I. INTRAVENOUS ADMINISTRATION OF NITROGEN MUSTARD ALONE AND WITH CORTICOTROPIN FOR RHEUMATOID ARTHRITIS

ARTHUR L. SCHERBEL, M.D.
Department of Rheumatic Disease

NITROGEN MUSTARD has been used for a variety of clinical diseases that manifest tissue and vascular reactivity, such as rheumatoid arthritis, rheumatic fever, systemic lupus erythematosus, periarteritis nodosa, dermatomyositis, and acute and subacute glomerulonephritis.[1-9] The action of nitrogen mustard (hereinafter termed *HN*$_2$) is inhibitory on accelerated growth of normal as well as of neoplastic cells.[10] Chemically, HN_2 is methyl-bis-(β-chloroethyl)-amine hydrochloride, an alkylating agent that replaces hydrogen with alkyl groups in organic molecules; it contains two reactive ethyleneimine groups[10] that inhibit actively growing and proliferating cells.

The basic mechanism of the inhibition is not understood; however, it has been postulated[11] that inhibition of enzymatic activity might account for its action, although to inhibit most enzymatic systems in vitro, a far higher concentration of HN_2 is needed than is possible to achieve in vivo. A more likely theory[12] takes cognizance of the high degree of reactivity of HN_2 with specific nucleoproteins that are essential to cellular reproduction. Viruses that are rich in nucleoproteins are highly susceptible to irreversible inactivation by HN_2, a susceptibility that appears to be directly related to viral nucleic acids. Viruses that contain largely or exclusively desoxyribonucleic acid are more readily inactivated by HN_2 than are those that contain predominantly ribonucleic acid. This selectivity of action suggests that HN_2 may act directly on desoxyribonucleic acid and, by interfering with the anabolism of this important nuclear constituent, render the cells nonproliferative.[11]

After intravenous administration of HN_2, development of the Shwartzman phenomenon is suppressed.[13,14] Becker[15] postulated that the mechanism of suppression is exerted through the reticuloendothelial system, primarily the vascular endothelium: these endothelial cells being rendered anergic are unable to react in a way that would be self-destructive.

Clinically, when the usual total dose of 0.4 mg. HN_2 per kilogram of body weight is administered intravenously over a period of four days, the only normal tissues that may be significantly suppressed are lymphoid tissue and bone marrow. McCarthy[16] was of the opinion that the combined use of corticotropin (hereinafter termed *ACTH*) and HN_2 reduced the suppressive effect of HN_2 on bone marrow, and alleviated nausea and vomiting. His patients with malignant lesions were given three or more total doses of 0.5 mg. HN_2 per kilogram of body weight within one year. Rollins and Shaw[17] did not confirm McCarthy's observation, but in their patients lymphopenia and leukopenia were transient and were not considered clinically significant.

We investigated the effects on rheumatoid arthritis of intravenously administered HN_2 during 1950 and 1951, and the combined administration of HN_2 with ACTH during 1951 through 1955.

Nitrogen Mustard

Material and methods. The series comprised 17 patients who had active rheumatoid arthritis for from 1 to 13 years. Four patients had grade 1 disease, four had grade 2, six had grade 3, and three had grade 4 disease.* In all patients there was involvement of at least two or more joints, manifested by persistent joint swelling and pain on motion. Activity was restricted severely in 4, moderately in 10, and slightly in 3 patients.

All patients were hospitalized throughout the course of treatment. HN_2, 1 mg. per milliliter in normal saline solution, was administered intravenously. Amobarbital sodium**, 0.20 gm., was given intramuscularly at the same time to alleviate nausea and vomiting. Ten patients received 0.1 mg. per kilogram of body weight on alternate days, and seven patients received 0.05 mg. per kilogram of body weight daily, for a total dosage of 0.4 mg. per kilogram of body weight. Each patient received a total of from 15 to 25 mg. HN_2.

