LONG TERM TREATMENT OF RHEUMATOID ARTHRITIS WITH PARA-AMINOBENZOIC ACID AND CORTISONE ACETATE*

By Leon L. Wiesel, M.D.
ASSISTANT ATTENDING PHYSICIAN

AND

A. Sidney Barritt, M.D.
ASSOCIATE ATTENDING PHYSICIAN
BROOKLYN, NEW YORK

(From the Department of Medicine and the Arthritis Clinic of The Brooklyn Hospital)

In previous publications[14,15], we have reported on the synergistic action of para-aminobenzoic acid and cortisone acetate in the treatment of rheumatoid arthritis when the para-aminobenzoic acid is administered orally and the cortisone acetate given intramuscularly. These findings have been confirmed by others[6,10,18]. Our present report concerns itself with the combined oral administration of cortisone acetate and the sodium or potassium salt of para-aminobenzoic acid** in patients with rheumatoid arthritis who have been treated for one year or more.

Method and Materials. The patients reported here are all well substantiated cases of rheumatoid arthritis from the arthritis clinic of The Brooklyn Hospital and from the private practice of one of us (L.L.W.). For purposes of comparison the majority of these patients were first placed on the cortisone regime originally recommended by Hench *et al*[4] for a period of one to two weeks and then the dose of cortisone acetate was reduced to 37.5 mg. given orally in 3 divided doses of 12.5 mg. each spaced equally through the waking portion of the day. On this dose of cortisone acetate prompt relapse occurred in all our patients within a matter of days. As soon as relapse became manifest 30 cc. of a 10% solution of sodium or potassium para-aminobenzoate in water was administered exactly one hour prior to each dose of cortisone acetate. In those patients whose response appeared to be too slow or inadequate the quantity of sodium or potassium para-aminobenzoate solution was increased to 45 cc. of 10% solution per dose. At intervals control periods were instituted by withdrawing the para-aminobenzoic acid until the signs and symptoms of rheumatoid arthritis increased in severity. Similarly cortisone acetate was withdrawn while para-aminobenzoic acid administration was continued.

Each patient was seen and examined by one of us at intervals of one to two weeks and careful record made of the subjective response, objective manifestations of rheumatoid activity and of evidence of hypercorticoidism and of reactions to para-aminobenzoic acid. Our patients were classified according to the standards of the American Rheumatism Association[13] and by a simple method employed in our clinic in which activity of the rheumatoid process is graded one to 4 plus and response to therapy is estimated on a percentage basis giving equal weight to the patients subjective complaints and to objective evidence of rheumatoid activity. This additional method of evaluation of therapeutic response has in our opinion proved to be a highly sensitive indicator of improvement and of relapse. It possesses the virtue of permitting the indication of complete or nearly complete relief of pain and stiffness without requiring evidence of cure of the underlying cause of rheumatoid arthritis. Since no claim of cure is being made or implied we are using both these methods of evaluation.

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**The sodium and potassium para-aminobenzoate used in this study were provided through the courtesy of Dr. W. R. Bond, Director of Clinical Research, of the A. H. Robins Co.

Results. The results obtained by this method of treatment are summarized in Table 1. A total of 31 patients were treated by this method for periods of one year or more. Twenty-three of these patients received large doses of cortisone acetate for a period of one or two weeks before receiving combined oral cortisone acetate and sodium or potassium para-aminobenzoate by the method here described. In 22 receiving large doses of cortisone at any time and their improvement has been quite satisfactory. Aside from weight gain which did not produce weight in excess of normal age-height-weight standards and rare mild rounding of the face we have not encountered any of the well known stigmata of hypercorticoidism. Two of these patients developed a toxic drug rash due to the para-aminobenzoic acid after 12 and

