THE TREATMENT OF RHEUMATOID ARTHRITIS COMPLICATED BY CHRONIC HYPERCORTISONISM, AND THE THEORETICAL CAUSAL ROLE OF CERTAIN AMINE OXIDASES

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THE recognition by Hench, Kendall, Slocumb, and Polley[1] in 1948 of the desirable effects exerted by cortisone and corticotropin on inflammation and swelling in patients with rheumatoid arthritis and associated diseases is considered one of the great medical discoveries of our time. However, it has since become apparent that the effect of these hormonal agents is not specific, that the desirable effect is only temporary, and that acute or chronic hypercortisonism may ensue from overdosage. The undesirable effects that may occur have been described by Slocumb, Polley, Ward, and Hench,[2] and include alteration in electrolyte and water metabolism, decrease in carbohydrate tolerance, acneiform eruption, hirsutism, striae, deposition of fat, menstrual disorders, hyperacidity, delay in wound healing, and hypertension. Chronic overdosage is variously evidenced by emotional instability, increased fatigability and muscle aching, inability to concentrate, and depressed psychomotor activity. When these signs and symptoms are present, withdrawal of the corticosteroids may be extremely difficult, and must be accomplished slowly and gradually over a period of months; during this period, the patient must co-operate fully with the physician and must get 12 to 14 hours of sleep nightly together with extra periods of rest during the day.[2] Too rapid reduction in dosage may result in a flare-up of the rheumatoid arthritis, and in some patients, corticosteroid therapy may have to be continued indefinitely.[2]

Recently Scherbel, Schuchter, and Harrison[3] reported a method of administering a combination of chemotherapeutic agents to patients with progressive and persistently active rheumatoid arthritis. Despite decrease of corticosteroid dosage, these patients showed sustained improvement and few side effects. We have also used this method of therapy effectively in patients with rheumatoid arthritis in whom chronic hypercortisonism had resulted from long-term hormonal overdosage. In our opinion, these patients were not at all likely to develop spontaneous remissions during an abrupt reduction in dosage of corticosteroid. It, therefore, can be assumed that the drugs other than the corticosteroid altered the disease significantly.

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From our findings in patients having rheumatoid arthritis with or without hypercortisonism, we believe that the central nervous system manifestations of both conditions result from the same biochemical alterations but that these alterations are exaggerated in patients having rheumatoid arthritis with hypercortisonism. It is the purpose of this paper to report the results of treatment in 16 patients having rheumatoid arthritis with chronic hypercortisonism, and to suggest a theoretical explanation of some of the manifestations of rheumatoid arthritis.

Methods

Sixteen patients with active rheumatoid arthritis complicated by chronic hypercortisonism comprise the series. The group consists of 12 women—5 of whom were premenopausal and 7 of whom were postmenopausal—and 4 men. The ages of the women ranged from 33 to 66 years; those of the men from 47 to 62 years. The duration of rheumatoid arthritis ranged from 1 to 11 years. Twelve patients had stage 2 and four had stage 3 disease; 11 patients were classified as being functional class 3 and five as functional class 4, according to criteria of the American Rheumatism Association.[4] Each patient had characteristic features of chronic hypercortisonism, and all had been taking corticosteroids for periods ranging from six months to seven years, in amounts equivalent to or more than 20 mg. of prednisone per day. Table 1 summarizes the data on the 16 patients.

Clinical Features in Patients with Chronic Hypercortisonism

All these patients had been treated elsewhere with corticosteroids as the sole therapeutic agent and had developed resistance to the hormone. As response to the hormone diminished, 10 of the patients voluntarily increased steroidal dosage without medical advice or supervision. The most common complaints of all patients on admission here were severe weakness, fatigability, and generalized muscle aching. Round facies, supraclavicular and cervicodorsal fat pads, and weight gain were the most frequent physical findings. Fifteen patients had gained from 6 to 30 pounds in weight. Twelve patients had 2 to 4 plus dependent edema of the lower extremities. Joint swelling of varying degree and moderate-to-severe pain on motion were present in all patients and had become more severe as response to the corticosteroid had diminished. Nine were emotionally unstable and had cyclic swings in mood. Seven complained of increased nervous tensions and persistent insomnia. Five noted difficulty in concentration and five were in states of moderately severe depression at the time of initial examination. Four appeared to have greatly increased pain sensitivity that limited their activity. Six had epigastric distress manifested by nausea, burning, and low-abdominal pain. Four of these six had peptic ulcers; three were duodenal ulcers and one was an antral ulcer. All ulcers healed on medical management while

