AN INVESTIGATION OF COMBINED TREATMENT WITH ACTH AND PARA-AMINOBENZOIC ACID IN RHEUMATOID ARTHRITIS

By

O. Z. Dalgaard

In 1951 Wiesel, Barritt & Stumpe stated that they had found a synergistic or additive effect of cortisone and sodium para-aminobenzoate (PABA) in treating 15 patients with rheumatoid arthritis. Two methods were used. They gave 9 patients large doses of cortisone until maximal improvement of the symptoms was obtained, and then reduced the dose of cortisone arbitrarily to 25 mg. daily by intramuscular injection. The patients, however, soon had recurrences with severe subjective and objective symptoms. These patients were treated with PABA in doses of 1.5 gm. every second hour 8 times daily, or 12 gm. daily in all, together with a single intramuscular injection of 25 mg. of cortisone. Compared with the improvement obtained with the large doses of cortisone the improvement was as good in 5 cases, somewhat less pronounced in 3 cases and a little better in 1 case. Using the other method, the authors treated 6 patients with 25 mg. of cortisone and 12 gm. of PABA daily. All the 6 patients improved considerably (80–95 per cent improvement). As soon as the symptoms had been alleviated, cortisone was replaced by a placebo; aggravation occurred very soon, so that PABA exerted no effect when used alone. The authors consider that they have shown that when using large doses of PABA together with small quantities of cortisone which exerted no effect at all when administered alone it is possible to obtain a satisfactory improvement of the symptoms in rheumatoid arthritis. Previous investigations have shown that

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PABA inhibits the inactivation of oestrogens in the liver. Owing to the great similarity between the structure of oestrogens and cortisone, and to the fact that cortisone is inactivated in the organism, Wiesel et al. (1951) thought that PABA possibly also prevented the decomposition of cortisone. The large quantities of PABA administered caused no side-effects apart from slight pyrosis, and with the combined treatment the patients did not develop the usual symptoms of overdosage with cortisone. The cost of the therapy was also considerably lower.

Oka (1952) confirmed the therapeutic results to some extent, although the effect in his cases was not quite as good as in those reported by Wiesel et al. Twenty patients with rheumatoid arthritis were treated with daily doses of 25 mg. of cortisone, partly by the mouth, partly by intramuscular injections, and with from 6 to 12 gm. of PABA. After a course of 25–44 days, cortisone was discontinued in 7 patients and after 34–50 days PABA was discontinued in another 7 patients. The joint symptoms became worse in both groups of patients. 6 gm. of PABA was as effective as 12 gm., and it made no difference whether cortisone was administered intramuscularly or orally. Beneficial results were obtained in 16 patients, whereas the effect was doubtful in the remaining 4 patients.

In summary these two investigations show that by simultaneous treatment with large doses of PABA and small doses of cortisone it is possible in the great majority of cases to obtain almost complete improvement of the symptoms in rheumatoid arthritis. With regard to the criterion of the cortisone effect, the authors of the two papers have had to be content with a general clinical estimate (as in any other cortisone treatment).

With regard to the pharmacology of PABA, the following may be mentioned (Ansbacher, 1944): Most investigators agree that PABA should be considered as belonging to the vitamin B complex. Strauss et al. (1941) found that, following the administration of 1 to 4 gm. of PABA, the maximal blood concentration was reached in 1 or 2 hours, and that 6 hours after the administration of 4 gm. only a very small proportion of PABA was present in the circulating blood, while the substance was completely excreted in the urine in the course of 12 hours. Similar findings have been made by other authors. The fact that PABA is eliminated so quickly from the organism was of importance in planning the table of dosages (see later), as the large amounts of PABA must be assumed to have been excreted in the urine within 24 hours after cessation of treatment. Scott & Robbins (1942) stated that PABA has a remarkably low toxicity. The mean lethal dose is 2.85 gm. per kg. in mice, over 6 gm. per kg. in rats and from 1 to 3 gm. per kg. in dogs. Strauss & Finland (1941) were unable to demonstrate undesirable effects in the case of massive doses administered to human subjects, and the investigators have also demonstrated the low toxicity of PABA; thus Zarafonetis et al. (1950) have administered from
18 to 24 gm. of PABA daily for weeks or months without producing any toxic
effects.

Furthermore, it should be mentioned that PABA exerts a slight, antithyroid
effect in doses of about 4 gm. daily (Goodwin et al., 1949).

I have found no mention in the literature that PABA has any analgesic or
antipyretic action.