TABLE 1.—DESCRIPTION AND RESPONSE TO THERAPY OF CASES OF RHEUMATOID ARTHRITIS

Name	*Age*	*Sex*	*Duration Arthritis (years)*	*Severity of Arthritis*	*Response Standard Doses Cortisone*	*Response Cortisone and PABA*	*Duration Cortisone and PABA*	*American Rheumat. Assn. Classification*		
								Anat.	*Funct.*	*Therap.*
L. W.	42	M	12	3 plus	90%	90%	3¼	ii	ii	ii
J. V.	35	F	4½	3 plus	90%	90%	2½	ii	ii	ii
A. C.	35	M	14	4 plus	90%	80%	2½	iv	iii	ii
R. B.	42	F	20	3 plus	100%	90%	2¼	iii	iii	ii
C. G.	28	F	12	4 plus	90%	90%	2	iv	iii	ii
D. R.	22	F	14	4 plus	80%	90%	2¼	iv	iv	ii
V. C.	34	F	1	3 plus	—	80%	1¾	ii	ii	ii
F. E.	56	M	7	3 plus	—	100%	2⅙	i	iii	i
O. L.	57	F	4	3 plus	90%	90%	2	iii	ii	ii
E. L.	62	F	8	3 plus	—	95%	1½	iii	ii	ii
B. R.	47	F	11	3 plus	90%	80%	2 1/12	iii	iii	ii
H. B.	52	F	9	3 plus	100%	100%	1½	ii	iii	i
M. F.	50	M	14	4 plus	—	75%	1⅓	iv	iii	ii
A. G.	48	F	2	4 plus	—	90%	1 7/12	iii	iv	ii
A. C.	65	F	20	2 plus	95%	90%	1¼	ii	ii	i
M. M.	59	F	23	3 plus	—	80%	1⅙	ii	ii	ii
D. P.	64	F	22	4 plus	80%	40%	1½	iii	iv	ii
E. R.	28	F	9	3 plus	90%	90%	1 1/12*	iii	iii	ii
E. D.	51	F	2	2 plus	—	100%	1	ii	ii	ii
M. F.	59	F	2	3 plus	90%	80%	2⅓	ii	ii	ii
M. A.	70	F	2	3 plus	90%	90%	2	ii	iii	ii
R. I.	27	F	1	4 plus	90%	100%	2	ii	iv	ii
H. C.	49	F	5	4 plus	100%	90%	1¾	iii	iv	ii
S. G.	37	F	4	4 plus	100%	80%	2	iii	iv	ii
G. S.	43	F	16	3 plus	100%†	80%	1	iii	iii	ii
E. P.	65	F	6	4 plus	80%	80%	1	ii	iii	ii
A. N.	65	F	25	2 plus	—	100%	1	ii	ii	ii
F. C.	48	F	18	2 plus	100%	100%	1*	i	ii	i
D. M.	38	M	3	3 plus	100%	90%	1	i	iii	ii
A. R.	41	F	7	4 plus	90%	90%	1	ii	iii	ii
L. P.	28	F	2	2 plus	100%	100%	1	i	ii	ii

* These patients developed toxic drug rash due to PABA.
† This patient could not tolerate standard doses of cortisone for more than one week.

of these 23 patients the improvement obtained by either method was quite comparable but in one patient improvement was far greater on large doses of cortisone alone. It is of more than passing interest that this patient insists on receiving sodium para-aminobenzoate but requires 75 mg. of cortisone acetate daily in order to maintain relief of arthritic manifestations equivalent to that obtained on 150 mg. of cortisone acetate alone. Eight patients were started on our regime without 13 months of therapy respectively. In these 2 patients this therapy had to be discontinued. In each case drug allergy developed when the drug was re-instituted after a control period. The only other complaints referable to the sodium or potassium para-aminobenzoate in this group of patients were some objection to the briny taste of the solution which could be overcome by the addition of flavoring and the occasional complaint of heartburn

which was easily controlled by the administration of whole milk.

The rate of improvement of patients on this form of therapy has been different from that obtained on conventional dose cortisone therapy. The euphoria which is so prominent on large doses of cortisone has not been noted in any of our patients. In severe cases improvement has been gradual and often maximal improvement has not been reached until therapy has been continued for as long as 60 to 90 days. This slow rate of improvement by the method here described has been speeded in other patients not included in this study in whom the interval between large dose cortisone therapy and the addition of para-aminobenzoic acid to small doses of cortisone has been omitted.

Conversely we have not had to interrupt treatment in any of our patients because of evidence of hypercorticoidism or because of the development of intercurrent infections, peptic ulcer, psychosis and the like. The purpose of our study has been the long continued suboptimal suppression of the manifestations of rheumatoid arthritis with a daily dose of cortisone acetate of 37.5 mg. Larger doses of cortisone acetate combined with para-aminobenzoic acid can and have been used but are not a part of this study.

The following case reports will serve to illustrate the response to combined treatment with cortisone acetate and sodium or potassium para-aminobenzoate:

Case Reports. CASE NO. 1: S.G., a 37-year-old white spinster, developed rheumatoid arthritis in 1947, with onset of moderate severity but with a rapid and relentless downward course. She became completely disabled and almost totally bedridden by January, 1950. In June, 1950, she was hospitalized and received intramuscular cortisone acetate with an average daily dose of 200 mg. for 60 days with marked but not complete subjective and objective improvement. From September, 1950, until January, 1951, she received a daily intramuscular dose of 50 mg. of cortisone acetate with marked increase in the subjective and objective manifestations of her disease. Between January and April, 1951, this relapse became exceedingly severe and the patient again became a total invalid, unable to care for herself.