Table 1.—*Summary of data on 16 patients having rheumatoid arthritis and chronic hypercortisonism*

Case number	Sex; pre-menopausal or post-menopausal	Age, years	Duration of disease, years	Disease severity*		Duration of steroidal treatment	Initial response to steroids	Time before steroid "escape," months	Duration of hospital-ization, days
				Stage	Functional class				
1	F; pre	38	1	3	3	7 mo.	Good	4	10
2	M	47	5	2	3	24 mo.	Poor	—	12
3	F; pre	33	2	2	3	7 mo.	Good	4	14
4	F; post	48	1	2	3	10 mo.	Good	3	12
5	M	54	6	2	3	10 mo.	Excellent	2	11
6	F; post	47	7	3	3	36 mo.	Good	12	14
7	F; pre	36	11	2	4	36 mo.	Good	8	14
8	M	51	4	2	3	12 mo.	Fair	2	14
9	F; post	49	1	2	3	9 mo.	Excellent	6	13
10	F; post	61	2	3	4	20 mo.	Good	11	29
11	F; post	66	4	2	3	48 mo.	Good	12	14
12	F; pre	43	6	2	4	6 mo.	Good	3	7
13	F; post	58	4	2	4	12 mo.	Poor	1-2	13
14	F; post	48	2½	3	3	20 mo.	Fair	2	12
15	F; pre	42	3	2	3	36 mo.	Good	9	15
16	M	62	10	2	4	7 yr.	Good	6	11

**Classification of American Rheumatism Association.*

Table 2.—*Symptoms and signs in 16 patients having rheumatoid arthritis with chronic hypercortisonism*

Case no.	Symptoms	Signs
1	Insomnia, irritability, increased nervous tension, fatigability, muscle aching, hyperalgesia, emotional instability	Weight gain, facial rounding, edema of lower extremities, multiple joint swellings, B.P. 140/85
2	Increased nervous tension, muscle aching, fatigability, insomnia, anorexia, hyperalgesia, irritability, emotional instability	Weight gain, facial rounding, edema of lower extremities, moderate plethora and osteoporosis, moderate multiple joint swellings, B.P. 100/68
3	Muscle aching, increased nervous tension, irritability, insomnia, depression, poor concentration, fatigability	Edema of lower extremities, facial rounding, weight gain, moderate osteoporosis, moderate swelling of joints of knees, ankles, wrists, B.P. 122/86
4	Insomnia, increased nervous tension, muscle aching, irritability, anorexia, increased pain sensitivity, fatigability, emotional instability	Facial rounding, plethora, edema of lower extremities, weight gain, moderate multiple joint swellings, B.P. 130/80
5	Muscle aching, increased pain sensitivity, activity restricted to chair, fatigability, emotional instability	Edema of lower extremities, facial rounding, supraclavicular and posterior cervical fat pads, weight gain, marked osteoporosis, duodenal ulcer, multiple joint swellings, B.P. 132/80
6	Insomnia, fatigability, muscle aching and weakness, depression and poor concentration, emotional instability	Facial rounding, supraclavicular and posterior cervical fat pads, edema of lower extremities, weight gain, marked osteoporosis, moderate swelling of joints of knees and ankles, B.P. 134/76
7	Insomnia, fatigability, muscle aching, hyperalgesia, nausea, vomiting, depression	Edema, facial rounding, plethora, weight gain, increased facial and body hair, marked multiple joint swellings, B.P. 112/76
8	Generalized muscle aching and soreness, weakness and fatigability, activity restricted to chair	Weight gain, facial rounding with plethora, supraclavicular fat pads, marked osteoporosis, duodenal ulcer, multiple joint swellings, B.P. 130/80