**Author's investigations**

The purpose of the present work was to examine whether PABA and ACTH
have a synergistic or additive effect in the treatment of rheumatoid arthritis. It has moreover been determined whether PABA alone might possibly in-
fluence the hormone production of the adrenal cortex.

It might be imagined that a synergistic or additive effect of PABA and
ACTH was caused either by PABA giving rise to an unspecific stimulation of
the pituitary (stress?), or by PABA inhibiting the decomposition in the liver of
the adrenal cortex hormones produced by the ACTH-stimulation.

**MATERIAL AND METHODS**

The present series comprises 5 patients with rheumatoid arthritis who were
treated with ACTH and PABA during the period March-August, 1952, and
5 control patients who were treated with PABA alone.

A general clinical estimate, counting of the circulating eosinophils and
measurement of excreted 17-ketosteroids were used as criteria of the effect.
The corticoid analysis was made in only one of the control patients. The
frequent clinical examinations of the patients were made in accordance with
Snorrason’s method (1951). Counting of the circulating eosinophilic leukocytes
was made according to V. Düngern’s method. Furthermore, the excretion of
17-ketosteroids in 24-hour urine was determined daily. These assays were made
in the Hormone Department, Statens Seruminstitut (chief: Chr. Hamburger).
On a few occasions the hormone assay of the urine was not possible because
some of the urine had been lost during the collection.

The ACTH preparation used was the Danish Acton (Vermehren, Frederiks-
berg chemiske Fabrikker). It was administered by intramuscular injections of
10 mg. (= 10 I. U.) in the morning. PABA was administered in doses of 1.5 gm.
8 times daily, or 12 gm. daily in all.

The level of the 17-ketosteroid excretion was determined at first in all the
patients by sending samples of urine for periods of from 3 to 5 days, as we had
to reckon with some variation in the hormone excretion in 24 hours. Sprechler
(1951) has shown that the steroid excretion is already increased on the first day
after the administration of ACTH, and this continues progressively until the
maximum is reached on the 3rd–5th day. The patients were thus at first given 10 mg. of ACTH + 12 gm. of PABA for 5 days. After an interval of 5 days they were given 10 mg. of ACTH and no PABA for 5 days, and after another interval of 5 days the same quantities of ACTH and PABA were administered again for 5 days. It thus became possible to see whether PABA exerted any effect whatever, as the two periods during which the patients were given both ACTH and PABA could be compared with the period during which they were given ACTH only.

The reason why the patients were given ACTH and PABA during 2 periods was that it could thus be decided whether the response of the adrenal gland to the effect had remained unchanged, as ACTH causes hypertrophy of the adrenal cortex.

Five control patients were given PABA for 5 days in the same dosages as mentioned above, and the 17-ketosteroid excretion was followed in all the 5 patients.

Experimental data

Table 1 gives the initials of the five patients, their case record numbers, sex, age, duration of the disease, clinical diagnosis, sedimentation rate, the effect of the therapy, complications, the duration of the effect, other therapy, stage, class and degree.

CASE RECORDS

Case 1. – A. B., case records No. 578/52.

The patient was a woman, aged 65, who in 1922 had been in hospital for a fortnight for rheumatic fever (?); there were no cardiac complications. In the spring of 1943 the patient developed rheumatoid arthritis with rise of temperature and swelling, redness and tenderness, at first of the finger-joints, later also involving wrists, knee- and ankle-joints. She had been admitted three times to Dept. III of Kommunehospitalet during the period 1943 to 1950; she was treated with sanocrysin, which was tolerated well at first and had a good effect, but later caused dermatitis. The patient was also treated with roentgen and neosolganol.

Soon after her discharge from the department in 1950 the patient became so disabled that she could hardly walk and could not conduct normal activities. The patient was re-admitted to the department in January, 1952. As early as the second day of treatment there was considerable subjective improvement. The pain in the joints decreased, and the mobility of the fingers was completely unimpaired, though she still complained of slight discomfort in her knees. During the intervals the patients again had some pain in the joints, but there
### Table 1.

Five patients with rheumatoid arthritis.