Laboratory and clinical findings. During treatment it was noted that white blood cell counts that had been elevated usually dropped to normal; normal total white blood cell counts usually did not change significantly. The differential blood count in most instances revealed a slight-to-moderate decrease in the percentage of circulating lymphocytes. Frequently the hemoglobin content increased within from 3 to 10 days after the administration of HN_2. The apparent rise in hemoglobin content was accompanied by a rapid decrease in the serum polysaccharide-protein ratio[19-21] and a fall in the erythrocyte sedimentation rate (Rourke-Ernstene method[22]). There were also a drop in serum alpha-2 globulin and a rapid reciprocal rise in albumin determined by electrophoresis.[23] Mild weakness usually occurred four to seven days after the administration of HN_2 and disappeared two to four weeks later.

One and three months after the termination of intravenous therapy, studies were made of 5 of the 17 patients for evidence of stimulation of adrenocortical function. No significant changes were demonstrated in the urinary excretion of 17-ketosteroids, in the uric acid-creatinine ratio, or in the percentage decrease of circulating eosinophils.

In all patients, redness, warmth, swelling, and tenderness of the joints disappeared within two to seven days after the onset of treatment. Temperatures that had been elevated dropped to normal within 24 to 48 hours. Aching and stiffness disappeared completely in eight patients, were moderately relieved in five, and persisted in four patients. Within six months after the administration

Grades of disease [18] are described in the footnote of Table 1.

***Amytal sodium, Eli Lilly & Co.*

Table 1.—*Data for 17 patients given HN_2 intravenously for rheumatoid arthritis*

Number of patients	Grade*	Class**				Response† to treatment after															
						2 weeks				2 months				4 months				6 months			
		1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
		Number of patients																			
4	1	0	2	2	0	3	1	0	0	2	2	0	0	2	1	1	0	1	2	1	0
4	2	0	1	3	0	3	1	0	0	3	1	0	0	1	1	2	0	1	1	2	0
6	3	0	0	3	3	2	2	2	0	0	4	2	0	0	3	2	1	0	0	4	2
3	4	0	0	2	1	0	1	2	0	0	0	2	1	0	0	2	1	0	0	2	1

Adapted in part from A.R.A. classification.[18]

**Grade:* *1—joint swelling, no joint destruction; 2—minimal cartilage or bone destruction; 3—subluxation; 4—ankylosis.*

***Class:* *1—asymptomatic, full activity; 2—minor symptoms, full activity; 3—moderate symptoms, light activity; 4—moderate-to-severe symptoms, light-to-no activity.*

†*Response:* *1—(excellent) asymptomatic; 2—(good) minor aches and pains; 3—(fair) slight persistence of joint tenderness and swelling; 4—(poor) moderate persistence or no relief of joint pain and swelling.*

of HN_2, 15 of the 17 patients had recurrence of symptoms in varying degrees of severity. Only two patients have remained asymptomatic for more than five years. Data for the 17 patients are summarized in Table 1.

Contraindications. Contraindications to the use of this amount of HN_2 in rheumatoid arthritis are infrequent. It is not recommended in advanced disease where there is little or no inflammation. If superficial veins are small or permeable, the drug is not administered. If an associated blood dyscrasia is present, HN_2 should be used with caution because of increased sensitivity of the hematopoietic system.

Comment. HN_2 is a powerful anti-inflammatory agent when administered intravenously to patients with acute or subacute rheumatoid arthritis. Because the disease activity is only temporarily suppressed, the value of the drug is limited.

Nitrogen Mustard Combined with Corticotropin

ACTH has been used successfully to suppress the inflammatory activity of rheumatoid arthritis. The metabolic effects that occur immediately after administration of ACTH result from the release of adrenocortical steroids and, in general, are similar to those that occur after administration of cortisone. Although the exact nature of the secretion of the adrenal cortex is unknown, on the basis of current evidence suppression of inflammation is believed to result from the release of hydrocortisone by ACTH. Aqueous preparations are rapidly absorbed and metabolized, necessitating multiple daily injections, but mixtures with gelatins and zinc are more slowly absorbed and consequently require fewer injections. Aqueous ACTH, 20 to 25 units diluted in 5 per cent dextrose solution, administered intravenously may cause a dramatically rapid suppression of symptoms related to disease activity, but this procedure has no apparent place in the continuing treatment of rheumatoid arthritis.[24] The dosage of intravenously administered ACTH that maximally stimulates the adrenal gland is considered to be 20 to 25 units administered continuously over a period of eight hours.[25] This amount of ACTH given intravenously daily for one week or more is likely to result in a state of acute hypercorticalism.