Table 2—continued

Case no.	Symptoms	Signs
9	Euphoria, increased nervous tension, muscle aching with hyperalgesia, poor concentration, fatigability, emotional instability	Facial rounding, plethora, edema of lower extremities, weight gain, multiple joint swellings, B.P. 140/60
10	Activity restricted to chair, fatigability, muscle aching, increased pain sensitivity, depression	Edema, facial rounding, plethora, weight gain, supraclavicular and posterior cervical fat pads, moderate multiple joint swellings, B.P. 110/70
11	Muscle aching with increased pain sensitivity, easy bruising, activity restricted to chair, increased fatigability	Weight gain, facial rounding, plethora, increased body and facial hair, edema of lower extremities, supraclavicular and posterior cervical fat pads, moderate osteoporosis, moderate multiple joint swellings, B.P. 160/80
12	Activity restricted to chair, hyperalgesia, increased fatigability, muscle aching, insomnia, nausea, emotional instability	Weight gain, facial rounding, supraclavicular fat pads, mild osteoporosis, mild multiple joint swellings, B.P. 120/70
13	Muscle aching in arms and legs, irritability, inability to concentrate, increased nervous tension, emotional instability, addiction to dihydromorphinone (Dilaudid) hydrochloride, fatigability	Weight gain, facial rounding, supraclavicular and posterior cervical fat pads, marked osteoporosis, moderate multiple joint swellings, gastric ulcer, B.P. 140/84
14	Generalized muscle aching, increased irritability and fatigability, increased nervous tension, poor concentration, insomnia, emotional instability	Facial rounding, weight gain, increased body and facial hair, edema of lower extremities, marked osteoporosis, duodenal ulcer, severe multiple joint swellings, B.P. 130/80
15	Generalized muscle aching, increased pain sensitivity, depression, increased fatigability, weakness, anorexia, easy bruising	Edema of lower extremities, weight gain, facial rounding, posterior cervical fat pads, plethora, severe multiple joint swellings, B.P. 116/74
16	Marked restriction of activity while taking steroid, muscle aching, increased fatigability, emotional instability, easy bruising	Weight gain, facial rounding, marked facial flushing, edema of lower extremities, supraclavicular fat pads, gynecomastia, marked osteoporosis with vertebral compression fractures, moderately severe multiple joint swellings, B.P. 126/78

administration of corticosteroids was maintained in a reduced dosage, never exceeding 7.5 mg. of prednisone daily. Table 2 summarizes the symptoms and signs in the 16 patients.

Blood pressures were not increased significantly; only one patient had a systolic pressure higher than 140 mm. Hg, and no patient had a diastolic pressure exceeding 90 mm. Hg. Four patients had fasting hyperglycemia, and in one of them control of the diabetes requires the use of insulin. Serum L.E. tests were performed in 14 of the 16 patients, while chronic hypercortisonism was present, and in all the tests were negative. In one patient the L.E. test became positive six weeks after combined treatment was started (at which time the patient showed excellent objective and subjective improvement). In the 16 patients the hemoglobin content of the blood ranged from 10 to 15 gm. per 100 ml., and the total leukocyte counts from 4,500 to 10,300 per cu. mm. Sedimentation rates were moderately to markedly elevated as determined by the Rourke-Ernstene method.[5] Serum polysaccharide concentrations[6] ranged from 176 to 268 mg. per 100 ml., with the ratio of polysaccharide to total protein[7] greater than 2.1 per cent in each instance.

Treatment

The patients in this study were hospitalized for periods averaging 13 days. In general, treatment varied only slightly among patients, and followed the pattern previously described.[3] Treatment was begun after laboratory studies were obtained; in all patients these included roentgenograms and determinations of peripheral blood counts, plasma protein and serum polysaccharide contents, erythrocyte sedimentation rates, and, in some patients, other special studies including peripheral blood L.E. and serum latex fixation tests.

