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# A STUDY OF CORTISONE AND OTHER STEROIDS IN RHEUMATOID ARTHRITIS*

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Soon after Hench, Kendall, Slocumb, and Polley (1949) announced their preliminary results in treating active rheumatoid arthritis with 17-hydroxy-11-dehydrocorticosterone ("compound E"), hereafter called "cortisone," two of us (W. S. C. C. and O. S.), with others, had an opportunity of visiting the Mayo Clinic and seeing for ourselves the remarkable and rapid results obtained with this substance. It was at once obvious that owing to the difficulties and high cost of production cortisone would not be available for some time in this country even for a limited clinical trial on a research basis.

Consequently the present group was formed with the object of testing, with concurrent metabolic studies, other steroids which were more readily available, and of devising methods by which improvement in rheumatoid arthritis could be assessed in therapeutic trials of any substances which might be thought to have a cortisone-like action.

On the occasion of a second visit to the Mayo Clinic by one of us (O. S.) a small supply of cortisone was made available to us at the instigation of Dr. Philip Hench.

The present report deals with the results of the administration of cortisone to five patients suffering from rheumatoid arthritis and 35 patients treated with other steroids.

## Methods

In this condition, in which the severity of the disease may fluctuate from day to day and criteria of activity depend to a large extent on the patient's own account of his pain and disability, assessment of improvement is notoriously difficult. Moreover, in addition to the normal variations which occur as a part of the natural history of rheumatoid arthritis, the psychological effect of giving a new treatment may be very considerable, as has recently been shown by Quin, Mason, and Knowelden (1950).

After discussion with Professor Bradford Hill it was decided to "screen" certain steroids by giving them to a small number of patients and assessing the results. In the event of a significant improvement occurring a second therapeutic trial was to be set up, in which the effect of the steroid would be compared with that of an inert substance indistinguishable from it in appearance, so that neither the patient nor those responsible for administering the injections and assessing the clinical results should know which compound was being given. The two substances, however, would be labelled in such a way that they could be identified in Professor Bradford Hill's department.

This latter method of trial was used in the case of cortisone on five patients who had previously received one of the other steroids; cholesterol was employed as the inert substance. Dr. J. Knowelden, lecturer in medical statistics at the London School of Hygiene and Tropical Medicine, working in Professor Bradford Hill's department, kindly handled this part of the trial.

The cases selected were patients suffering for more than six months from polyarthritis of the rheumatoid type, with symmetrical involvement of the peripheral joints, and tenderness, restricted range of movement, loss of weight, anaemia, and a raised erythrocyte sedimentation rate (E.S.R.). Cases with radiological evidence of minimal joint destruction were chosen so that restoration of full joint movement was still theoretically possible.

Patients were admitted to hospital for the trials and were all volunteers. They were not necessarily confined to bed, and in some cases they returned home for a part of each day so that they were able to judge for themselves whether there was improvement in their ability to carry out domestic duties. Patients were selected from outpatients attending the West London Hospital and the Arthur Stanley Institute of the Middlesex Hospital, and were admitted to the West London Hospital, the Hospital

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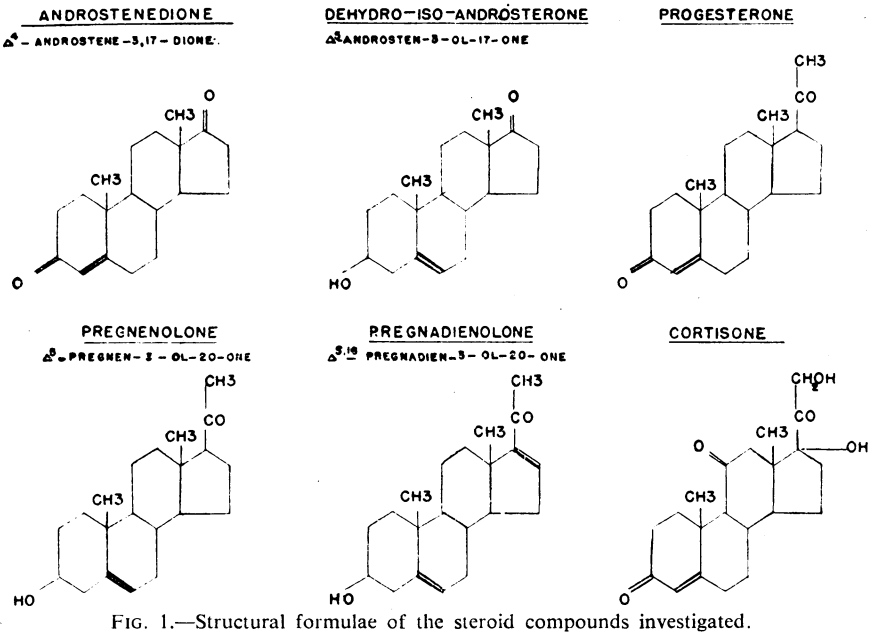


FIG. 1.—Structural formulae of the steroid compounds investigated.

of St. John and St. Elizabeth, or St. Mary Abbots Hospital. Each section of the metabolic studies was, however, carried out in the same laboratory in each case.

