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# TRIALS OF CORTISONE ANALOGUES IN THE TREATMENT OF RHEUMATOID ARTHRITIS

BY

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In 1954 the first report appeared of a controlled trial of aspirin *versus* cortisone in the treatment of early cases of rheumatoid arthritis (Medical Research Council-Nuffield Foundation Joint Committee, 1954). The trial showed that, after treatment for a year, the group receiving cortisone (mean dose 75 mg. daily) had fared no better than that receiving only aspirin. Some of the patients had had radiographs taken of their hands and feet at the start of the trial and at the end of the first year. Bone erosion was found to have advanced in both groups. The score for advance was slightly greater in the aspirin group, but the difference was not statistically significant. In a second trial of patients who had had rheumatoid arthritis for a mean duration of 7 years (Empire Rheumatism Council, 1955), the findings were essentially the same. Again the deterioration seen in serial radiographs was almost as much in the cortisone-treated group as in that receiving only aspirin.

Many research workers interested in the rheumatic diseases turned away from the study of corticosteroids at this point. To them corticosteroids were just non-specific suppressors of the inflammation arising from a disease process, and had no effect upon the rheumatoid process itself. Little importance was attached to the observation that a rheumatoid patient might respond well to a moderate dose of cortisone and subsequently lose the benefit gained while still on the same dose.

When the delta 1-2 analogues of cortisone and cortisol (prednisone and prednisolone) became available, further controlled trials were started. The first was a controlled trial of cortisone *versus* prednisone in rheumatoid patients who were in their second, third, or fourth year of cortisone treatment (Medical Research Council-Nuffield Foundation Joint Committee, 1957). The prednisone-treated group fared much better than the cortisone-treated group, but the significance of this finding was obscured by the relatively larger dose of prednisone given. This is well shown in Fig. 1 (opposite), which gives the mean doses, erythrocyte sedimentation rates and strengths of grip of the 21 patients from this Centre who took part in the trial. Had a 1 to 5 prednisone to cortisone dose been employed, the therapeutic superiority of prednisone, of which we are now aware, would have been apparent. More recently, fourteen patients from this trial who had been kept on cortisone for a second year were transferred to prednisolone. On this occasion the dose ratio employed was 1 to 6 prednisolone to cortisone. By the end of 6 months their mean erythrocyte sedimentation rate (Wintrobe) had fallen from 24·6 to 15 mm./hr, and their mean strength of grip had risen from 271 to 299 mm. Hg (both hands). In the previous year, while they were on cortisone therapy, there had been no change in these indices.

The second prednisone trial was for patients with rheumatoid arthritis of 3 to 24 months' duration who had not previously received corticosteroid therapy. The control group received analgesics *ad lib* (Medical Research Council-Nuffield Foundation Joint Committee, 1959). The superiority of prednisone was quickly apparent in those of our patients (21) who were in this trial. At the end of the first year practically all the radiographs that showed a marked advance in bone erosion were found to belong to the group treated with analgesics! Since many of these patients were receiving phenylbutazone, the question arose whether prednisone favourably affected the course of rheumatoid arthritis or whether phenylbutazone affected it *unfavourably*. It was easy to imagine that an analgesic like phenylbutazone relieved a lot of pain and thereby allowed destructive changes to proceed more rapidly. A comparison between the advance in bone erosion seen during phenylbutazone therapy and aspirin therapy was therefore called for; so we reviewed the radiographic changes seen in those of our patients who received aspirin in the first aspirin-cortisone trial, together with those in the patients who received aspirin in the second cortisone-aspirin trial in whom the disease was of short duration. We found that the advance in bone

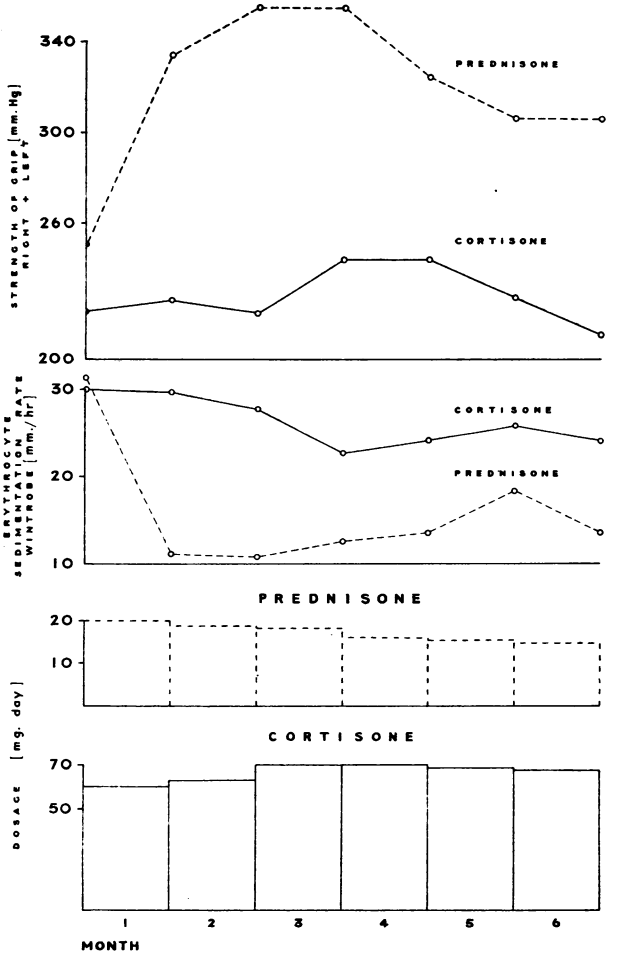



Fig. 1.—21 patients who had received cortisone for a year or more allocated at random to continue with cortisone or change to prednisone.