Our concept of treatment has been described in earlier reports.[3, 8-11] Initially corticotropin and nitrogen mustard are administered to suppress rapidly the inflammation of rheumatoid arthritis. The antimalarial drugs and small doses of prednisone are given to maintain the disease suppression induced by intravenous corticotropin and nitrogen mustard. Iproniazid is administered to alleviate the central nervous system manifestations characteristic of rheumatoid arthritis and possibly to potentiate the effect of maintenance drugs.

Twenty-five milligrams of promazine hydrochloride* was injected intramuscularly and then aqueous corticotropin, 10 units in 500 ml. of 5 per cent dextrose in water, was intravenously administered. One-half hour later 2 mg. of nitrogen mustard** was injected into the intravenous tubing. Intravenous therapy was continued daily for five days, but on the second day the dose of nitrogen mustard was increased to 3 mg. and continued at this dose for the rest of the five-day period. On the initial day of intravenous therapy the oral dosage of corticosteroid was reduced immediately to 7.5 mg. of prednisone or its

**Sparine hydrochloride, Wyeth Laboratories.*

***Mustargen hydrochloride, Merck Sharp & Dohme, Division of Merck & Co., Inc.*

equivalent daily, and was further decreased as improvement became apparent. To maintain the suppression of the disease which resulted from the intravenous administration of ACTH and nitrogen mustard, one of the antimalarial agents, chloroquine phosphate** (250 mg. daily) in seven patients or hydroxychloroquine sulfate+ (200 mg. three times daily) in nine patients, was administered with the oral corticosteroid. The dosage of iproniazid++ initially was 50 mg. daily, which was gradually reduced as improvement in central nervous system manifestations occurred.

Intraarticular injections were given every other day to each patient with moderate-to-marked joint swelling. The wrists, knees, ankles, and occasionally the elbows and small joints of the fingers were injected from two to four times with combined nitrogen mustard—hydrocortisone tertiary-butylacetate ++ prepared as follows[8]: 0.5 mg. of nitrogen mustard diluted in 0.5 ml. saline solution was mixed with 1 ml. hydrocortisone acetate,† hydrocortisone tertiary-butylacetate, or prednisolone tertiary-butylacetate†† (25 mg. per milliliter).

After completion of five days of intravenous therapy the patients were observed for minor relapses while oral medication—prednisone, an antimalarial agent, and iproniazid—was continued. If muscle aching, weakness, or joint pain occurred within the first few days, corticotropin and nitrogen mustard were again administered intravenously, but the dose of nitrogen mustard was reduced to 1 mg. while the dose of corticotropin was maintained at 10 units added to 500 ml. of 5 per cent dextrose in water. The total dose of nitrogen mustard administered intravenously over a period of two weeks ranged from 14 to 17 mg. In patients with rheumatoid arthritis who had side effects from hormonal overdosage, the total white blood cell count was seldom altered by the dose of nitrogen mustard given. Lymphopenia appeared during the first few weeks of combined-drug therapy; we believe this condition primarily resulted from the action of nitrogen mustard although lymphocyte counts were somewhat low in 12 of the 16 patients before intravenous therapy was started.

Physical therapy was begun after the third day, when general strength had improved and muscle aching had diminished, and was continued throughout the period of hospitalization. During this time the patients also were given instructions for physical therapy to be carried out at home.

Orthopedic measures usually were carried out after the first week of therapy, when indicated, and shoes were fitted during the second week of therapy, after edema of the lower extremities had subsided.