When first seen by one of us (L.L.W.) in April, 1951, the patient was totally disabled and could not care for her simplest wants. She was hospitalized and in order to evaluate any possible adrenal atrophy was given 100 mg. of ACTH daily for 10 days with rapid production of eosinopenia and with moderate improvement manifested by lessening of pain, but in spite of this, she was still unable to care for herself or to walk. At this time there was evidence of marked rheumatoid activity in both feet, ankles, knees, both hands, elbows and shoulders. There was roentgenographic evidence of marked bony destruction of both ankle and wrist joints and there was fibrous fixation of both wrists and elbows.

After the initial course of ACTH she was given 30 cc. of sodium para-aminobenzoate solution followed in one hour by 12.5 mg. of cortisone acetate this being repeated three times daily. She improved slowly on this dosage until by May 10, 1951, she was able to walk, wear shoes and care for herself. This medication was continued until October 27, 1951, at which time she had achieved between 80 and 90% relief of symptoms. Sodium para-aminobenzoate was discontinued at this time for purposes of control and daily dose of 50 mg. of cortisone acetate in 4 divided doses given. After 3 weeks on this regime she developed increasing pain and swelling in several joints and sodium para-aminobenzoate was again given. From December 8, 1951 to August 14, 1952, she was maintained on 45 cc. of sodium para-aminobenzoate solution and 12.5 mg. of cortisone acetate administered 3 times daily in the usual manner with relief estimated at 80%. Early in 1952, she sought and obtained employment as a file clerk and typist and has been steadily employed at this occupation since then. In August, 1952, sodium para-aminobenzoate was again withdrawn and relapse became manifest after an interval of 6 weeks. Combined therapy was again instituted and has been employed steadily since that time. The patient has pain and some swelling in single joints on occasion, usually after an upper respiratory infection but has

been able to continue at her employment without loss of time.

CASE NO. 2: F.E., a 56-year-old colored male, developed rheumatoid arthritis in 1943, which became so severe that he abandoned work as a shipfitter. He received gold therapy elsewhere with good response for 2 years but then became gradually worse. When first seen by us in January 1951, he was totally disabled and on home relief. He had marked involvement of both hands precluding their use other than for personal care and moderately severe involvement of both elbows and knees. He was given 2 gm. of sodium para-aminobenzoate followed by 12.5 mg. of cortisone after an interval of one hour, 3 times daily. Within 2 weeks he experienced complete relief of pain and swelling and exhibited only residual stiffness of the fingers. Medication was continued until June 6, 1951, when the sodium para-aminobenzoate was discontinued. For 12 weeks he remained well but then relapsed severely. On September 26, 1951, sodium para-aminobenzoate was resumed. Thirty cubic centimeters of sodium para-aminobenzoate solution was given one hour before each dose of 12.5 mg. of cortisone for a total of 3 such doses daily. On October 10, 1951, relief of pain and swelling was complete and within a few weeks even stiffness had disappeared. From December 26, 1951 to January 23, 1952, the sodium para-aminobenzoate was withheld while the cortisone acetate was continued and relief was maintained. From January 23, 1952 to March 12, 1952, the patient abandoned all treatment and developed a severe exacerbation. From March 12, 1952 to May 7, 1952, he was given 37.5 mg. of cortisone acetate daily without relief. On May 12, 1952, 30 cc. of sodium para-aminobenzoate solution was added to the cortisone by the usual method and the patient manifested rapid relief. Combined therapy was continued until October 12, 1952, when the sodium para-aminobenzoate was discontinued. He has remained asymptomatic since then on 37.5 mg. of cortisone acetate daily without recurrence. The patient has been gainfully employed since June, 1952.

CASE NO. 3: H.C., a 49-year-old married white female, first developed rheumatoid arthritis in 1946 with gradual onset pain, swelling and stiffness of both hands, wrists, elbows, shoulders, knees and ankles. With the aid of salicylates she was able to continue to work in spite of pain until December, 1950, when following a respiratory infection she became totally disabled. In January, 1951, she was given intramuscular cortisone by her family physician and received a daily dose of 100 mg. until June, 1951. During this period she was fairly well controlled and was able to care for herself with only moderate pain but could not walk more than half a block. In June, 1951, she began to develop increasing pain and swelling in spite of continued treatment and became so discouraged that she discontinued treatment.

