III. THE EFFECT OF ISONIAZID AND OF IPRONIAZID IN PATIENTS WITH RHEUMATOID ARTHRITIS

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DEPRESSION, exhaustion, anxiety, conversion, and other emotional reactions characteristically accompany chronic debilitating diseases and may limit the patients' recovery from their primary disease or even prevent satisfactory improvement. To many of these patients the desirable effects that result from the administration of the hydrazides, especially iproniazid, include a generalized sense of well-being, increase in appetite, gain in weight, and decrease in fatigability. However, constipation, lightheadedness, postural hypotension, dysuria, loss of libido, muscular irritability, hyperactivity of deep reflexes, paresthesia, nervousness, excessive dreaming, and insomnia may also occur.[28] At times, an increase in the frequency and the severity of convulsions occurs in epileptics, and psychotic episodes develop in predisposed patients.[29] Discontinuation of the hydrazides after prolonged administration is at times associated with irritability, restlessness, excessive dreaming, headache, vertigo, and nausea. This "withdrawal syndrome" is observed more frequently after discontinuation of iproniazid than after isoniazid therapy. It usually appears within 24 to 48 hours after cessation of therapy and persists with gradual regression for approximately 10 to 14 days. Occasionally, vitamin-B deficiency syndromes occur, suggesting that under certain conditions these drugs may compete in the body with nicotinic acid.[30] Today, most authorities believe that isoniazid is a safe drug for long-term usage but that iproniazid, in the dosage of 300 mg. daily used for the treatment of tuberculosis, too frequently produces toxic reactions. The mechanism of the action responsible for the effects of the hydrazides is not known, but it probably is related to an alteration in enzyme systems that affect certain components of the autonomic nervous system.[31]

In June 1952 we began to investigate the effect of the hydrazides on subjective and objective manifestations in patients with rheumatoid arthritis. It is widely known that there often is a lack of correlation between the patient's symptoms and the degree of disease activity as determined objectively. Many patients with active rheumatoid arthritis display emotional immaturity, depression, hostility, and dependency; the degrees of disturbance vary among the patients. Anorexia associated with loss in weight may be a serious problem, and fatigability may limit even a modest amount of activity. When these symptoms predominate, a low pain threshold usually is present. In evaluating the effect of isoniazid and iproniazid in a group of patients with active rheumatoid arthritis, we considered both the emotional disturbance and the objective disease manifestations.

Methods

Seventy-four adults having active rheumatoid arthritis of varying severity of from 1 to 12 years' duration were treated with isoniazid or iproniazid and were followed for two to five years. Forty-four patients (20 of whom were hospitalized) initially received isoniazid orally, 100 mg. three times daily; and 30 (21 of whom were hospitalized) initially received iproniazid orally, 50 mg. three times daily for from one to three months, after which time the dosage was gradually reduced to 25 mg. daily or every other day. Each of the 74 patients also received from 10 to 25 mg. of pyridoxine (vitamin B_6)daily in order to prevent peripheral neuritis.[30]

Forty-one patients were hospitalized initially for treatment, and during hospitalization, bed rest, physiotherapy, and aspirin from 4 to 6 gm. daily, supplemented the administration of the hydrazide. The other 33 patients were outpatients during the entire course of treatment.

All patients were seen at one- or two-month intervals during a two-year period, and more than half of the patients still are under observation and return for examination at three-month intervals. Complete blood counts and routine urinalyses were obtained at weekly intervals for the first month and at monthly intervals for one year, after which time they were obtained at three-month intervals. Sedimentation rates, serum polysaccharide-protein ratios, and electrophoretic patterns of plasma proteins were determined at monthly intervals for 12 to 18 months. Bromsulphalein excretion and serum bilirubin values were determined at two-month intervals. Urea clearance was tested at three-month intervals.

After one year of treatment with the hydrazides, those patients who had not improved satisfactorily then were given a combination of a hydrazide and a corticosteroid in dosages that by themselves were insufficient to suppress disease activity.

Results

Alterations in affect. In patients receiving isoniazid, improvement in symptoms was slow and undramatic; whereas, in those receiving iproniazid, significant improvement occurred within 3 to 10 days.

In patients receiving iproniazid the first response was a gradual increase in their generalized sense of well-being. Patients who formerly were depressed began to smile faintly, to show interest in their immediate surroundings, and presently to note an improvement in appetite. Many patients commented that they were beginning to feel as they had felt before they developed rheumatoid arthritis. Although joint pain and swelling still were present, these joint manifestations appeared to be tolerated better and were less cause for concern than they had been; most of the hospitalized patients began to use their joints more and noted a generalized increase in strength. However, as these subjective

changes occurred, there was little or no objective change in the involved joints that could not be explained on the basis of bed rest or of physiotherapy.