Maintenance Therapy

Prior to discharge from the hospital the patients were instructed in the administration of depot corticotropin, which we believe is an important feature

**Aralen phosphate, Winthrop Laboratories.*
***Plaquenil sulfate, Winthrop Laboratories.*
+Marsilid phosphate, Hoffmann-La Roche, Inc.
++Hydrocortone-T.B.A., Merck Sharp & Dohme, Division of Merck & Co., Inc.
†Hydrocortone acetate, Merck Sharp & Dohme, Division of Merck & Co., Inc.
††Hydeltra-T.B.A., Merck Sharp & Dohme, Division of Merck & Co., Inc.

of the combined program of therapy.[3] During the two to four weeks after discharge from the hospital, 10 units was administered twice a week, after which 10 units was administered once a week; this dosage was maintained until the patient was asymptomatic. The dosage of prednisone was reduced from 7.5 mg. daily to 3 mg. daily after nine months of treatment in eight patients and after 13 months of treatment in three patients. Four patients have continued to receive 7.5 mg. daily and for one patient treatment was discontinued.

One of the antimalarial agents was administered with the corticosteroid to each of the patients, as previously described. Most of the patients have remained on maintenance therapy usually consisting of chloroquine phosphate, 250 mg. daily, or hydroxychloroquine sulfate, 600 mg. daily. The antimalarial agent was the last drug to be reduced in dosage and its administration was not stopped until after the patient had become asymptomatic and results of laboratory studies had been normal for three months.

The dosage of iproniazid was initially 50 mg. daily and after two to four weeks, depending upon improvement in central nervous system manifestations, it was reduced to 25 mg. daily. The dosage was decreased as elevation of mood became apparent; elevation in mood was directly associated with signs of recovery of autonomic balance and increased deep reflexes. The dosage usually was maintained for two to three months, after which time it was further reduced to and maintained at 10 mg. daily. Administration of iproniazid usually was stopped after the patient had recovered sufficiently to permit corticosteroid to be withdrawn.

Intraarticular injections were continued at monthly intervals until joint swelling subsided. Initially each of the 16 patients received intraarticular injections into one or more joints, and 15 of the 16 required at least one additional injection after discharge from the hospital. Usually intraarticular injections were not necessary after the second or third month of therapy.

Results

All patients improved significantly, both objectively and subjectively, while in the hospital for an average period of 13 days. Improvement manifested by decrease in muscle aching and stiffness and an increase in strength usually was observed after the first or second intravenous injection of corticotropin and nitrogen mustard. After three days, 12 patients had significant improvement in both subjective and objective manifestations characterized by less aching and stiffness, increased strength and appetite, less nervousness and insomnia, and elevation of mood without euphoria. Temperatures, if elevated before treatment, usually fell rapidly to normal within 24 hours after treatment had been begun and remained normal during the period of hospitalization. After five days of treatment, fatigability diminished almost completely in four patients and was apparent with moderate activity in four patients. The remaining eight patients responded less rapidly although improvement appeared in six patients after two weeks and in two patients after three weeks. Rounding of

the face, plethora, and fat pads in the supraclavicular and cervicodorsal regions began to diminish by the fifth day in most of the patients. After two weeks five patients lost the appearance characteristic of hormonal overdosage and in seven patients it was noticeably decreased. Only 3 of the 15 patients who continued therapy still had slight rounding of the face without plethora after two months of treatment. Each patient lost from 8 to 24 pounds in weight during the first month of treatment. Excess perspiration of the hands and feet was noted in nine patients and disappeared completely in four patients before they were discharged from the hospital; in the remaining five, it subsided within six weeks. Twelve of the 16 patients stated that they tolerated a cool environment better than they had previously. Serial intraarticular injections of hydrocortisone and nitrogen mustard and intravenous injections of corticotropin and nitrogen mustard were highly effective in rapidly reducing swelling and inflammation of the synovialis and adjacent connective tissue. Joint and tendon swelling with adjacent muscle spasm began to subside by the third day and in most instances was still apparent by the end of the first week of therapy. By the end of the second week most of the swelling had subsided in 13 of 16 patients and was reduced by more than half in three patients. After three weeks only 1 of the 16 patients had joint swelling that had not subsided satisfactorily.