When first seen by us she was very much depressed and showed marked involvement of both hands, wrists, shoulders, knees, ankles and feet. At this time she was unable to care for her simplest wants. Since she was quite disabled she was hospitalized. She received full doses of cortisone acetate intramuscularly and obtained complete subjective relief of pain and obtained major objective improvement of swelling, heat and joint tenderness. After 2 weeks of this treatment the dose of cortisone was reduced to 12.5 mg. given orally 3 times daily with 30 cc. of 10% solution of sodium para-aminobenzoate preceding each dose of cortisone acetate by one hour. On this regime she relapsed partially until relief of rheumatoid manifestations was estimated at only 80% at the end of one week. This regime was continued until on February 25, 1952, relief of arthritic manifestations had reached 100%. This relief was maintained until June 17, 1952, at which time the sodium para-aminobenzoate was withdrawn for control purposes. Partial relapse became manifest 2 weeks after the control period had been initiated and full relapse was evident 69 days after initiation of control on a daily dose of 37.5 mg. of cortisone acetate. On October 8, 1952, the sodium para-aminobenzoate was re-instituted and the patient improved rapidly. Since that time she has been able to maintain complete relief of the manifestations of rheumatoid arthritis on this treatment. She has been continuously employed at her usual occupation as a clerk since October, 1951.

Discussion. We have purposely limited this report to a group of patients who have been treated by this method for one year or more because the course of rheumatoid arthritis is quite unpredictable and prone to spontaneous remissions. As nearly as is possible we have tried to exclude the influence of spontaneous remissions by

instituting control periods up to the point of at least partial relapse at frequent intervals.

That para-aminobenzoic acid and cortisone act synergistically has been shown by a number of clinical studies[6,10,14,15,18]. Para-aminobenzoic acid alone in doses up to 24 gm. per day for 4 weeks failed to produce significant clinical improvement in rheumatoid arthritis[18]. In the doses we have employed, para-aminobenzoic acid alone has failed to suppress the manifestations of rheumatoid arthritis. The mechanism of synergistic action of cortisone and para-aminobenzoic acid is under investigation.

Our original theory was based on the known interference of para-aminobenzoic acid with the inactivation of female sex hormone by liver tissue. Our premise that cortisone must follow a similar metabolic pathway in the body has since been substantiated by the experimental results of others[7,12]. We have been able to demonstrate by *in vitro* experiment that the known destruction of cortisone by liver tissue is markedly inhibited by the addition of para-aminobenzoic acid to the substrate[16]. The mechanism of this interference can only be inferred at this time. We have previously demonstrated that tetraethylthiuram disulphide acts synergistically with cortisone in much the same manner as does para-aminobenzoic acid[17]. Tetraethylthiuram disulphide is known to interfere with various oxidative enzymes and with oxygen consumption by the liver[5,11]. Tetraethylthiuram disulphide may act as a competitive hydrogen ion acceptor[9]. Therefore it is quite possible that para-aminobenzoic acid acts by inactivating hepatic oxidative enzymes or by competing with cortisone for these enzymes or one or more of the co-enzymes. Further investigation of the intermediate steps of this reaction is in progress.

We wish to emphasize the fact that we have been able to maintain patients with rheumatoid arthritis on sodium or potassium para-aminobenzoate and cortisone acetate for periods up to 3 years without encountering any of the dire side effects observed by others with the usual doses of cortisone[8], and with satisfactory sub-optimal suppression of the symptoms and signs of rheumatoid arthritis. We have not encountered glycosuria, hypertension, psychosis, hirsutism, obesity, striae, tuberculosis, periarteritis nodosa or any other serious side reaction. The only difficulty we have observed has been a tendency for upper respiratory infections to persist longer than usual in patients on this therapy. Exacerbations of rheumatoid activity following upper respiratory infections have been fairly common. These exacerbations have yielded to continued treatment in all cases studied.

To date the combination of para-aminobenzoic acid and cortisone in the doses employed has proved to be a useful method for the clinical suppression of rheumatoid arthritis with the advantage of relative safety and the ability to maintain therapy for long periods without the development of refractoriness, side reactions or serious complications. It should be emphasized that for the purpose of investigation we have limited ourselves to a dose of cortisone acetate so small that in itself it has proved completely ineffective in overcoming rheumatoid manifestations in the cases studied. Larger doses can be used and have been employed with para-aminobenzoic acid in the suppression of the manifestations of the various collagen system diseases. In general it has been our impression that the addition of

para-aminobenzoic acid increases the anti-inflammatory or antiphlogistic action of a given dose of cortisone acetate two to threefold. This potentiation has not been accompanied by a similar increase in the incidence of "side reactions." Studies directed at an explanation of this apparent paradox are now under way.

Summary and Conclusions. 1. Thirty-one patients with active rheumatoid arthritis were treated with a combination of para-aminobenzoic acid and cortisone for a period of one year or more.

2. Thirty of these patients showed improvement comparable to that obtained with a much larger dose of cortisone acetate administered alone.

3. The incidence of evidence of hypercorticoidism was negligible. Other known complications of cortisone therapy were absent.

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