<table>
<thead>
<tr>
<th>No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
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<tr>
<td>Initials</td>
<td>A. B.</td>
<td>A. P.</td>
<td>C. E.</td>
<td>N. J.</td>
<td>G. N.</td>
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<td>Case record No.</td>
<td>578/52</td>
<td>693/52</td>
<td>1263/52</td>
<td>1484/52</td>
<td>1492/52</td>
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<td>Male</td>
<td>Female</td>
<td>Female</td>
</tr>
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<td>54</td>
<td>47</td>
<td>66</td>
<td>56</td>
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<td>Duration of disease before treatment</td>
<td>9 years</td>
<td>12 years</td>
<td>4-5 years</td>
<td>4 years</td>
<td>25 years</td>
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<td>Rheumatoid arthritis, cholelithiasis</td>
<td>Rheumatoid arthritis, psoriasis</td>
<td>Rheumatoid arthritis, bronchiectases, anemia simplex</td>
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<tr>
<td>S. R.</td>
<td>67 → 43</td>
<td>31 → 31</td>
<td>57 → 11</td>
<td>58 → 23</td>
<td>29 → 12</td>
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<tr>
<td>Effect</td>
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<td>No real improvement</td>
<td>Complete improvement</td>
<td>Real improvement</td>
<td>Real improvement</td>
</tr>
<tr>
<td>Complications</td>
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<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
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<tr>
<td>Duration of the effect</td>
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<td>About 1 week</td>
<td>4 weeks</td>
<td>A few days</td>
<td>1 week</td>
</tr>
<tr>
<td>Other therapy</td>
<td>Massage, walking exercises</td>
<td>None</td>
<td>Tar baths</td>
<td>Massage</td>
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<td>Stage</td>
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<td>3, active</td>
<td>3, active</td>
<td>1, active</td>
<td>3, active</td>
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<tr>
<td>Class</td>
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<td>3 → 2</td>
<td>2 → 1</td>
<td>4 → 3</td>
<td>3 → 2</td>
</tr>
<tr>
<td>Degree</td>
<td>2 (3)</td>
<td>3 (2)</td>
<td>1 (3)</td>
<td>2 (3)</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>
Effect of ACTH and PABA in a 63-year-old woman with rheumatoid arthritis. (10 mg. of ACTH intramuscularly daily for 3 periods of 5 days, and 12 gm. of PABA daily for 2 periods of 5 days).

was even progression during the entire course of treatment, so that, when discharged, the patient was able to walk a short distance by means of a stick. The patient was given massage and walking exercises 6 times weekly during the whole period of treatment. The S. R. decreased from 67 mm. to 43 mm./hr.

Roentgenologic examination showed severe arthritic changes in the wrists with halisteresis, obliteration of the articular space, and ankylosis. The finger-joints also showed halisteresis and arthritic changes with small destructions of almost all the joints. Roentgenologic examination of the knee-joints showed arthritis with slighter arthrotic changes.

Stage: 4, active.
Class: 4 → 3.
Degree: 2 (−3), indicative of real improvement caused by the treatment.

Case 2. - A. P., case record No. 693/52.
The patient was a woman, aged 54, who had been in hospital 4 times for rheumatic fever, the first time in 1929, the last in 1938. She began to develop rheumatoid arthritis in 1940. The patient had been treated with gold salts 4 times in all in different hospitals, the last in January 1951. In 1932 pernicious anaemia was diagnosed, in 1951 gall-stones. The patient was last treated for her rheumatoid arthritis in December 1951 with light-therapy in the department of physical medicine of Kommunehospitalet. The patient was admitted to this department in January, 1952, because of pain and swelling of almost all her joints, slight rise of temperature and loss of weight. Soon after admission
Effect of ACTH and PABA in a 54-year-old woman with rheumatoid arthritis. (10 mg. of ACTH intramuscularly daily for 3 periods of 5 days, and 12 gm. of PABA daily for 2 periods of 5 days).

The patient was given large doses of ACTH and was thus freed from pain, whilst at the same time her general health and the mobility of the joints improved considerably. The S. R. fell from 52 to 18 mm./hr. The effect of the treatment lasted only a few days.

The combined treatment with ACTH and PABA was commenced 2 months later. There was some improvement of the patient's general health and joint affection, but the effect was not so marked as that with large doses of ACTH. Swelling and pain recurred in the joints during the intervals. When the patient was discharged, the rigidity and pain in the joints was somewhat less pronounced than before the treatment, but there was no considerable improvement.

On April 14th the patient had an attack of biliary colic, which perhaps accounts for the increased 17-ketosteroid excretion in the urine and the fall in the number of circulating eosinophilic leukocytes (see the curve). The sedimentation rate remained unchanged, 31 mm./hr.

Stage: 3, active.
Class: 3 → 2.
Degree: 3 (−2), indicating that the treatment did not result in any real improvement.

Case 3. – C. E., case record No. 1263/52.
Effect of ACTH and PABA in a 47-year-old man with rheumatoid arthritis. (10 mg. of ACTH intramuscularly daily for 3 periods of 5 days, and 12 gm. of PABA daily for 2 periods of 5 days).