Objective response. A gain in weight was the most consistent objective response to hydrazide therapy; it occurred in 10 of the 44 patients receiving isoniazid and in 26 of the 30 patients receiving iproniazid. Increases ranged from 3 to 24 pounds during the first month of treatment and then usually tapered sharply; however, eight patients continued to gain weight and eventually their obesity became a problem.

Before treatment the temperature was elevated above 100 degrees F. in 30 patients (11 subsequently received isoniazid and 19 iproniazid) who were hospitalized. In 21 of these patients (6 receiving isoniazid and 15 receiving iproniazid) it returned to normal within three weeks.

Objective improvement in the joint manifestations was not consistent in either group. Only 10 of the 44 patients who received isoniazid had significant relief of joint manifestations after six months, and 20 of the remaining 34 were given supplemental doses of cortisone after one year because of an unsatisfactory response to treatment. During the first three weeks joint swelling and tenderness on pressure subsided in 9 of 21 hospitalized patients receiving iproniazid. In seven additional patients receiving iproniazid there was partial relief of inflammation after five weeks. Joint manifestations had subsided completely in 20 of 30 patients receiving iproniazid after six months and in an additional three patients after one year.

Laboratory findings. Isoniazid caused no significant change in the hemoglobin content, red blood cell count, white blood cell count, or differential cell count. Urinalyses revealed no abnormalities. Erythrocyte sedimentation rates became normal in 2 patients, and were decreased 50 per cent or more in 18 patients. The serum polysaccharide-protein ratios decreased in 26 of the 44 patients.

In 16 of the 30 patients receiving iproniazid, there was a decrease of 1 to 2 gm. in hemoglobin content during the first month of therapy. In 10 of these patients the hemoglobin content increased to the original value or exceeded it during the subsequent six months. No changes were noted in peripheral white blood cell counts or in urinalyses. The sedimentation rates fell to normal within six months in eight patients, and were decreased 50 per cent or more in five patients. The serum polysaccharide-protein ratios decreased in 22 of the 30 patients.

Side effects and toxicity reactions. It soon became obvious that the desirable subjective improvement resulting from the hydrazides was intimately associated with the effects on the central, autonomic, and peripheral nervous systems. These included constipation, loss of libido, lightheadedness, postural hypotension, blurring of vision, hyperactivity of deep tendon reflexes, and clonus. Symptoms were most prevalent when iproniazid had been given in doses of 150 mg. daily for two or three months. Palms that had been cold and moist became warm and dry, and within a few months palmar erythema appeared in 20 of the 44 patients receiving isoniazid and in 16 of the 30 patients receiving

iproniazid. Deep tendon reflexes became hyperactive between the second and third month of therapy in 20 patients receiving 300 mg. or more of isoniazid, and in all patients receiving 75 mg. or more of iproniazid. The hyperactivity was more pronounced in those patients receiving iproniazid, and usually was accompanied by mild muscular irritability manifested by coarse fascicular muscular contractions and spasms that usually were noted when the patient was in a relaxed state, especially while in bed before going to sleep. Through experience it was learned that hyperactivity was an indication that the drug immediately should be reduced in dosage or should be temporarily discontinued.

Five patients receiving iproniazid, 150 mg. daily for three months, developed clonus; three had mild clonus and two had severe generalized clonus with marked postural hypotension and hyperexcitability which persisted for two or three days after administration of the drug had been stopped. In the two patients having severe generalized clonus all joint manifestations disappeared, but they reappeared when the hyperactive state had subsided a few weeks later. In all five patients while clonus was present, plasma cholinesterase (pseudocholinesterase) levels were greatly decreased, but increased as signs of toxicity disappeared. It is interesting that cholinesterase levels also are decreased during pregnancy[32] when rheumatoid arthritis frequently improves. Bromsulphalein excretion was temporarily impaired in three of these patients: retention ranged from 20 to 27 per cent for two or three months. Serum bilirubin values remained normal. After the toxic manifestations had disappeared, administration of iproniazid, 25 mg. on alternate days, was resumed without ill effect in each of the five patients. Withdrawal symptoms manifested by headache, irritability, and excessive dreaming occurred in three of these five patients after administration of iproniazid was abruptly discontinued. These symptoms subsided after from three to six days.