Each ten-day trial followed a period of observation in hospital of at least a week, during which a full assessment was carried out, as well as during and after the trial period.

### Assessment of Effect

The following criteria were used in assessing the results of the trials:

1. Answers to standard questions were recorded on a "Wirek" magnetic wire recorder, so that the whole interrogative interview could be reproduced at a later date for consideration by both observer and patient. The following are examples of the standard questions used: "How long does it take you to dress?"; "Can you dress fully without assistance?"; "How many tablets do you take daily to relieve the pain?"; "How many times nightly do you wake up with pain?"

2. Repeated examination by the same observer of joints for tenderness on firm pressure, swelling, and range of movement, the results being charted as follows: "1" is recorded when firm pressure over a joint gives rise to pain; "2" when it causes the patient to wince; "3" when the affected limb is in addition involuntarily withdrawn.

3. The grip test.—A blood-pressure cuff is folded up and sewn together into a suitable shape to be gripped in the palm of the hand and is inflated to 30 mm. Hg. The patient is then asked to squeeze it as tightly as he can, and the pressure recorded on the manometer is noted. The mean of three grips with each hand is taken.

4. Certain functional tests using most of the joints of the body, such as walking, climbing a standard set of steps, putting on a coat, getting up and down from a chair. These movements were timed, and could be assessed simply as "positive" or "negative." The tests most often repeated are those which the patient can just accomplish, because they most clearly demonstrate the degree of disability. They may vary from case to case.

5. Patient's own assessment.—During the period of observation patients were taught to assess their own condition from day to day, taking "100" as the "base-line" condition before the trial began. Subsequent figures above 100 indicated deterioration, whereas those under 100 denoted improvement.

6. Certain haematological studies, such as the erythrocyte sedimentation rate, the eosinophil count, and the haemoglobin percentage.

7. Filming certain standard movements before and after therapeutic trials in some cases.

8. Metabolic studies.—In selecting the urinary estimations to be undertaken in the present study it was decided to confine the investigations to those which were reported to have yielded significant results in the early published work on cortisone. These were: (1) 17-ketosteroids, estimated by the method of Callow, Callow, and Emmens (1938). (2) Pregnanediol, determined by a modification of the method of Sommerville, Gough, and Marrian (1948) in which the second and third reprecipitations from aqueous ethanol were replaced by washing with petroleum ether. (3) Corticoids, estimated by the periodic acid oxidation method, using a procedure similar to that described by Corcoran and Page (1948). The conditions of the hydrolysis and extraction were rigidly standardized in order to obtain comparable results. (4) Uric acid. (5) Creatinine. (6) The uric acid/creatinine ratio. Metabolic studies were undertaken on six patients receiving progesterone (Fig. 2), four patients receiving pregnenolone (Fig. 3), two patients receiving dehydro-*iso*-androsterone (Fig. 4), three patients receiving androstenedione, one patient receiving pregnadienolone, and four patients receiving cortisone (Figs. 5 and 6).

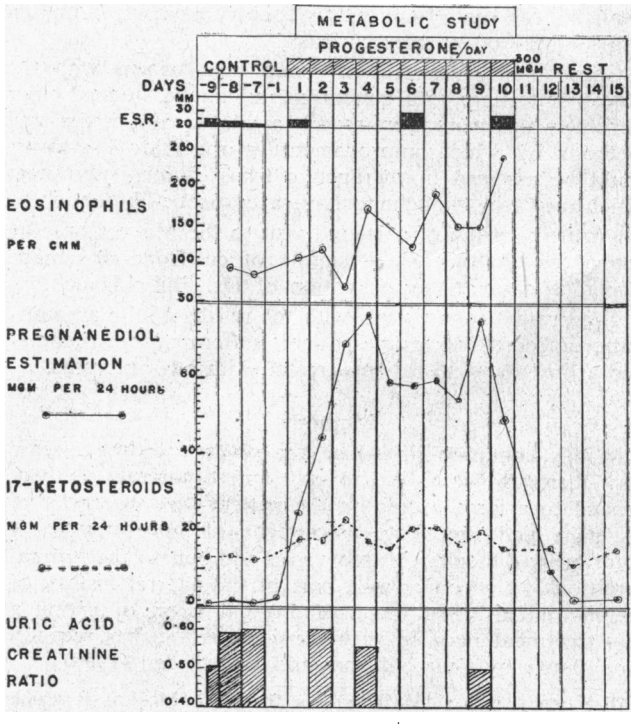


FIG. 2.—A metabolic study of a therapeutic trial with progesterone.