Ten patients were given 20 units and 10 patients were given 10 units of aqueous ACTH intravenously in 1 liter of 5 per cent dextrose in water daily during a six-hour period for 10 days. Seven of the 10 patients receiving 20 units showed early signs of acute hypercorticalism between the sixth and eighth days of treatment, and 1 of the 10 patients receiving 10 units of ACTH showed similar characteristics after the tenth day. Joint manifestations and general symptoms subsided rapidly in all patients receiving 20 units and in six patients receiving 10 units of ACTH. Relapse was rapid in all instances, usually occurring within from one to five days after ACTH had been discontinued.

Inasmuch as HN_2 or ACTH when administered intravenously causes rapid suppression of inflammation in rheumatoid arthritis, we decided to observe the effect of these agents administered simultaneously, but each in smaller doses

than those used when it was administered alone, in order to reduce the possibility of toxic reactions or side effects from either drug.

Material and methods. Two hundred sixty-three patients who have received combined ACTH and HN_2 infusions since June 1951 were observed for four or more years. In this group were 221 patients who had various stages of rheumatoid arthritis, 18 patients who had both rheumatoid arthritis and a positive test for lupus erythematosus, 12 patients who had psoriasis and rheumatoid arthritis, 8 patients who had palindromic rheumatism, and 4 patients who were more than 16 years of age and who had active Still's disease. Table 2 summarizes the data of the study.

The total dosage of HN_2 for a course (five to seven days) was 0.2 mg. per kilogram, or 2 to 3 mg. daily. The usual dosage of ACTH was 10 units diluted in 500 ml. 5 per cent dextrose in water and administered intravenously over a period of four hours. One-half hour after the intravenous administration of ACTH had been started, HN_2 was given intravenously directly through the rubber tubing used for the ACTH. To alleviate nausea and vomiting, 50 mg. of promazine hydrochloride* was given orally one hour before intravenous treatment was begun.

Results. The effects of these drugs were evaluated two weeks after injection (Table 2), inasmuch as the action desired was quick suppression of systemic symptoms and joint manifestations. In 88 per cent of 263 patients there was rapid and complete or almost complete relief of joint manifestations, toxicity, and fever. Disease activity, as reflected by an increase in the erythrocyte sedimentation rate, serum alpha-2 globulin, and serum polysaccharide-protein ratio, lessened but did not subside completely. Frequently in acute or subacute rheumatoid arthritis, lupus erythematosus, and occasionally in palindromic rheumatism, the response to these therapeutic agents was dramatic and appeared within from 24 to 48 hours. The most difficult form of arthritis to suppress was rheumatoid arthritis associated with psoriasis. In approximately 40 per cent of the 221 patients with rheumatoid arthritis the disease became temporarily migratory during induction therapy. Often these migratory joint manifestations appeared after having been absent for a number of months or years. Fleeting, erythematous, maculopapular dermatoses appeared in approximately 20 per cent of these 221 patients. The lesions were most prominent over the face, chest, arms, and legs. The temperature was elevated above 100 degrees F. in 71 per cent of the 263 patients and fell rapidly to normal in 88 per cent of this group within seven days after therapy was begun. In the majority of cases other medication, to be described, maintained the suppressed state satisfactorily; but in 11 per cent or 28 of the 263 patients a second course of combined ACTH and HN_2 was given within one year.