Uncommon side effects. Four patients developed a maculopapular skin eruption within one month after beginning isoniazid therapy. In all four the dermatitis disappeared when the drug was stopped and iproniazid was substituted. One 37-year-old woman after two months of isoniazid therapy developed rather severe edema of the entire body. No cause was found, but the edema disappeared when the drug was stopped. Two patients developed jaundice, believed to be due to toxic hepatitis; both had proved mild cirrhosis before isoniazid was administered. One patient had biliary cirrhosis at the time a cholecystectomy was performed before isoniazid was started. The other patient had a long history of excessive drinking of alcoholic beverages when he developed rheumatoid arthritis; at the time that the jaundice occurred, a liver biopsy confirmed the diagnosis of portal cirrhosis. Both patients recovered uneventfully from the toxic hepatitis.

The incidence of peripheral neuropathy in patients who received either isoniazid or iproniazid alone or in combination with other drugs was 0.7 per cent. In each instance administration of the drug was stopped and 30 mg. of pyridoxine daily was administered; hyperesthesias and paresthesias disappeared within approximately four weeks.

Effect of a Combination of a Hydrazide and a Corticosteroid

The next step in our study led to supplementing the hydrazides with corticosteroids in dosages that in themselves were insufficient to suppress rheumatoid activity satisfactorily.

Methods. One hundred and one patients having active rheumatoid arthritis of varying severity and duration received one of the hydrazides and one of the corticosteroids. The patients were grouped as follows (Table 1): *group 1*—47 patients, isoniazid and cortisone; *group 2*—20 patients, isoniazid and prednisone; *group 3*—20 patients, iproniazid and cortisone; *group 4*—14 patients, iproniazid and prednisone. Twenty of the 47 patients in group 1, initially received isoniazid alone for one year, during which time response to therapy was considered unsatisfactory. All patients were examined at one- or two-month intervals for one year or more.

Results. All patients with relatively early or nonprogressive disease (grade 1) responded satisfactorily to therapy utilizing any combination of a hydrazide and a corticosteroid (Table 1). However, patients with more advanced disease (grades 2, 3, 4) did not respond so completely or so consistently to the combination of isoniazid and cortisone in the doses used, as those patients who received isoniazid and prednisone, iproniazid and cortisone, or iproniazid and prednisone. Of the 20 patients with grade 2 disease receiving isoniazid and cortisone, only 7 became asymptomatic, as compared to 6 of the 7 patients receiving isoniazid and prednisone. All patients with grade 2 rheumatoid arthritis receiving iproniazid and either cortisone or prednisone became asymptomatic within one year after starting medication. As a group, the 20 patients with grades 3 and 4 rheumatoid arthritis who were receiving isoniazid and cortisone responded unsatisfactorily, inasmuch as only 1 patient became asymptomatic and 14 had a poor response to therapy. Of the 15 patients having grades 3 or 4 rheumatoid arthritis who were receiving iproniazid and either cortisone or prednisone, 5 became asymptomatic while 4 did not improve significantly during the same period of time. These findings suggest that the corticosteroid was the primary drug responsible for the relief of joint manifestations and that prednisone was more effective than cortisone. However, the combination of iproniazid and cortisone appeared to be as effective in relieving joint manifestations as any of the other combinations of a hydrazide and a corticosteroid.

The majority of patients receiving any combination of these drugs gained weight and developed moon facies, plethora, and supraclavicular fat pads, despite the relatively small doses of corticosteroid that were used. Approximately one third of the younger women developed menstrual irregularities after six months of therapy: menses occurred more frequently, and occasionally there was menorrhagia that ceased when the medication was discontinued.

Contraindications. The hydrazides appear to be safe to use in the dosages recommended. However, they are contraindicated in patients having hepatic disease, severe anxiety states, epilepsy, and alcoholism.

Table 1.—*Results of combined hydrazide-corticosteroid therapy for rheumatoid arthritis in 101 patients*

Group no.	No. of patients	Grade*	Class** 1	2	3	4	Duration of disease in years	Drug combination	Response† after 2 years of treatment: Good	Fair	Poor
			No. of patients						No. of patients		
1	7	1	1	3	3	0	1 to 3	Isoniazid, 100 mg. t.i.d.	6	1	0
	20	2	0	10	8	2	1 to 7	Cortisone, 12.5 mg. t.i.d.	7	10	3
	14	3	0	4	8	2	1 to 12		1	4	9
	6	4	0	2	3	1	1 to 16		0	1	5
Total	47		1	19	22	5			14(30%)	16	17
2	4	1	0	3	1	0	1 to 2	Isoniazid, 100 mg. t.i.d.	4	0	0
	7	2	0	2	3	2	1 to 8	Prednisone, 1.0 to 2.5 mg. t.i.d.	6	1	0
	6	3	0	1	4	1	2 to 6		2	2	2
	3	4	1	0	1	1	3 to 10		0	1	2
Total	20		1	6	9	4			12(60%)	4	4
3	5	1	0	2	3	0	1 to 2	Iproniazid, 10 to 25 mg. daily	5	0	0
	6	2	0	2	4	0	1 to 6	Cortisone, 12.5 mg. t.i.d.	6	0	0
	4	3	0	2	2	0	3 to 7		3	1	0
	5	4	0	2	0	3	3 to 10		1	2	2
Total	20		0	8	9	3			15(75%)	3	2
4	4	1	0	2	2	0	1 to 3	Iproniazid, 10 to 25 mg. daily	4	0	0
	4	2	0	2	2	0	1 to 12		4	0	0
	4	3	1	1	1	1	1 to 6	Prednisone, 1.0 to 2.5 mg. t.i.d.	1	2	1
	2	4	0	1	1	0	4 to 8		0	1	1
Total	14		1	6	6	1			9(64%)	3	2
Total	101		3	39	46	13			50(50%)	26	25