Over-all improvement in most instances was characterized by an irregular and unpredictable course. Of the 15 patients in whom treatment was continued, two had a relapse two and three weeks, respectively, after leaving the hospital and both favorably responded quickly and without major incident to two intravenous injections of 10 units of aqueous corticotropin and 2 mg. of nitrogen mustard while administration of chloroquine phosphate, corticosteroid, and iproniazid was continued. In the remaining 13 patients, minor flares and relapses were frequent but never severe and appeared to be modified or incompletely suppressed. They became less severe and less frequent as each week passed. The one patient for whom treatment had to be discontinued, initially responded slowly but steadily and was apparently doing satisfactorily until six weeks after discharge from the hospital when she developed persistent nausea and anorexia from chloroquine phosphate. Her physician recently reported that she has not been able to continue taking either of the antimalarial agents.

Intraarticular injections were administered to nine patients for from two to three months at two to four week intervals because complete disappearance of joint swelling did not occur or swelling again appeared in one or more joints after activity had been increased. Joint swelling has subsided completely and has not returned in these nine patients.

Dosage of medication was reduced in six patients between the sixth and ninth months after treatment had begun; and in three of these patients the administration of corticosteroid was eventually stopped after one year and the patients have been satisfactorily maintained on an antimalarial agent for one year. Two years after the onset of combined treatment, the disease of four patients remains controlled with 7.5 mg. of prednisone daily in addition to an antimalarial agent and depot corticotropin 10 units weekly. Three patients have been receiving

treatment for nine months and in each the disease remains well controlled with only minor occasional muscle aching or stiffness and no recurrence of joint swelling. Two patients have been treated for less than six months and in each the disease remains satisfactorily controlled up to the present time. Twelve of the 15 patients show none of the clinical features characteristic of hormonal overdosage.

Toxicity reactions. Despite the use of multiple drugs, few toxicity reactions have occurred in our patients. We believe that the incidence of these reactions is low because the dose of each of the agents, with the exception of the antimalarial drugs, has been small.

The *antimalarial agents* caused a significant toxicity reaction in only one of our 16 patients. As noted above, that patient was unable to tolerate chloroquine phosphate or hydroxychloroquine sulfate because of persistent nausea and anorexia, and the combined therapy had to be terminated after six weeks. Two other patients had anorexia and mild nausea which subsided spontaneously after one month of treatment. In one patient receiving chloroquine phosphate a morbilliform dermatitis developed four weeks after therapy had been started; the dermatitis disappeared after administration of that drug was stopped but did not reappear during the subsequent administration of hydroxychloroquine sulfate. Hematologic abnormalities did not occur in any of these patients nor in any of the more than 650 other patients to whom we have given antimalarial agents.[8-11]

Iproniazid caused no toxicity reaction in any of the 16 patients. The drug was initially administered in small dosage. When increased neuromuscular tone (hyperactive deep tendon reflexes) was observed, the dosage was reduced. The dosage of iproniazid ranged from 50 mg. daily to 10 mg. every other day; once the maintenance dosage was established, it could be administered as long as necessary without causing toxicity reactions.

Transient nausea which was rarely associated with vomiting occurred in all patients after they had received *nitrogen mustard* intravenously, but this was easily controlled by the use of promazine hydrochloride.

Although occasional urticarial manifestations thought to be due to an allergic reaction to the intravenous use of *corticotropin* have been previously reported,[9] none of these 16 patients reacted in that manner. Administration of the *corticosteroids* caused no toxicity reactions in these patients.

Discussion:

Theoretical Role of Amine Oxidases

Patients having chronic progressive rheumatoid arthritis with chronic hypercortisonism constitute a therapeutic challenge. In most instances response to therapy heretofore has been disappointing and withdrawal symptoms have prevented rapid reduction in dosage of the corticosteroid. We believe that in

those patients cyclic swings in mood, emotional instability, and inability to concentrate are central nervous system manifestations characteristic of rheumatoid arthritis, appearing in an exaggerated state, and that the mesenchymal reaction is due to hormone "escape." The entire picture is further complicated by hypocorticalism resulting from the oral administration of cortisone or related hormones. Improvement in our patients was characterized by a decrease in both the mesenchymal reaction and the central nervous system manifestations.