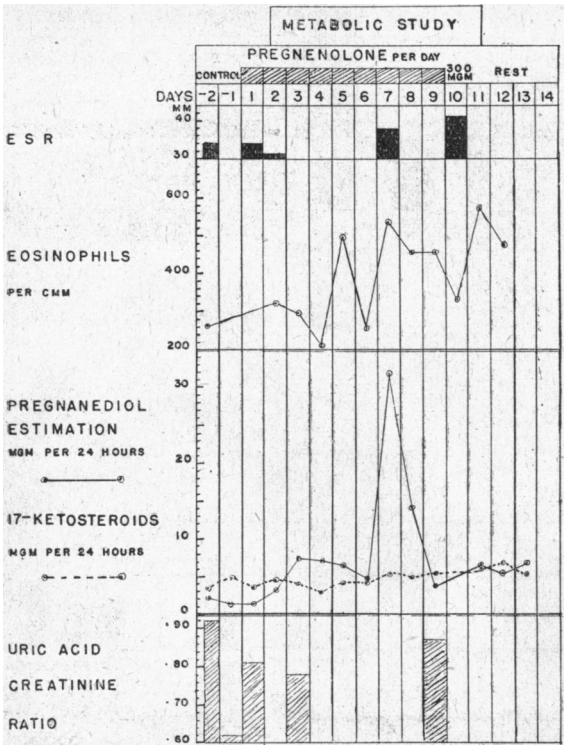


FIG. 3.—A metabolic study of a therapeutic trial with pregnenolone.

## Materials

The steroid compounds investigated, other than cortisone, were androstenedione, dehydro-*iso*-androsterone, progesterone, pregnenolone, and pregnadienolone. Their structural formulae are shown in Fig. 1.

It was decided to use high doses of each steroid because it had been shown by the original workers at the Mayo Clinic that only high doses of cortisone would produce results in rheumatoid arthritis. The compounds were in most cases dissolved in ethyl oleate, and the chief factor limiting dosage was the volume of injected oil that the patient could tolerate.

## Results

The accompanying Table is a summary of the results of administration of cortisone and other steroids in 40 cases of active rheumatoid arthritis.

*Androstenedione.*—Six patients were given 100 mg. daily for ten days. There was no clinical improvement in any case. The metabolic study showed a rise in 17-ketosteroids excretion. The uric acid/creatinine ratio showed a steady rise during the administration of androstenedione, but with all the other compounds this ratio fluctuated in a manner which did not indicate any significant trend.

*Results of Administration of Cortisone and Other Steroids in 40 Cases of Rheumatoid Arthritis*

| Substance Used For Ten Days | No. of Cases | Improvement | | | No Apparent Effect | Toxic Effect Sufficient to Stop Treatment | Made Worse |
|---|---|---|---|---|---|---|---|
| | | Dramatic | Marked | Slight | | | |
| Progesterone .. (300-500 mg./day) | 12 | | 1 | | 8 | 2 | 1 |
| Pregnenolone .. (100-300 mg./day) | 8 | | | | 8 | | |
| Androstenedione (100 mg./day) | 6 | | | | 6 | | |
| Dehydro-*iso*-androsterone (300 mg./day) | 4 | | | 1 | 3 | | |
| Pregnadienolone (200 mg./day) | 5 | | | | 3 | 2 | |
| Cortisone .. (Day 1, 300 mg., Day 2, 200 mg. Day 3-10, 100 mg.) | 5 | 4 | 1 | | | | |

*Dehydro-iso-androsterone.*—This compound was administered to four patients in daily doses of 300 mg. Slight transient improvement was recorded in one case only. Fig. 4 shows the results of a metabolic study. The increased output of 17-ketosteroids will be noted.

*Progesterone.*—Twelve patients (ten women and two men) were treated with 300–500 mg. daily for ten days. In every case there was a marked rise in sedimentation rate during progesterone administration. Only in the following case was any improvement seen.

*Case 1.*—A married woman aged 55 had been disabled with rheumatoid arthritis for six years. Five days after the injection of 300 mg. of progesterone daily she showed marked improvement, being able to run up and down the ward and raise her arms in a way she had been unable to do for three years. The improvement was maintained on 500 mg. daily until the end of the trial period, but when the inert control substance was administered she relapsed to her former state. No improvement occurred during a further period of treatment with 300 mg. of progesterone daily.

This suggests that progesterone is not so effectively metabolized in rheumatoid arthritics as in normal individuals. In this connexion it is of interest that the pregnanediol output was low (13.5 mg./24 hours) in the first period of progesterone administration, when there was marked improvement, and much higher (45 mg./24 hours) during the second course of progesterone, which proved ineffective. It seems possible that the progesterone was being more efficiently utilized during the first course of administration, and that this coincided with the beneficial effect.

Fig. 2 shows a metabolic study performed during a therapeutic trial with progesterone.

*Pregnenolone.*—No improvement was recorded in the eight cases of the present series. Fig. 3 shows the results of a metabolic study. There was no significant change other than an unexplained rise in the pregnanediol excretion on the seventh day. The E.S.R. rose during treatment.