The patient was a man, aged 47, who had been suffering from psoriasis since his childhood. During the last 4–5 years he had had periods of pain in the joints, especially in the hands and feet, and a rise in temperature. To begin with, he had no symptoms between the attacks, but recently, before admission, there had been constant pain in the joints, swelling and impaired mobility, so that it had been difficult for the patient to manage his work and to conduct normal activities. As early as the first day of treatment the patient was almost and on the second day entirely, free from pain, and the mobility of the joints had improved considerably. There were no recurrences during the intervals, and the patient was discharged completely well. The S. R. fell in the course of treatment from 57 mm. to 11 mm./hr.

Roentgenologic examination of the hands showed signs of incipient rheumatoid arthritis with pronounced halisteresis in finger-joints and wrists and a few small rarefactions caused by destructive processes. Halisteresis was seen in the feet.

Stage: 2, active.
Class: 2 → 1.
Degree: 1, indicative of complete improvement.

The patient was a woman, aged 66, who had been suffering from rheumatoid arthritis since 1948. The same year she was admitted for this complaint to Bispebjerg Hospital; she could not tolerate gold salt treatment. In June 1952, the patient was admitted to Dept. III. Kommunehospitalet, for broncho-pneumonia sin. (and rheumatoid arthritis). During the last 6 months before admission the patient had been almost completely helpless because of pain in the joints and impairment of mobility, especially in knee- and elbow-joints. The patient had only been able to move about a little in her rooms by means

![Graph showing weight, eosinophiles, and 17-ketosteroids over time.

Fig. 4.
Effect of ACTH and PABA in a 66-year-old woman with rheumatoid arthritis. (10 mg. of ACTH intramuscularly daily for 3 periods of 5 days, and 12 gm. of PABA daily for 2 periods of 5 days).
of a crutch, and could not conduct normal activities at all. A fortnight after she had recovered from her pneumonia, the combined treatment with ACTH and PABA was commenced. In the course of treatment there was a good subjective improvement, with less pain and better function of the joints. The pain in the joints was rather pronounced during the intervals. The S. R. fell from 58 mm. to 23 mm./hr. The patient had massage.

Roentgenologic examination of elbow-joints and knee-joints showed diffuse halisteresis and arthrosis articulatio cubiti sin. et genus sin.

Stage: 1, active.
Class: 4 → 3.
Degree: 2 (-3).

The rheumatoid arthritis in this patient improved to some extent, so that, when discharged, she was able to walk with a stick and a crutch.

Case 5. – G. N., case record No. 1492/52.

The patient was a woman, aged 56. She was said to have had rheumatic fever with recurrences 10–12 times at the age of 25, but had never been in hospital for this reason. Since 1927 the patient had been suffering from
rheumatoid arthritis and had been treated with gold salts 3 times, the last in 1950. In 1951 she was treated in Dept. III of Kommunehospitalet with ACTH and carbon-arc light; there was a marked improvement. The patient was admitted in July 1952, owing to increasing pain and impairment of movement of the joints, especially in the hands, for the past 3–4 months. She had had a rise in temperature (38°). It has been difficult for her to manage even light housework. The treatment resulted in some improvement, though there was a slight worsening during the intervals. The patient also had massage. Roentgenologic examination of both hands showed considerable, diffuse halisteresis of all bones, including those of the wrist, and loss of substance, especially juxta-articularly on the third finger around the first interphalangeal joint, indicative of rheumatoid arthritis. The S. R. fell in the course of treatment from 29 mm. to 12 mm./hr.

Stage: 3, active.
Class: 3 → 2.
Degree: 2 (−3), indicative of real improvement caused by the treatment.

CONTROL CASES

(6) An undergraduate, aged 27, who had essentially been in good health previously.

![Graph](https://via.placeholder.com/150)

**Fig. 6.**
Effect of PABA in a 27-year-old subject. (12 gm. of PABA daily for 5 days).

(7) E. P., case record No. 907/52.
Diagnoses: Fibrositis dorsi et glutealis, observation for degeneratio disci intervertebralis.
Effect of PABA in a 58-year-old subject. (12 gm. of PABA daily for 5 days).

A woman, aged 58, who was given physical treatment during her stay in hospital.
Essentially in good health previously.

Effect of PABA in a 63-year-old subject. (12 gm. of PABA daily for 5 days).
E. G., case record No. 915/52.
Diagnoses: Fibrositis dorsi et glutealis, degeneratio disci intervertebralis, cholecystitis antea, nervosismus, obesity.
A woman, aged 63, who had been admitted twice previously for cholecystitis. Had been suffering from sciatica for many years (30). She was given physical treatment in this department.