Scherbel, Schuchter, and Harrison[3] have reported the effect of chemotherapeutic agents in patients having rheumatoid arthritis. Because of the characteristic response to these drugs, we postulate that certain biochemical alterations are present in rheumatoid arthritis with or without hypercortisonism.

The primary site of chemical or physicochemical action of adrenal steroids remains obscure although the crucial role of the hormones in the maintenance of homeostasis is well established. For the most part the actions of the cortical hormones have been described in terms of the response of other physiologic systems rather than in terms of primary mechanisms of action. It is generally agreed that patients with rheumatoid arthritis do not show quantitative or qualitative evidence of abnormalities of the adrenal steroids although it is possible that abnormalities are present in their intermediary metabolism. West[12] recently reported that in patients having rheumatoid arthritis there was no correlation between disease activity and the output of 24-hour urinary 17-hydroxycorticosteroids. He interpreted this finding to mean that the disease did not constitute a "stress" to the patient and questioned whether this in itself did not constitute a defect of the disease. He did not interpret this to mean that the corticosteroids played no part in the disease manifestations.

Iproniazid is one of the most consistently effective therapeutic agents that influences central nervous system manifestations characteristic of rheumatoid arthritis. Improvement is manifested by elevation in mood, generalized relaxation, disappearance of excessive sweating, and altered vasomotor reactivity. An increase in muscle tone and in muscle strength rapidly becomes apparent. However, constipation and decreased libido accompany the improvement. Because of the cumulative effect of iproniazid, deep tendon reflexes increase and muscle fasciculations appear after a few weeks to a few months of therapy. Swelling, redness, and tenderness, as well as aching and stiffness, of the joints do not subside rapidly; the gradual improvement in joint manifestations early in treatment usually can be related to increased rest and physical therapy. However, after from six to nine months of treatment, diminished disease activity usually is apparent. If toxicity reactions to overdosage of iproniazid occur—manifested by excitability, persistent clonus, and marked hyperactivity of deep reflexes—joint manifestations diminish, but again appear as toxicity subsides.

It has been shown by Zeller and Barsky[13] that iproniazid inhibits the activity of monoamine oxidase. The primary role of this copper-catalyzed enzyme is to inactivate amines, including serotonin, norepinephrine, and epinephrine. Recently, serotonin has been considered to enter into the functions of the autonomic and central nervous systems. Serotonin is believed to be necessary for normal mental processes, and interference with its action in the brain leads to

mental disorders and neurological dysfunction.[14] Brodie and Shore[15] have suggested that serotonin rather than acetylcholine may be the neurohormonal agent for the central parasympathetic system and that norepinephrine may be the chemical transmitter of the central sympathetic system.

If the concept proposed by Brodie and Shore is correct and if the effect of iproniazid which we have observed in patients with rheumatoid arthritis is confirmed, it is possible that the over-all effects in these patients are manifested by alterations in activity of amine oxidases or in metabolic alterations of one or more of the various amines inactivated by amine oxidases.

Although we believe that the biochemical alterations involved in rheumatoid arthritis are more complicated than described here, for the sake of simplicity we base our concept on the unproven view that a major biochemical defect in rheumatoid arthritis may involve amine oxidases or one or more of the various amines inactivated by the oxidases or both. The clinical features characterizing rheumatoid arthritis can be divided into two groups: those resulting from or resembling the effect of increased activity of amine oxidases within the central nervous system; and those resulting from or resembling the effect of decreased activity of amine oxidases within tissues outside the central nervous system, primarily mesenchyme. Increased oxidase activity within the central nervous system, by inactivating serotonin and other amines, could cause the many and varied central nervous system manifestations characteristic of rheumatoid arthritis. Diminished activity of serotonin would result in depressed psychomotor activity, emotional instability, and other mental aberrations characteristic of rheumatoid arthritis. A delay in transmission of nerve impulses would occur across synapses in the central sympathetic and parasympathetic autonomic nervous system, resulting in autonomic imbalance. Delayed transmission of impulses through cholinergic somatic nerves to muscle would account in part for muscle weakness or atrophy and diminished deep reflexes.