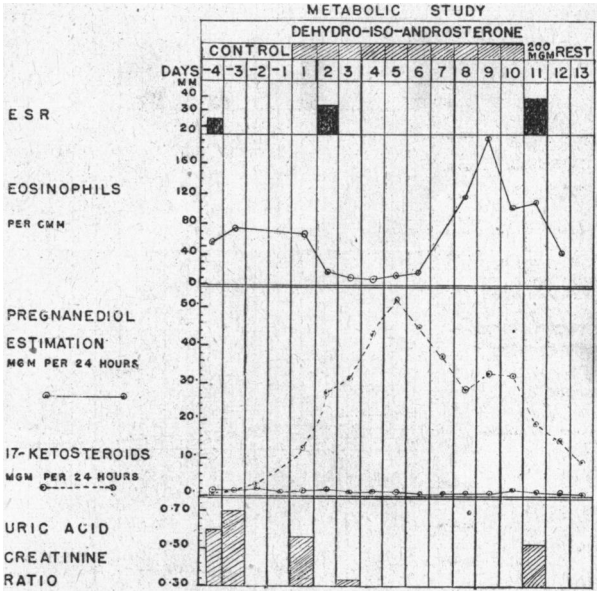


FIG. 4.—A metabolic study of a therapeutic trial with dehydro-*iso*-androsterone.

*Pregnadienolone.* — This substance was administered in arachis oil in doses of 200 mg. daily for ten days to five patients. In two cases the injections had to be discontinued because of urticarial reactions. In no case was there any improvement.

### Cortisone

Five patients were given cortisone and the inert substance, the materials being labelled so that the observers did not know which was the active and which the control compound. After the clinical results had been assessed it transpired that cholesterol had been given first in three cases and cortisone in the remaining two: 300 mg. was administered on the first day, 200 mg. on the second day, and 100 mg. daily for the following eight days.

In all five patients the E.S.R. fell significantly during the cortisone trials. There was no marked rise in haemoglobin percentage in any case, though all the patients were anaemic. The number of eosinophils was considerably diminished throughout the trial (except in one case in which they rose on the eighth day), though they did not disappear completely. There was a sharp rise when cortisone administration was discontinued. In the two cases in which 17-ketosteroids were repeatedly estimated the level rose when cortisone was given, returning to normal subsequently. Similarly, the urinary corticoids rose during treatment, sometimes to three or four times the original level. Less than 2% of the administered cortisone was excreted in the urine as "corticoid" (that is, formaldehydogenic neutral lipid). This agrees with the findings of Sprague *et al.* (1950).

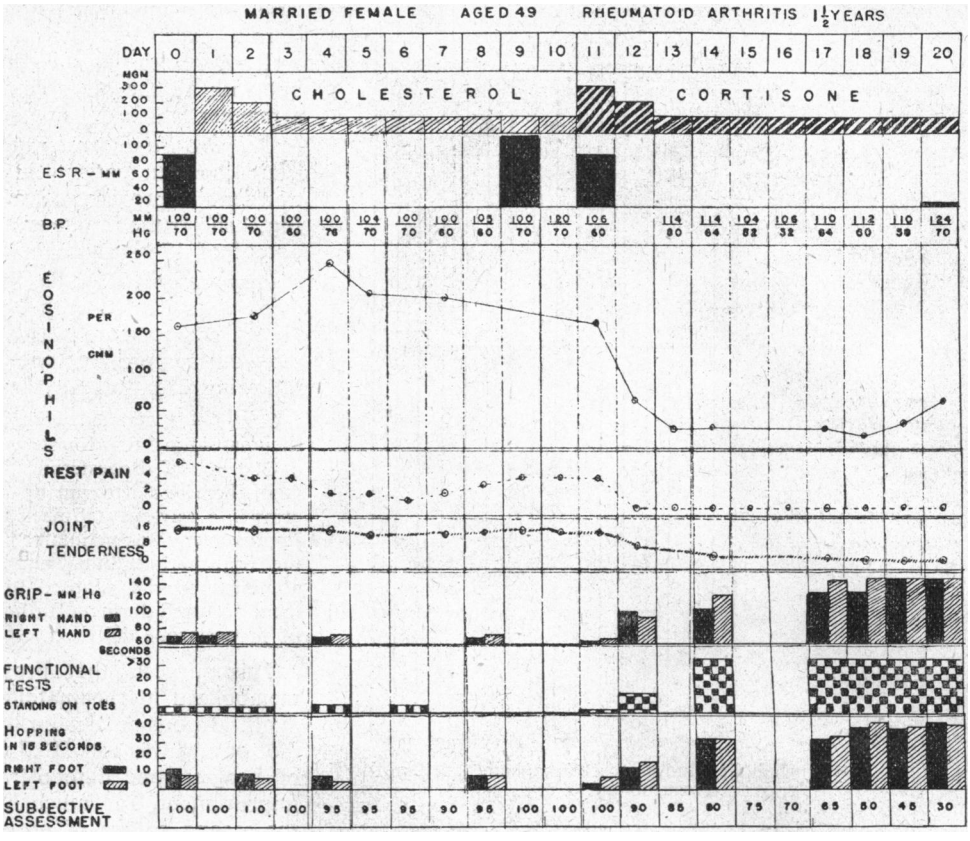


FIG. 5.—Showing the continued improvement throughout a trial with cortisone. (Case 2.)

