy the patient continued to have unstable disease associated with minor exacerbations, the dosage of ACTH was increased to 10 units twice weekly. Usually this increased dosage was necessary for only a few weeks, after which time the routine dosage was again administered. As improvement occurred and the corticosteroid was diminished in dose or stopped, ACTH was continued in the routine dosage for a few weeks after which time it was gradually reduced over a period of a few weeks and then it was stopped. When corticosteroid was restarted, ACTH, 10 units weekly, again was added to the therapeutic program.

Hydrazides. Isoniazid alone (in the dosage of 100 mg. three times daily) was inconsistently and incompletely effective in relieving joint manifestations. The action of iproniazid (in the dosage of 50 mg. three times daily for one month and then 25 mg. daily or every other day) was more consistent and relatively rapid, but the drug had to be used sparingly and adjusted to the response of the patient. Isoniazid and iproniazid were used alone or in combination with small doses of steroid, and as oral maintenance therapy in the program of combined-drug therapy before the antimalarial drugs were available. However, the hydrazides still are used when the antimalarial drugs are not tolerated or when there is a possibility of associated tuberculosis. Pyridoxine, from 10 to 25 mg. daily, was given with the hydrazides as prophylaxis against peripheral neuropathy. Withdrawal symptoms were not apparent when administration of the hydrazides was stopped.

Iproniazid we consider to be especially useful as a temporary adjunct to therapy in selected patients with various degrees of depression and emotional instability. Irrespective of the program of therapy decided upon for the patient, iproniazid can be administered in dosages of 50 mg. daily for from a few weeks to a few months, after which time the dosage gradually can be tapered to 25 mg. or less daily or every other day. After the patient has gained in weight and his strength and a sense of well-being have returned, administration of the drug can be stopped. Withdrawal effects were not apparent with this dosage schedule.

Intraarticular therapy. The program of combined chemotherapy discussed so far is effective mainly in suppressing constitutional symptoms, soft-tissue swelling, and acute or subacute inflammatory joint lesions. However, those joints that have been involved for years may have thick pannus formation and varying degrees of joint effusion which respond only partially to oral and parenteral therapy; often several of the larger joints may be resistant to treatment. Generally, an increase in the dosage of the medication being used will do little more than produce toxic reactions. Intraarticular injections of hydrocortisone or a related steroid may be of some value when this problem exists, but their effect is only temporary, usually lasting for from three days to three weeks. To prolong the effect of intraarticular therapy, small doses of HN_2 were mixed with a steroid in a ratio of 0.5 mg. of HN_2 (diluted in 0.5 ml. of normal saline

solution) to 25 mg. (1 ml.) of intraarticular steroid. This combination proved to be safe and effective, and in addition resulted in prolonged suppression of inflammation in wrist, knee, ankle, proximal interphalangeal, metacarpophalangeal, and elbow joints, which in many instances had been suppressed for only a few days or weeks.

When there were severe chondromalacia of the patella, advanced destruction of cartilage between the tibia and femoral condyles, severe pain on motion, and absence of fluid formation within the joint, the injections consisted of only hydrocortisone tertiary-butylacetate (H.T.B.A.) or a related steroid.

In more than 2000 intraarticular injections in which HN_2 was combined with H.T.B.A. or a related steroid, there has been no case of tissue sloughing or scarring. From our experience during the past three years, we believe that most joints (as described in part II) where persistent synovitis exists, but the disease is still potentially reversible, should be injected routinely at the onset of the combined chemotherapeutic program. These joints should be injected three times at from three- to four-day intervals. After one month, two or three additional injections at weekly intervals may be given. The results after two or three years have shown no complications from the use of HN_2, but 10- and 20-year follow-up studies are necessary to evaluate fully the cellular alteration that is produced by HN_2.

Chronic hypercortisonism. Slocumb [49-51] has described a syndrome termed *hypercortisonism* which results from prolonged hormonal overdosage and is characterized by emotional instability, fatigability, muscle and joint aches, and diffuse mesenchymal reactions that tend to simulate systemic lupus erythematosus and periarteritis nodosa. According to Slocumb, the problem of relieving hypercortisonism is more complicated than merely the stopping of hormonal therapy, since this may result in exchanging the undesirable effects of exogenous chronic hypercortisonism for the equally distressing effects of endogenous hypocorticalism (decrease of more than one and possibly all of the adrenocortical steroids) and its diffuse mesenchymal reaction. He states that treatment of hypercortisonism at best is slow, difficult, and perhaps inadequate because of the limited knowledge regarding the underlying biochemical and other mechanisms. The recommended treatment necessitates the patient's co-operation and involves extra rest and gradual reductions in the dosage of corticosteroids; it may have to be continued for longer than several months.