A. G., case record No. 1609/52.
Diagnoses: Sciatica sin., obesity, miseries.
A man, aged 58, who had essentially been in good health previously. In 1928 he overstrained himself by lifting and has since been troubled by pain in his back. A disc prolapse was diagnosed in 1952. He was given physical treatment in this department.

Effect of PABA in a 58-year-old subject. (12 gm. of PABA daily for 5 days).
Effect of PABA in a 22-year-old subject. (12 gm. of PABA daily for 5 days).

(10) O. H., case record No. 1725/52.
Diagnoses: Fibrositis regio gluteales dext., observation for disc prolapse. A man, aged 22, who had been previously in good health but had had sciatica pain in the right leg for the past 5 months; physical treatment was effective.

The 4 patients with sciatica were not given any PABA until the treatment of this disease had been completed and they had become free from pain.

None of the 5 controls had any complaints after the administration of PABA, which was given in the same doses as in the patients with rheumatoid arthritis.

RESULTS

The combined effect of small doses of ACTH and large doses of PABA in 5 patients with rheumatoid arthritis was a slow and even improvement of the symptoms in 3 of the patients, without the dramatic effect which is often seen after the large doses of ACTH. There was some aggravation during the intervals, but it was not possible to demonstrate any great difference from a purely clinical point of view. The improvement approached the dramatic in only one patient (Case 3), whereas there was no real improvement in the last patient (Case 2). There were no side-effects after the large doses of PABA nor any
symptoms of overdosage with ACTH. A follow-up showed that the effect lasted only from a few days to one month.

In the five control patients, PABA gave rise to only a slight increase of the 17-ketosteroid excretion, while it exerted no definite influence on the 17-ketosteroid excretion and the number of circulating eosinophils in the patients with rheumatoid arthritis.

DISCUSSION

A very interesting paper has been published recently by Cronheim et al. (1952). They have studied the effect of salicylic acid and related substances on the adrenal-pituitary system in rats. They showed that salicylic acid, benzoic acid and certain other related substances produce a significant fall in the ascorbic acid content of the adrenal glands, indicating a state of activity. However, this does not apply to para-aminobenzoic acid (and para-aminosalicylic acid). These investigations suggest that salicylic acid, through a specific direct or indirect action, influences the pituitary gland, the result being an increased liberation or production of ACTH.

Selye (1950) has put forward the theory that stress increases the secretion of ACTH. Intoxication is also included by Selye in the concept of stress. It has also been observed clinically in several cases that rheumatoid arthritis has either subsided spontaneously or improved considerably in the case of stress action such as fever, or if the patient has developed jaundice. The possibility can not be ignored that the large doses of PABA may perhaps have exerted a toxic effect on the liver. Cruikshank & Mitchell (1951) have reported 3 deaths among children, and it is considered that the large doses of PABA may have contributed to the fatal result, as autopsy revealed severe fatty degeneration of the liver, the heart and the kidneys: it has been possible to reproduce such changes in animal experiments in rats and guinea pigs, and thus the use of large doses of PABA in children is not without risk.

It may be mentioned in this connection that Boe & Stoa (1952) have studied the combined effect of acetylsalicylic acid and another of the vitamins of the B complex, calcium pantothenate. However, they found no definitely better effect with the combined treatment than was to be expected with salicylic acid therapy alone.

In this country, Kalbak (1951) has combined small doses of ACTH with sanocrysin with good results.

SUMMARY AND CONCLUSIONS.

Five patients with rheumatoid arthritis were treated with daily doses of 10 mg. of ACTH intramuscularly and 12 gm. of sodium para-aminobenzoate (PABA)
orally for 2 periods of 5 days and with 10 mg. of ACTH only for a period of 5 days.

Frequent clinical examinations were made.

Complete improvement was seen in only one patient, in 3 there was a real improvement, while the last patient showed no real improvement.

PABA exerted no influence on the 17-ketosteroid excretion or on the number of circulating eosinophilic leukocytes, which were followed daily.

In 5 control patients who were given 60 gm. of PABA in the course of 5 days no definite increase of the 17-ketosteroid excretion was found.

No side-effects were observed in the course of treatment.

Owing to the small number of patients who were treated with ACTH and PABA, no definite conclusions can be drawn, but the results suggest that even large doses of PABA exert no definite synergistic or additive effect in combination with small doses of ACTH.

It is stressed that PABA in large doses may be toxic, and that it exerts some antithyroid effect.

REFERENCES