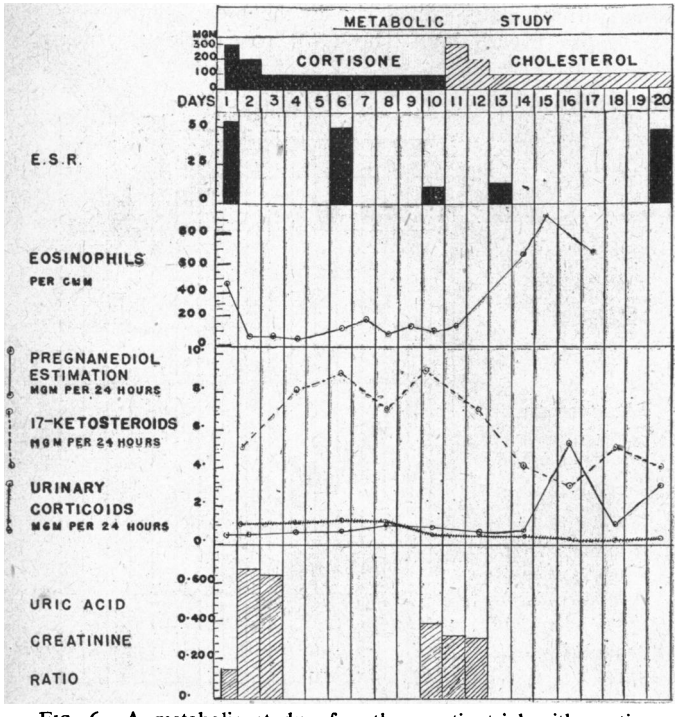


FIG. 6.—A metabolic study of a therapeutic trial with cortisone. (Case 4.)

Four patients gained from 2 to 4 lb. (0.9 to 1.8 kg.) in weight in ten days. There was marked increase in uric acid excretion; in one case the figure rose from 95 mg./24 hours to 429 mg./24 hours on the first day, and to 618 mg./24 hours on the second day of cortisone administration. The urinary creatinine figure rose from 699 mg./24 hours to 968 mg./24 hours on the second day.

All five patients receiving cortisone were women—two of the pre-menopausal, and three of the post-menopausal age. The treatment did not interfere with the menstrual cycles of the former or induce uterine bleeding in the latter.

### Case 2

A married woman of 49 had suffered for one and a half years from rheumatoid arthritis, starting in the feet and gradually spreading to the knees, hands, and shoulders with development of nodules on the fingers. She was unable to do her cooking or housework, could not put on her dressing-gown unaided, or hold a cup of tea with one hand. She was taking 10 tablets of codeine daily and was awakened each night with pain. In the previous six months the erythrocyte sedimentation rates were repeatedly found to lie between 50 mm. and 60 mm. in one hour (Westergren). Previous trials with two other steroids had failed to help her.

The response to cortisone was dramatic. On the second day of administration she could hold a pot of tea with one hand and slept throughout the night; on the third day she could put on her dressing-gown unaided. After this she was allowed to go home each day and found she was able to cook

and undertake housework without pain, though it tired her to do so. Fig. 5 indicates the continued improvement throughout the trial.

One month later the residual improvement was considered to be about half as much as she had attained during the course of cortisone therapy, although the E.S.R. had risen to 54 mm. in one hour within a week of discontinuing the injections.

**Case 3**

An unmarried woman aged 41. The onset, seven months previously, had been febrile with rapid deterioration, and at the beginning of the therapeutic trial she was completely bedridden and in constant pain. The E.S.R. while she was attending as an out-patient was 100 mm. in one hour (Westergren) and had fallen to 60 mm. in one hour after she had been in hospital three months. She had failed to improve while receiving the cholesterol injections, but the improvement with cortisone was dramatic. After receiving 300 mg. on the first day she no longer complained of pain at rest, and on the third day she could get out of bed unaided and stand for a minute. Her grip improved from 60 to 140 mm. Hg with the right hand. The E.S.R. fell from 60 mm. to 20 mm. in one hour during the course of cortisone injections, and she assessed her improvement at 50% at the end of the 10-day course.

A month later she retained half the improvement she had shown during treatment and the E.S.R. had risen to 42 mm. in one hour.

**Case 4**

An unmarried woman of 55 had suffered from rheumatoid arthritis for three years with a gradual onset involving the knees and spreading to the hands, wrists, elbows, ankles, and shoulders. Previous therapy and steroid trials had failed to help her. She showed marked "ganglionic" swellings at the interphalangeal and wrist joints and could raise her arms only with difficulty. She could walk fairly well, but had been unable to take a bath without assistance for two years. The interphalangeal, wrist, elbow, shoulder, knee, and foot joints were tender on pressure and the E.S.R. had remained at 50 to 60 mm. in one hour each week for the previous two months.