Michotte[16] has reported that the excretion of norepinephrine is decreased in patients with rheumatoid arthritis, resulting in an altered excretion ratio of norepinephrine to epinephrine. He also found that an infusion of 0.1 per cent procaine hydrochloride, a potent inhibitor of monoamine oxidase, caused an increase in the excretion of norepinephrine, resulting in a normal ratio of norepinephrine to epinephrine.

The second group of clinical features involve tissues outside the central nervous system, primarily mesenchyme. The reaction characterized by inflammation and proliferation of connective tissue can be explained theoretically by alterations in the oxidases and amines that are the reverse of those previously described within the central nervous system. In the peripheral tissues the amine oxidases would be decreased, causing increased activity of tissue serotonin. We feel that there is at least suggestive evidence that serotonin in the tissues can act as an irritant and produce an inflammatory action and may act as a stimulant of connective tissue and produce fibroblastic proliferation. The various mechanisms of action that have been considered will not be discussed here except to state that we have observed an acute synovial reaction following the local injection of minute amounts of serotonin. These will be reported in

detail elsewhere. Numerous descriptions of fibrotic right-sided valvular heart lesions and fibrous tissue masses surrounding pelvic organs and low-abdominal arteries have been reported in patients with metastatic carcinoid tumors, suggesting a correlation between serotonin and proliferation of fibrous tissue.

The high incidence of relapse in patients having rheumatoid arthritis treated with a corticosteroid, and the central nervous system manifestations following hormonal overdosage indicate that the hormones alone are not capable of adequately suppressing the disease activity. The activity of various neurohormonal agents appears to be progressively diminished during corticosteroid therapy, further indicating that the adrenocortical hormones do not prevent increased oxidase activity or diminished neurohormonal amine activity in the central nervous system.

Significant improvement appeared in our patients coincident with apparently increased neurohormonal activity which resulted from the administration of the amine-oxidase inhibitor iproniazid. This improvement allowed a reduction in the dosage of corticosteroid, further emphasizing the relationship between the adrenal corticosteroids and the neurohormonal agents.

The effect of the antimalarial agents (chloroquine phosphate and hydroxychloroquine sulfate) in patients with rheumatoid arthritis has not been established, but it is our opinion that their primary action is on tissues outside the central nervous system, and that these drugs should be used for long-term maintenance therapy. We have discussed the action of nitrogen mustard previously.[8,9] It is of primary importance in producing rapid suppression of joint inflammation after which time disease activity is more easily controlled.

In the past, numerous nonspecific therapeutic agents have been recommended for treatment of rheumatoid arthritis but none has been found completely satisfactory. It is possible that many of these agents temporarily influenced certain amines or amine oxidases resulting in transient suppression of disease activity. We believe that further work is necessary to clarify the role of the amine oxidases and the various amines in rheumatoid arthritis and many other diseases.

Summary

The findings and results of treatment in 16 patients having rheumatoid arthritis complicated by hypercortisonism indicate that therapeutic agents other than corticosteroids have a significant effect in such patients. Improvement in each of these patients began a few days after initiation of combined-drug therapy although the dosage of corticosteroid had been rapidly reduced.

We believe that the central nervous system manifestations in patients with rheumatoid arthritis are the result of certain biochemical alterations that are exaggerated in patients having rheumatoid arthritis with hypercortisonism.

We have divided the clinical features characterizing rheumatoid arthritis into two groups: those manifest in the central nervous system and those in tissues outside this system. It has been theorized that the central nervous system manifestations result from, or resemble the effect of, increased activity of amine

oxidases or decreased activity of the neurohormonal amines or a combination of these actions. Outside the central nervous system, manifestations appear primarily in the mesenchymal tissues, and result from, or resemble the effect of, decreased activity of amine oxidases or increased peripheral activity of certain amines or both.

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