During the past two years 15 patients having hypercortisonism who were referred to us have been treated with slightly modified combinations of the drugs that we are using for severely active rheumatoid arthritis. In each instance the dosage of prednisone or prednisolone was reduced abruptly to 2.5 mg. three times daily. Iproniazid was administered in dosages of 50 to 100 mg. daily, depending upon the degree of psychomotor depression. (Usually the daily dose of iproniazid was 100 mg. for 7 to 10 days, 75 mg. for one week, and then 50 mg., after which time it was further reduced and regulated according to the improvement in the patient's affect and the activity of the deep reflexes as described on page 96.) Simultaneously, ACTH, 10 units in 500 ml. 5 per cent dextrose in

water, and HN_2, 2 to 3 mg., was infused over a period of four or five hours daily for seven days, as described on page 75. Usually symptoms began to subside on the first or second day of therapy. On the eighth day intravenous therapy was omitted and the patients were closely observed for return of symptoms. If mild symptoms returned, two or three more daily intravenous injections of ACTH and HN_2 were administered. If moderate symptoms returned, from three to five more daily intravenous injections were given. The total dose of HN_2 never exceeded 25 mg. during one course of therapy. Hydroxychloroquine sulfate, from 600 to 800 mg., was started at the time that prednisone or prednisolone was reduced in dosage to 7.5 mg. daily. Subjective improvement usually began on the third or fourth day: fatigability and weakness diminished and strength increased. After the intravenous therapy was completed, 10 units of repository ACTH was given three times weekly for three weeks after which time it was reduced gradually and maintained at 10 units weekly.

Patients usually were hospitalized for from two to four weeks, during which time facial rounding and fat pads in the supraclavicular and cervical regions began to subside significantly. Patients treated two years ago in this manner have remained improved and show no indications of chronic hormonal overdosage.

Our clinical results support the theory that these patients have exogenous hypercortisonism that subsides as the corticosteroid is rapidly decreased in dosage, and endogenous hypocorticalism that within 24 to 48 hours responds to intravenously administered ACTH and HN_2. However, this theory does not explain why the intravenous administration of HN_2 and ACTH also suppresses the hypercortisonism that results from excessive intramuscular administration of ACTH and that is characterized by endogenous hypercorticalism and endogenous anterior hypopituitarism. A possible explanation is that HN_2 through an unknown mechanism of action alters the response of the connective tissue to ACTH and corticosteroids so that these tissues again become sensitive to the suppressive action of the hormones.

Treatment of patients with hypercortisonism will be reported in more detail elsewhere. In brief, most patients have improved significantly and they are being maintained on a combined-drug program that eliminates the need for large doses of ACTH or of a corticosteroid.

Comment

The results of our program of combined-drug therapy for rheumatoid arthritis have been encouraging in most of our patients. One of the most important features of the combined therapeutic program has been the low incidence of toxic reactions related to hormone therapy. Sensitivity reactions to ACTH occurred in only 5 of the 254 patients. In 12 patients active duodenal ulcer was present at the time that treatment was started, and in two patients active duodenal ulcer developed after therapy had been started. These patients were treated with a conservative ulcer program while therapy for rheumatoid arthritis was continued. No instance of psychosis developed during therapy, and aggravation of hypertension and of diabetes was not clinically significant in this

series of patients. Our program is flexible and is adjusted on the basis of the activity of the disease in the individual patient. The theoretic effect of each drug of the entire therapeutic program on disease activity is depicted in Figure 1.

