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THE SYNERGISTIC ACTION OF PARA-AMINOBENZOIC ACID AND CORTISONE IN THE TREATMENT OF RHEUMATOID ARTHRITIS

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THE beneficial effects of cortisone on rheumatoid arthritis are now well established[8,9,11]. Unfortunately these effects are not lasting and the majority of patients require continued administration of cortisone to insure continued relief. Since cortisone affects a number of metabolic processes[10] there have been undesirable side reactions[8,9,10] with the customary dosage schedules. Efforts have been made to produce relief from the symptoms of rheumatoid arthritis with smaller doses of cortisone and at the same time to reduce undesirable side actions and the high cost of treatment[5,6]. The search for synergistic agents to enhance the action of cortisone has so far been disappointing.

The authors became interested in the mechanism involved in the response of certain diseases of the collagen system to the administration of para-aminobenzoic acid which was established by Zarafonetis and his coworkers[13]. The metabolic effects of this substance have been studied extensively[2]. An impressive fact was that the known inactivation of estrogenic hormones by the liver[4,7,14] is inhibited by the addition of para-aminobenzoic acid[3]. The great similarity in structure of cortisone and the estrogens and the fact that the major portion of parenterally administered cortisone is inactivated in the body made it plausible to attempt to inhibit the destruction of cortisone by the simultaneous administration of para-aminobenzoic acid. Initial experiences with this method were encouraging[12]. The present report concerns the results obtained in the first 15 cases treated by this method for a significant period.

Method. For purposes of evaluation a controlled study was employed. Since the objective appraisal and grading of rheumatoid arthritis is fraught with pitfalls, each patient was used as his own control. All patients studied had moderately severe or severe rheumatoid arthritis which had previously proved refractory to other forms of treatment.

The 2 methods used for study were:

1. Patients were started on full dosage schedules of cortisone acetate until maximum relief of the symptoms of arthritis was obtained. This was usually for a period of 1 week. The daily intramuscular dose of cortisone was then reduced arbitrarily to 25 mg. On this dose all of our patients developed prompt relapse with severe subjective and objective symptoms and signs within a short time. When this relapse was established the sodium salt of para-aminobenzoic acid was given orally in doses of 1.5 gm. every 2 hours during the waking period for a total of 8 doses or 12 gm. per day in addition to the single daily intramuscular injection of 25 mg.

TABLE 1.—RESULTS IN 9 CASES OF RHEUMATOID ARTHRITIS TREATED BY METHOD 1 (CORTISONE ALONE, THEN CORTISONE + NaPABA*)

					Control Period on Standard Dose of Cortisone		*Period of Combined Treatment with Cortisone and NaPABA*	
Case	*Age*	*Sex*	*Duration of Disease (yr.)*	*Severity*	*Time (days)*	*Relief (%)*	*Time (days)*	*Relief (%)*
E. R.	69	F	10	4+	30	90	68	90
L. W.	39	M	9	3+	10	100	277	90
J. V.	32	F	2½	3+	7	90	102	90
E. R.	28	F	9	3+	14	90	145	90
A. C.	65	F	20	2+	7	95	78	80
A. C.	37	M	12	4+	14	80	103	80
W. V.	65	M	¾	3+	14	85	79	90
J. O'C.	31	M	7	3+	7	90	106	90
A. W.	56	M	4	3+	7	95	126	80

* Sodium para-aminobenzoate

TABLE 2.—RESULTS IN 6 CASES OF RHEUMATOID ARTHRITIS TREATED BY METHOD 2 (CORTISONE + NaPABA*)

							Relapse on Placebo Treatment	
Case	*Age*	*Sex*	*Duration of Disease (yr.)*	*Severity*	*Degree of Relief on Combined Cortisone and NaPABA Treatment (%)*	*Duration of Combined Treatment (days)*	*Interval (days)*	*Degree*
B. R.	47	F	11	3+	80	128	2	full
O. C.	60	F	⅔	2+	90	85	4	partial
A. M.	38	F	3	3+	90	80	3	full
M. W.	43	F	18	3+	80	88	3	full
R. D'A.	28	F	2	3+	95	114	4	full
E. T.	34	F	11	4+	85	134	4	full

* Sodium para-aminobenzoate

of cortisone acetate. When relief of arthritic manifestations was again established and maintained for variable periods of time, control periods were introduced by the substitution of a placebo for the cortisone.