The response to cortisone was dramatic. By the third day she had no pain at rest and the joints were less swollen and no longer tender. On the seventh day she could extend her arms above her head 20 times in one minute, and on the eighth day she took a bath without assistance. During the period of observation she had been unable to jump, but on the tenth she could do so 40 times in one minute. The E.S.R. fell from 54 to 11 mm. in one hour during the trial. She assessed her improvement as 60%.

A month later she had completely relapsed and the E.S.R. had risen to 50 mm. in one hour within 10 days of cortisone being discontinued. The metabolic study is shown in Fig. 6.

**Case 5**

A married woman aged 38 had suffered from rheumatoid arthritis for three and a half years, starting during her fifth pregnancy involving the hands, wrists, ankles, and feet, with mild joint pains. These became severe three months after parturition and progressed rapidly. She lost 2½ st. (15.9 kg.) in weight, and for the last nine months had suffered from lassitude. She took an hour to dress herself and was unable to carry out most of her household duties, such as holding plates and work involving kneeling. The fact that the E.S.R., which had been 40–50 mm. in one hour for the previous four months, had dropped to 17 mm. just before the trial, however, suggested that the condition might be entering a stage of remission.

The response to cortisone was dramatic, but not as rapid as in the three previous cases. On the second day she no longer complained of pain at rest and most of the tenderness had disappeared, but she did not consider herself much improved until the third day, when she could kneel for the first time without pain. After the fourth day she improved more rapidly, and by the tenth day she could climb on to her bed easily and unaided. The grip of her right hand had strengthened from 100 to 200 mm. Hg and the left hand 90 to 185 mm. Hg. The E.S.R. fell from 17 mm. to 6 mm. in one hour. She assessed her improvement as 50%.

During the subsequent 10-day course of cholesterol injections she retained about half the improvement she had achieved, although the E.S.R. rose again to 23 mm. in one hour. A month later she retained the same degree of improvement, although the E.S.R. had risen further to 43 mm. in one hour.

**Case 6**

An unmarried woman of 30 had suffered from mild rheumatoid arthritis for four and a half years. Though she was able to continue her clerical work she complained of marked stiffness on rising and a chronic effusion in the left knee. The interphalangeal, metacarpo-phalangeal, and wrist joints and the left knee and mid-tarsal joints were tender, and she was taking an average of 10 codeine tablets daily. The E.S.R., which had fluctuated between 16 mm. and 60 mm. in one hour during the last year, was 20 mm. at the beginning of the clinical trial.

The response to cortisone was marked but not dramatic. The left knee was no longer painful at rest and the wrist-joint tenderness was less, although it did not entirely disappear. The effusion in the left knee subsided. She assessed her own improvement as only 30%, in spite of the fact that she was able to go up and down a flight of steps in eight seconds at the end of the trial, whereas previously it had taken her double that time.

A month later she had retained all her improvement and the E.S.R. was 12 mm. in one hour.

## Discussion

### Progesterone

Sommerville, Marrian, Duthie, and Sinclair (1950) found that rheumatoid arthritics of both sexes excrete an unusually high proportion of intramuscularly administered progesterone in the urine as pregnanediol. This suggests inadequate metabolism of progesterone, and the observation in one case of the present series, that the pregnanediol excretion was higher when the progesterone proved clinically beneficial than later when it failed to reproduce clinical benefit, would support this contention. Alexander and Duthie (1950) reported five cases treated with progesterone in doses lower than those used in the present study, with no improvement.

### Pregnenolone

Davison *et al.* (1950) reported improvement in cases of rheumatoid arthritis and ankylosing spondylitis with 300 mg. daily and also in lower dosage. They noticed clinical improvement within a week, with reduction in the E.S.R., and claimed that, although pregnenolone is less rapidly effective than cortisone or adrenocorticotrophic hormone (A.C.T.H.), it appears to be free from toxic effects and is cheap and easy to make. Ishmael *et al.* (1949) reported promising results in various rheumatic conditions, including rheumatoid arthritis, with 100 mg. daily. Freeman *et al.* (1950) claimed good results with pregnenolone by mouth in daily doses of 500 to 700 mg. Stock and McLure (1950) obtained objective improvement in three cases out of ten treated for two weeks with 200 mg. daily. Guest *et al.* (1950) treated 17 cases, of which only one showed improvement.

It was impossible to detect any improvement in the eight patients given pregnenolone in the present series.

### Pregnadienolone

This compound has a double bond between $C_{16}$ and $C_{17}$. It seemed possible, therefore, that it might give rise to a metabolic derivative in which the double bond had been converted into a hydroxyl substituent at the 17-carbon atom, such as is found in compound E and "compound F." It did not prove effective, however, in clinical trial.

### Cortisone

Mason, Myers, and Kendall (1936) reported on the physiological activity of the crystalline compound E which they had isolated from the adrenal cortex. The same compound was also isolated by Wintersteiner and Pfiffner (1936) and by Reichstein (1936).