Toxic reactions were limited to nausea (occurring in approximately 40 per cent of the patients), vomiting (occurring in approximately 10 per cent), and generalized urticaria, believed to be due to ACTH (occurring in less than 2 per cent).

**Sparine hydrochloride, Wyeth Laboratories.*

Table 2. — *Data for 263 patients given ACTH and HN_2 intravenously for rheumatoid arthritis*

Number of patients	Diagnosis	Grade*				Class**				Response† after 2 weeks of therapy			
		1	2	3	4	1	2	3	4	1	2	3	4
221	Rheumatoid arthritis	37	60	83	41	0	71	102	48	161	43	11	6
18	Rheumatoid arthritis with lupus erythematosus	6	12	0	0	0	13	5	0	15	2	1	0
12	Psoriasis and rheumatoid arthritis	3	5	2	2	0	3	7	2	0	5	5	2
8	Palindromic rheumatism	8	0	0	0	0	2	4	2	3	2	2	1
4	Still's disease	0	1	2	1	0	0	2	2	1	0	1	2
Total 263										180	52	20	11

Adapted in part from A.R.A. classification.[18]

**Grade:* *1—joint swelling, no joint destruction; 2—minimal cartilage or bone destruction; 3—subluxation; 4—ankylosis.*

***Class:* *1—asymptomatic, full activity; 2—minor symptoms, full activity; 3—moderate symptoms, light activity; 4—moderate-to-severe symptoms, light-to-no activity.*

†*Response: 1—(excellent) asymptomatic; 2—(good) minor aches and pains; 3—(fair) slight persistence of joint tenderness and swelling; 4—(poor) moderate persistence or no relief of joint pain and swelling.*

Contraindications. Contraindications to the use of combined HN_2 and ACTH are similar to those discussed for HN_2 alone. In addition, the combination should not be used in a patient who has severe diabetes, infection, psychosis, advanced hypertension, or is allergic to ACTH.

Discussion

The combination of HN_2 and ACTH intravenously administered in a dose that for each drug was less than the usual dose when the drug is administered by itself, produced an effect that appeared to be synergistic, and resulted in an unusually low incidence of toxic reactions in a large number of patients with rheumatoid arthritis. The potentiating effect from the use of both agents occurred consistently and probably resulted from multiple-drug action rather than from an increase in one single pharmacologic action common to both agents.

In patients with various diseases, including carcinoma, lymphoma, arteritis or rheumatoid arthritis, treated with HN_2 or with combined ACTH and HN_2, it frequently was observed that the incidence of bone marrow depression depended not only on the dosage of HN_2 but also on the nature of the disease being treated. The hematopoietic system in patients with lymphoma or blood dyscrasia usually was more sensitive to HN_2 than that in patients receiving HN_2 for other diseases. Investigators [16,17] have shown that the effect on a normal hematopoietic system when HN_2 is used to suppress certain types of carcinoma is not clinically significant. We have noted a similar effect in patients with so-called collagen disorders.[9] Usually the effect of a small dose of HN_2 will be more noticeable on the inflammatory reaction involving the connective tissues than it will be on that involving the hematopoietic system. However, in patients with systemic lupus erythematosus, both the connective tissue and the hematopoietic system are sensitive to the effect of HN_2. In these patients, symptoms usually are suppressed by a total dose of 10 mg. of HN_2 in 2-mg. doses over a period of five days, combined with ACTH 10 units daily in 1 liter of 5 per cent dextrose in water. If symptoms are not adequately suppressed after one or two weeks, administration of one half of this amount of HN_2 and ACTH is repeated.

Combined ACTH and HN_2 has been particularly effective in acute and subacute rheumatoid arthritis, in acute and subacute systemic and disseminated lupus erythematosus, in palindromic rheumatism, and in hypercortisonism resulting from excessive use of corticosteroids. There was no clinical evidence of ill effects in those patients in whom it was used more than once within one year as treatment for exacerbations that were difficult to control. The indications for the administration of combined ACTH and HN_2 and the manner in which these drugs are utilized in the combined-drug program are discussed in part V.