2. Other patients were started immediately on a single daily intramuscular dose of 25 mg. of cortisone acetate and 12 gm. of sodium para-aminobenzoate were given orally in 8 divided doses of 1.5 gm. at 2-hour intervals during the waking period. When relief of arthritis was well established, control periods were introduced by replacing the cortisone acetate with placebo injections.

All patients were seen at least once weekly during the period of study by one of the authors and both subjective and objective findings were recorded.

Results. Fifteen patients were treated by these methods in the arthritis clinic or in private practice. Table 1 lists the results obtained in 9 patients treated by the first method. Table 2 lists the results obtained in 6 patients treated by the second method.

All the patients treated showed marked improvement both subjectively and objectively. The percentage of improvement recorded is based on the degree of lessening of pain and stiffness and ability to return to work reported by the patient and the observed degree of disappearance of swelling and tenderness recorded by one or more of the observers.

By employing the first method it was possible to compare the improvement of arthritic symptoms and signs obtained on full dosage schedules of cortisone acetate with that noted with a single dose of cortisone acetate of 25 mg. administered intramuscularily and 12 gm. of sodium para-aminobenzoate administered orally in divided doses. The improvement in arthritic manifestations when so compared was the same in 5 cases, somewhat less in 3, and slightly greater in 1 on the combined treatment schedule.

The second method used did not permit comparison of the results obtained with those obtained on full cortisone doses since these patients did not receive more than 25 mg. of cortisone acetate per day at any time. All 6 patients showed marked improvement in their arthritic manifestations. That this was not a coincidence was amply shown by the very rapid reappearance of arthritic signs and symptoms during the control periods when cortisone was replaced by a placebo.

Case Reports. The following case reports are presented to illustrate the response obtained.

CASE 1. J. V., a 32-year old white housewife, was first seen in the arthritis clinic on September 27, 1950. She gave a history of 2½ years of joint pain and swelling which had become progressively worse in spite of various oral and parenteral treatments administered elsewhere. She exhibited fusiform swelling of all proximal interphalangeal joints of both hands, and swelling, heat, and stiffness of both wrists and both knees. At this time the sedimentation rate was 35 mm. in ½ hour and 69 mm. in 1 hour and the blood count showed a moderate hypochromic anemia. She was given 200 mg. of cortisone acetate intramuscularly and then received 100 mg. daily for an additional 6 days. On the seventh day she reported that pain and stiffness had been relieved about 90% and there was no demonstrable swelling of any joint. The daily dose of cortisone acetate was reduced to 25 mg. On the fifth day at this dosage level the patient developed marked pain, and demonstrable swelling of the proximal interphalangeal joints of both hands, the right wrist, and the right knee was present. Sodium para-aminobenzoate was then given orally in doses of 1.5 gm. every 2 hours during the waking period with a total daily dose of 12 gm. in addition to the single daily intramuscular dose of 25 mg. of cortisone acetate. Within 1 week on this schedule there was moderate relief of pain and disappearance of swelling in all joints except the right wrist. At the end of 2 weeks of this treatment the patient was free from all pain and there was no residual swelling of any joint. The patient was able to carry out all her household duties. The cortisone acetate was then replaced by a placebo injection without the patient's knowledge. Within 2 days there was recurrence of pain and stiffness of the proximal interphalangeal joints of both hands and the right knee. The pain and swelling progressed until at the end of 1 week the placebo injection was replaced by corti-

sone acetate in daily doses of 25 mg. By the eighth day of resumption of cortisone the patient reported that she was completely free of pain and swelling. The treatment was continued until January 17, 1951, at which time it was stopped for purposes of evaluation. The patient remained symptom free for 4 weeks and then noted gradual return of pain and swelling in all joints involved.