The metabolic effects of this and other cortical compounds have been reviewed by Venning (1948). Recently the results of metabolic studies on patients with rheumatoid arthritis treated with cortisone have been published by Sprague *et al.* (1950). Carlisle (1950) has summarized its clinical uses.

In the original series of 14 patients studied at the Mayo Clinic (Hench *et al.*, 1949) all responded dramatically with loss of stiffness, pain, and tenderness, and improvement in articular and muscular function, often within 48 hours. Sedimentation rates decreased within one or two weeks. Every patient except one relapsed when treatment was discontinued.

Boland and Headley (1949) reported the results of treating eight cases of rheumatoid arthritis with cortisone. In five the disease was severe and the initial dose of 300 mg. was followed by 100 mg. daily for seven days. All improved "rapidly and remarkably" except for one diabetic patient, who improved more slowly but also relapsed more slowly when the drug was withdrawn. Lower doses (50 mg. daily for 10 to 15 days) were given in the three less severe cases, and by the end of the course the clinical manifestations had subsided almost completely and the sedimentation rate was normal. No side-effects were noted.

Hench *et al.* (1950) reported a further series of 21 patients. Improvement was either "marked" or "very marked" except in one case in which it was only moderate. According to these experienced workers the sequence of events is usually as follows: decreased stiffness and aching; diminished tenderness and swelling within the first 12 to 48 hours; complete relief of pain and sometimes swelling during the first week.

Freyberg (1950) recorded 17 cases treated with cortisone with uniformly good results, which could be maintained with 100 mg. three times a week.

Boland (1950) reviewed the literature concerning 160 cases of rheumatic disease, mostly rheumatoid arthritis, which had been treated with cortisone. In rheumatoid arthritis results have with very few exceptions confirmed the dramatic findings of Hench *et al.* (1949).

Side-effects can best be avoided and clinical remission maintained by giving 200 mg. of cortisone on the first day and subsequently 100 mg. daily until the clinical symptoms and E.S.R. subside (usually in two to eight weeks). Dosage is then gradually reduced to the lowest level that will control the condition.

The present study records the results of the first European clinical trial of cortisone in the treatment of rheumatoid arthritis, and each of the five patients treated has shown unequivocal response which completely confirms the claims of the American workers.

*Eosinophils.*—Most authors (Thorn *et al.*, 1950) report that whereas with A.C.T.H. there is complete disappearance of eosinophils starting about six hours after the first injection, with cortisone there may be no significant eosinopenia. In the present series there was a marked diminution in eosinophils, which was maintained while cortisone was administered.

### Side-effects

Side-effects consisting in sodium retention, leading to oedema, alkalosis, glycosuria, acne, hirsutism, striae, and the rounding of the face seen in Cushing's syndrome, have occasionally been recorded after prolonged cortisone therapy. With the recent tendency to use lower maintenance doses, however, they occur less commonly, and according to Baehr and Soffer (1950) are more likely to be seen during the treatment of such acute conditions as disseminated lupus erythematosus than in rheumatoid arthritis. Boland (1950) suggests that they should be referred to as "signs of hyperadrenalism" rather than as "toxic effects."

Freyberg (1950) has encountered no serious complications in a series of 17 patients treated with cortisone, some for as long as 160 days. Hench *et al.* (1950) reported mild and reversible side-effects in eight out of 21 patients treated for periods of up to seven months; in four patients the side-effects were pronounced.

Treatment had to be discontinued in the present series on four occasions (see Table)—in two cases because of an urticarial reaction, presumably to the vehicle, and in the others on account of severe pain at the site of the injection. No side-effects occurred in any of the cases treated with cortisone, although a careful watch was kept for signs of oedema, rounding of the face, acne, glycosuria, and hypertension.

The psychological reactions of the patients were interesting; all were delighted with their improvement, but none was unnaturally excited or displayed euphoria or exhibitionism. This may be because they were warned, as had the patients receiving the other steroids, that there was a ten-day supply only for each of them and that it would therefore be necessary to discontinue treatment at the end of that time even if improvement occurred.

### Summary

Forty patients suffering from rheumatoid arthritis have been submitted to clinical trials with cortisone and five other steroid compounds.

The following criteria were used to assess the effects of these compounds: (1) Recorded interviews before, during, and after treatment. (2) Filming of certain movements in selected cases. (3) Assessment of joint tenderness and range of movement. (4) Functional tests such as walking, climbing steps, putting on a coat, and mounting a chair. (5) Personal assessment of improvement by the patient. (6) Eosinophil counts, erythrocyte sedimentation rate, and haemoglobin determination. (7) Urinary 17-ketosteroid, pregnanediol, and "corticoid" estimations.

Cortisone was used in five cases, with cholesterol as a control substance. Although it was not known at the time of administration which compound was being used, the dramatic clinical effects of cortisone were immediately obvious.