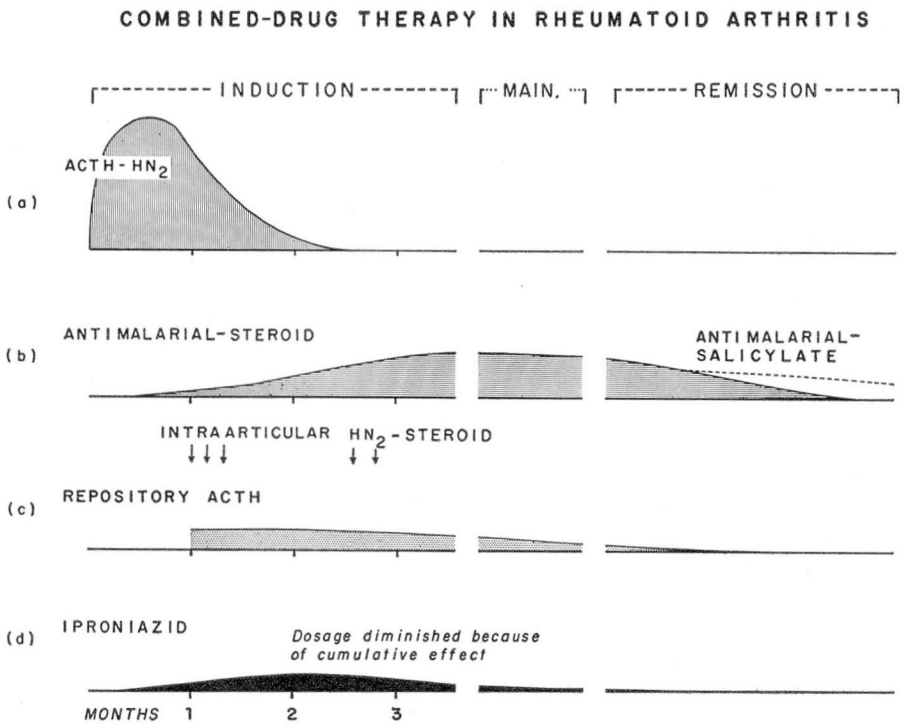

Fig. 1. Scheme of combined-drug therapy: Treatment is flexible and for convenience is divided into three phases. The induction phase includes (a) intravenously administered ACTH-HN_2: *ACTH*, 10 units, and *HN_2* from 2 to 3 mg., daily in 500 ml. of 5 per cent dextrose and water for 5 to 10 days. During this time maintenance therapy(b) is started, which does not become effective immediately: *Hydroxychloroquine sulfate*, from 400 to 600 mg. daily, or *chloroquine phosphate*, from 250 to 500 mg. daily, is administered with *prednisone* or *prednisolone*, from 3 to 7.5 mg. daily. (c) *Repository ACTH*, 10 units, intramuscularly administered weekly is started after induction therapy has been completed; the dosage may vary slightly during the first few months of treatment. The limitations of ACTH and corticosteroids are realized, despite their great effectiveness in suppressing disease activity; they are used intermittently in small doses, primarily as supplemental agents. (d) *Iproniazid*, from 50 to 100 mg. per day, is administered for from three to six weeks and then is reduced gradually.

Intraarticular injections are given when persistent but reversible joint inflammation is present.

The second or maintenance phase of therapy depicts the full effect of combined administration of *antimalarial-corticosteroid agents*, *repository ACTH*, 10 units administered at 7 to 10 day intervals, and *iproniazid*, finally reduced to 10 mg. daily or on alternate days as mood improves.

The third or remission phase depicts reduction in corticosteroids and antimalarial agents. *ACTH* is gradually reduced in dosage and administration is stopped when administration of the corticosteroid has been stopped. (b) *Salicylate* is substituted for corticosteroid as improvement occurs; it may be used as needed for minor aching and stiffness. If relapse occurs the drugs can again be administered as described.

Two hundred fifty-four patients who received combined-drug therapy, including one of the antimalarial agents as oral maintenance therapy, were followed for two years. Joint improvement, as determined objectively, was considered to be excellent or good in 223 of the 254 patients. One hundred sixty-one of these 223 patients received supplemental intraarticular injections of HN_2 and a steroid to obtain this degree of improvement. Emotional instability and depressed psychomotor activity observed in 187 of the patients were improved significantly in 125 patients.

We believe that our results were influenced by the patient's co-operation and motivation, and that these in turn were improved by the medication administered for that purpose while other medication was being used to suppress the objective disease manifestations.

Summary and Conclusions

1. Rheumatoid arthritis is a complex, fluctuating, systemic disease of unknown etiology, for which no single therapeutic agent to date is consistently or predictably effective.

2. A flexible program of chemotherapy is being utilized, from the oral administration of sodium salicylate alone, to the oral, intravenous, intramuscular, and intraarticular administration of multiple drugs (HN_2, corticosteroids, antimalarials, iproniazid).

3. With a variable therapeutic program, in our experience, it usually has been possible to achieve rapid suppression of acute disease, and to maintain suppression of chronically active disease through long-term therapy; fluctuating disease has become more stable and affect has been improved.

4. The incidence of toxic reactions and side effects has been minimal in relation to the number of drugs used.

5. The combined-drug regimen has given many additional months of gainful employment to certain patients who had responded unsatisfactorily to single therapeutic agents and who heretofore had been unemployable during periods of disease activity.

6. A program of therapy similar to that for severe, active, rheumatoid arthritis is suggested as being applicable to hypercortisonism.

7. Contraindications to the use of combined-drug therapy are few, notably hepatic disease and bone marrow depression.

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