CASE 2. R. D. A., a 28-year old white housewife, was seen in private practice on December 7, 1950. Generalized pain and swelling of the joints, which had begun 2 years previously after an attack of acute tonsillitis and had confined her to bed for 6 weeks, had persisted in spite of physiotherapy, intravenous injections, and a course of chrysotherapy which was abandoned after 3 months because of failure to obtain any relief.

Examination revealed fusiform tender swelling of the proximal interphalangeal joints of both ring fingers, swelling of the metacarpophalangeal joints of both hands, marked swelling and tenderness of the right wrist, and mild swelling of the left wrist. There was subjective pain in both elbows and knees and the right ankle without objective evidence. The sedimentation rate was 18 mm. in ½ hour and 30 mm. in 1 hour.

This patient was immediately started on a single daily intramuscular injection of 25 mg. of cortisone acetate and received three 0.5 gm. tablets of sodium para-aminobenzoate every 2 hours for a daily total dose of 12 gm. At the end of 1 week the only change noted was a decrease of pain while at rest but no objective changes could be found. At the end of 2 weeks of therapy the patient reported marked relief from pain, and the previously noted swelling of the interphalangeal and metacarpo-phalangeal joints had disappeared. After 3 weeks of this treatment the improvement in pain was estimated by the patient to be 80%, since she felt tired and stiff after doing housework all day. After 4 weeks of treatment there was 95% relief from pain, since the only discomfort reported was slight stiffness for about half an hour after arising and there was no objective evidence of joint disease. At this time the daily injection of cortisone was replaced with a placebo. After 4 days of placebo injection the patient reported joint pain and stiffness and the right ankle became visibly swollen, warm, and tender. Pain continued to increase and on the seventh day the placebo injection was replaced with 25 mg. of cortisone acetate. Pain and swelling subsided gradually over a period of 1 week. When last seen on March 22, 1951, the patient felt fine and was able to do all her housework. At this time the sedimentation rate was 8 mm. in ½ hour and 18 mm. in 1 hour. This patient gained a total of 15 pounds during the period of treatment.

CASE 3. A. C., a 65-year old white housewife, was seen in the arthritis clinic on September 13, 1950, with a history of rather mild rheumatoid arthritis involving the hands, wrists, elbows, shoulders, and knees of 20 years' duration. About 2 years previously this had become quite severe, especially in the left knee and the right shoulder, and greatly limited her activity. She obtained no relief from a course of gold therapy administered elsewhere. There was slight swelling of the proximal interphalangeal joints of the right hand. The knee joints were warm and swollen and crepitation could be elicited. X-ray examination revealed evidence of osteoarthritis of the knees and hands in addition to the swelling. Treatment with cortisone acetate was begun with an initial dose of 200 mg. which was followed by a daily intramuscular dose of 100 mg. for 6 days. At the end of this period there was a great deal of euphoria and pain and stiffness were almost completely relieved. Slight swelling and warmth to touch could be demonstrated in the left knee. The daily intramuscular dose of cortisone was reduced to 25 mg. and in 5 days there was complete return of pain and stiffness of the previously involved joints with demonstrable swelling and heat in both knees. Sodium para-aminobenzoate administration was then begun in doses of 1.5 gm. at 2-hour intervals for a daily total dose of 12 gm. in addition to the single daily intramuscular injection of 25 mg. of cortisone acetate. On this the patient gradually regained her previous degree of improvement until at the end of 3 weeks of combined treatment she estimated her relief from pain and stiffness to be 90%. At this time there was still some swelling and warmth in her left knee. Roentgen examination of the knees again showed marked osteoarthritic changes in the left knee. Therapy was continued until December 13, 1950, at which time it was stopped. The final estimate of the degree of improvement on the combined therapy was 80%. When last seen in February, 1951, she had no relapse.

Discussion. Studies on these patients demonstrate that the combined use of cortisone and sodium para-aminobenzoate permits satisfactory sub-optimal control of the manifestations of rheumatoid arthritis with an arbitrarily chosen dose of cortisone acetate which,

by itself, is completely ineffective in controlling the manifestations of rheumatoid arthritis. The sodium para-aminobenzoate in the dosage employed has produced no evidence of any beneficial results when administered alone.