The other steroid compounds employed were androstenedione, dehydro-*iso*-androsterone, progesterone, pregnenolone, and pregnadienolone. These proved ineffective, except in one case treated with progesterone in which there was a remission of symptoms, which was not repeated when a second course was administered.

We wish to acknowledge the valuable assistance given to us by the following pathologists and biochemists and their assistants: Dr. H. E. Archer, West London Hospital; Dr. A. G. Signy, St. Mary Abbots Hospital; and Dr. R. G. L. Waller, West London Hospital.

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Sir Jack Drummond, F.R.S., of Boots Pure Drug Co., Ltd.; and pregnenolone and pregnadienolone by Dr. B. M. Merriman, of British Drug Houses Ltd. Other substances, including material for controls, were kindly supplied by the following firms: Messrs. Allen and Hanburys Ltd., Bayer Products Ltd., Benger Laboratories Ltd., Ciba Laboratories Ltd., and Roche Products Ltd.


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A "Brochure of Instruments and Accessories for Radio-isotope Applications" has just been issued by the Scientific Instrument Manufacturers Association (of Great Britain, Ltd.) in collaboration with the Atomic Energy Research Establishment, Harwell. It is likely to be a useful booklet for all interested in employing radio-isotopes in their work, since it is in effect a directory to all instrument manufacturers, to consultants capable of advising in work of this kind, and to the suppliers of radio-isotopes (at Harwell and at the Radiochemical Centre, Amersham), as well as providing a short discussion on the kinds of instruments to be employed in different situations. Thus Geiger-Müller counters may register either the total radiation they receive in a given time or the rate at which they receive it; they may be sealed off or have an arrangement for introducing the substance to be assayed for radioactivity actually into the counter tube. Scintillation counters contain phosphors which sparkle as gamma rays strike them, and a device for counting the flashes. Ionization chambers measure in a given time the total radiation due to nuclear particles striking the atoms of gas in the chamber. Several kinds of instruments are available for health monitoring. A small direct-reading ionization chamber set in a fountain-pen-like cylinder measures the cumulative exposure to radiation of the person who wears it in his pocket. A hand-and-foot monitor looks something like a weighing-machine, on which the person under examination stands. Under its platform are two G.-M. counters, which measure the radiation from dirt on the shoes, while at arm height are pockets into which the hands can be thrust to have their radioactivity assayed by further adjacent counters. Two frisking probes are counters attached to the sides of the machine by long flexible leads. It is interesting to note that no less than six different firms make G.-M. counters, and eight produce monitoring instruments. In addition to the official isotope information office at Harwell there are also three private firms of consultants in this field of work. Copies of the brochure can be obtained free of charge from the publishers.

# INSULIN AND E.C.T. IN TREATMENT OF RHEUMATOID ARTHRITIS

## REPORT ON A PILOT SERIES OF CASES


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Insulin has been used as a "tonic" and as a method of increasing weight in rheumatoid arthritis for a number of years (Copeman, 1931). The more recent theories of the part played by the pituitary adrenal mechanism in this disease have suggested another reason for this type of therapy. Cannon *et al.* (1924) found that insulin hypoglycaemia provoked the liberation of adrenaline, and since then evidence has been produced which is claimed to show that the adrenal cortex can be stimulated in this way, either directly in hypophysectomized animals or indirectly by stimulation of the pituitary with liberated adrenaline (Langecker, 1928; Miller *et al.*, 1941; Godlowski, 1947). It seemed that this explained the benefit obtained from insulin shock therapy and electric convulsion therapy (E.C.T.) in many mental disorders. Moreover, it had been noted that the combination of rheumatoid arthritis and epilepsy was extremely rare. On the suggestion of one of us (M. H. L. D.) it was decided to treat a pilot series of cases of active rheumatoid arthritis with insulin hypoglycaemia and a second series with E.C.T., and observe the clinical and biochemical results.

### Methods and Techniques

All patients were suffering from active rheumatoid arthritis, and in addition to insulin therapy all received the same basic regime of treatment, which included rest splints, remedial exercises, and physiotherapy. Treatment was not begun until patients had had two weeks' basic physical treatment in hospital.

The method used was based on the modified insulin technique as described by Sargant and Slater (1948). Attempts were made to induce hypoglycaemic reactions every morning for five days each week, leaving Saturday and Sunday free of treatment. Treatment was carried out over a period of three or four weeks. A good hypoglycaemic reaction was indicated by marked flushing and sweating, weakness, drowsiness, and tremor. The reaction was normally interrupted three hours after the dose of insulin by a meal containing 16 oz. (454 g.) of mashed potatoes flavoured with an egg, or other suitable breakfast dish, together with bread-and-butter, jam, porridge, and sugared tea. Only if the patient went into sopor or coma, or had convulsions, was hypoglycaemia interrupted earlier by intravenous glucose. This had to be carried out in four patients (Cases 21, 23, 30, 33).

Patients were assessed clinically every week, before, during, and just after treatment, and also at varying periods after treatment was completed. The assessment included observations on the general feeling of well-being, mental outlook, subjective pain (including rest pain),