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:* *Good—no symptoms, full activity; Fair—mild-to-moderate symptoms, full activity; Poor—moderate-to-severe symptoms, limited activity.*

Comment

It was concluded from this study that the hydrazides had little effect on objective joint manifestations. However, improvement of affect occurred when there was depressed psychomotor activity, leading us to believe that the treatment may cause midbrain stimulation which, if carefully controlled, is desirable in these patients. Iproniazid was more effective than isoniazid and we found it to be a safe drug for long-term use when properly administered. The dosage of iproniazid ranged from 50 to 150 mg. daily for the first week and then was gradually reduced at weekly intervals over a period of two or three weeks. The maintenance dose was determined by administering a sufficient amount of iproniazid to elevate mood and yet not result in marked hyperactivity of the deep reflexes. The potentially cumulative action of iproniazid always was considered when dosage increases were necessary for short periods of time. When the deep reflexes reacted briskly without clonus, the dosage of iproniazid was further reduced to and maintained at 10 to 15 mg. daily. This small dosage of iproniazid has been sufficient to maintain the desirable mental stimulation that is initially produced by a larger dosage. When the dosage of iproniazid was individualized as described, it could be used for prolonged therapy without the occurrence of toxic reactions; withdrawal symptoms did not occur when the drug was stopped.

The favorable effects of the hydrazides, especially iproniazid, on subjective manifestations in patients with rheumatoid arthritis were the most interesting and perhaps the most significant findings of this study. The mechanism of action is not known, but it probably is related to alteration of enzyme systems. We believe that multiple alterations in enzyme systems, rather than inhibition of monoamine oxidase by itself, are responsible for the numerous effects observed in various connective tissue diseases. We have observed inhibition of plasma cholinesterase in patients who had toxic reactions due to overdosage of hydrazides. When clinical signs of toxicity were apparent, liver function was temporarily depressed, as manifested by delayed excretion of Bromsulphalein. It was not determined from our studies whether the decrease in plasma cholinesterase was due to a specific action of the hydrazide or was a secondary manifestation related to temporary depression of liver function. In addition, palmar erythema usually appeared three to six months after the hydrazide had been started. It is possible that there was impaired inactivation of estrogen by the liver. Inhibition of liver function has been observed also by Wiesel and his group,[33] who reported a delay in hepatic inactivation of cortisone and related compounds. However, they believe that the therapeutic activity of cortisone seems to increase without at the same time producing the undesirable side reactions noted with doses of cortisone large enough in themselves to produce an equal degree of anti-inflammatory activity. In our studies we were unable to confirm this observation and we believe that the toxic side effects of cortisone increased in proportion to the increased therapeutic activity obtained with a relatively small dose of cortisone. No advantage was noted in using the combination of isoniazid and cortisone to obtain this effect since the advent of the newer more powerful corticosteroids.

We also have observed a direct stimulating action on the healing of small ischemic ulcers frequently seen at the tips of the fingers and over the dorsum of the interphalangeal joints in patients with scleroderma and systemic lupus erythematosus, especially when the drug was applied locally in the form of a 3 to 5 per cent iproniazid ointment in a lanolin or petrolatum base.

Conclusion

In patients with rheumatoid arthritis and certain other connective tissue diseases, the hydrazides appear to have multiple unrelated effects that probably result from alterations in certain enzyme systems. Inhibition of monoamine oxidase and cholinesterase has been observed. The utilization of pyridoxine is increased; this vitamin is essential in the enzyme systems that decarboxylate many amino acids, and influences the metabolism of tryptophane. Clinically the hydrazides exert a stimulating effect on the central and autonomic nervous systems, and occasionally may produce a peripheral neuropathy. They have a depressing effect on liver function, and a local stimulating action on the healing of tissues.