Careful observation has failed to demonstrate any of the undesirable side effects which are fairly common with the usual dosage schedules of cortisone acetate. The euphoria and subsequent depression so often seen have been completely absent. Edema has not been noted in spite of the relatively high sodium intake due to the sodium para-aminobenzoate given. Moderate gain in weight has been noted, but since most of the patients were at or below optimum weight this has not been troublesome. It was not found necessary to institute any rest periods and it is believed that no marked adrenal cortical inhibition was produced with the doses employed. Aside from mild heartburn, which can be corrected by supplying milk, no toxic reactions to the sodium para-aminobenzoate used were noted.

The additive or synergistic action of cortisone and para-aminobenzoic acid requires further elucidation. The only explanation which can be advanced at this time is based on the similarity in structure and therefore probable similarity of fate in the body of the estrogens and corticosterone. The known inhibition of destruction of the estrogens by the liver by para-aminobenzoic acid suggests one plausible mechanism. Further investigation of this mechanism is certainly indicated and may lead to the discovery of even better synergistic agents. Recent work suggests that the corticosteroids may exhibit their beneficial effects on rheumatoid arthritis by the suppression of the action of some of the intra-cellular enzyme systems[1]. That this effect, at least on hyaluronidase, can be reversed by the addition of sulfhydryls would suggest the possibility that the synergistic effect of cortisone and para-aminobenzoic acid is produced in a similar fashion.

Work now under way tends to prove that the synergism between cortisone and para-aminobenzoic acid exists when both substances are administered orally. Results with oral dosage will form a separate report.

The effectiveness of the combined treatment in these cases warrants further use of this method. At a time when the supply of cortisone is so far short of the demand, a method which spares the amount of cortisone required per patient would seem to be of value.

Summary and Conclusions. The theoretic considerations leading to the trial of the simultaneous administration of cortisone and para-aminobenzoic acid have been presented. The results obtained with the method outlined have been tabulated. They have been comparable with those obtained by the administration of much larger doses of cortisone alone, with the additional advantage of a reduction in reactions. An additive or synergistic action of these two compounds in the treatment of rheumatoid arthritis has been shown. The degree of success obtained in 15 cases warrants further and more extensive use of this method.

REFERENCES

1. **Anderson, G. E., Wiesel, L. L., Hillman, R. W.,** and **Stumpe, W. M.:** Proc. Soc. Exper. Biol. & Med., **76:** 825, 1951.
2. **Ansbacher, S.:** Vitamins & Hormones, **2,** 215, 1944.
3. Idem, **Wisansky, W. A.,** and **Martin, G. J.:** Fed. Proc., **1,** 99, 1942.
4. **Biskind, G. R.,** and **Meyer, M. A.:** Proc. Soc. Exper. Biol. & Med., **53,** 91, 1943.

5. **Boland, E. W.**, and **Headley, N. E.**: J. Am. Med. Assn., **141**, 301, 1949.
6. Idem: Ibid., **144**, 365, 1950.
7. **Doisy, E. A., Thayer, S. A.,** and **Van Bruggen, J. T.**: Fed. Proc., **1**, 202, 1942.
8. **Hench, P. S., Kendall, E. C., Slocumb, C. H.,** and **Polley, H. F.**: Proc. Staff Meet., Mayo Clin., **24**, 181, 1949.
9. Idem: Arch. Int. Med., **85**, 545, 1950.
10. **Sprague, R. G., Power, M. H., Mason, H. L., Albert, A., Mathieson, D. R., Hench, P. S., Kendall, E. C., Slocumb, C. H.,** and **Polley, H. F.**: Arch. Int. Med., **85**, 199, 1950.
11. **Thorn, G. W.**, and Others:New England J. Med., **242**, 783, 1950.
12. **Wiesel, L. L., Barritt, A. S.,** and **Stumpe, W. M.**: Brooklyn Hosp. J., **8**, 148, 1950.
13. **Zarafonetis, C. J. D., Curtis, A. C.,** and **Grekin, R. H.**: Univ. Hosp. Bull., Ann Arbor, **13**, 122, 1947.
14. **Zondek, B.**, and **Sklow, J.**: Proc. Soc. Exper. Biol. & Med., **49**, 629, 1942.