Mean dose, erythrocyte sedimentation rate, and strength of grip for each group for the first 6 months of the trial.

erosion during a 2-year period was of the *same order* as that seen in our patients who received phenylbutazone in the second prednisone trial.

Table I (overleaf) shows the present "*x*-ray score" for our patients in the second prednisone trial.* There thus remained little doubt that the slowing up, and in some cases arrest, of bone erosion in the prednisone-treated patients was due to the prednisone given.

Prednisone and prednisolone are the first substances shown to have a favourable effect on the course of rheumatoid arthritis, using objective data, in a fully controlled trial. Unfortunately, as is well known, they fall far short of our needs. Using the maximum safe doses for maintenance therapy, some patients with severe disease receive little relief and in the majority who do benefit the degree of benefit appears to diminish as the years go by. Further, many would say that the mean dose of prednisolone that we have used, namely 11 mg. a day, is not a safe dose. This being so, it is encumbent upon us to study each new promising cortisone analogue, in controlled trials, in the hope that one may be found that is of greater value. The questions to be asked are:

(1) Will the new analogue be effective, in a safe dose, when prednisolone has ceased to be so?

* It should be mentioned that many of the patients in the prednisone trials received prednisolone in the second and third years, since there was no evidence to suggest that prednisone and prednisolone differed qualitatively.

TABLE I

RADIOGRAPHS OF SIXTEEN PAIRS OF HANDS AND FEET FROM PATIENTS IN THE ANALGESICS GROUP AND TWENTY PAIRS OF HANDS AND FEET FROM PATIENTS IN THE PREDNISONE-PREDNISOLONE GROUP GRADED BY DEGREE OF CHANGE IN BONE EROSION SEEN AFTER MEAN INTERVALS OF 30 AND 36 MONTHS RESPECTIVELY. OBSERVED CHANGES ARE EXPRESSED AS A PERCENTAGE FOR EACH GROUP.

| Therapy | Mean Interval (mths) | Change in Bone Erosions (per cent.) | | | | |
|---|---|---|---|---|---|---|
| | | Advance | | | No Change | Healing |
| | | +++ | ++ | + | | |
| Analgesics, mainly Phenylbutazone .. | 30 | 37·5 | 19 | 37·5 | 6 | 0 |
| Prednisone-Prednisolone (mean dose 11 mg.) .. .. .. .. .. | 36 | 0 | 20 | 20 | 55 | 5 |

(2) Will it be more effective than prednisolone *ab initio*?

(3) Will it maintain its effect for a longer period than prednisolone?

## Present Investigations

Below are reports of some controlled trials of triamcinolone (16 hydroxy 9α fluoro prednisolone). It has been our experience, in the four trials mentioned above, that our own comparatively small group of participants have behaved in the same way as the total groups, so that we feel justified in drawing some conclusions from the groups of 9, 17, and 31 patients who were studied by us, and whose cases are reported in this paper.

(1) *Efficacy of Triamcinolone after Prednisolone.*—In order to answer the first question, 34 patients suffering from rheumatoid arthritis, who had been receiving prednisolone continuously for more than a year, were allocated at random to continue with prednisolone or to change to triamcinolone. In order to make a fair comparison, it was necessary to choose maximum safe dose levels for prolonged therapy for each hormone. The choice made will be considered in the discussion. Table II shows the composition of the groups after the exclusion of three patients who fell out for reasons unconnected with the trial. Certain differences were seen between the groups that may favour the triamcinolone group. A study of other similar controlled trials has shown that the overall progress is reflected most clearly in the changes in the erythrocyte sedimentation rate and in the strength of grip.

TABLE II

CHARACTERISTICS OF TREATMENT GROUPS AT BEGINNING OF TRIAL

| Drug .. .. .. .. .. .. .. .. .. .. .. .. | Prednisolone | Triamcinolone |
|---|---|---|
| Number of Patients .. .. .. .. .. .. .. .. .. | 17 | 14 |
| Sex .. .. Male .. .. .. .. .. .. .. .. .. | 6 | 3 |
| Sex .. .. Female .. .. .. .. .. .. .. .. .. | 11 | 11 |
| Mean Age (yrs) .. .. .. .. .. .. .. .. .. .. | 55 | 44½ |
| Range (yrs) .. .. .. .. .. .. .. .. .. .. | 42-67 | 35-60 |
| Mean Duration of Rheumatoid Arthritis (yrs) .. .. .. .. .. .. | 12½ | 9½ |
| Range (yrs) .. .. .. .. .. .. .. .. .. .. | 1-32 | 2-34 |
| Mean Duration of Previous Prednisolone Therapy (yrs) .. .. .. .. | 2 | 2 |
| Range (yrs) .. .. .. .. .. .. .. .. .. .. | 1-2¾ | 1-2¾ |
| Mean Dose of Prednisolone before Start of Trial (mg./day) .. .. .. .. | 11·2 | 11 |
| Range (mg./day) .. .. .. .. .. .. .. .. .. | 10-15 | 5-15 |
| Mean Grip (mm. Hg) Right/Left .. .. .. .. .. .. .. .. | 106/111 | 122/131 |
| Range (mm. Hg) Right/Left .. .. .. .. .. .. .. .. | 50/40-210/240 | 45/50-240/202 |
| Mean Erythrocyte Sedimentation Rate (Wb) (mm./hr) .. .. .. .. | 26 | 23·4 |
| Range (mm./hr) .. .. .. .. .. .. .. .. .. | 6-41 | 8-43 |
| Mean Functional Capacity* .. .. .. .. .. .. .. .. | 2·6 | 2·6 |

* Gradings of functional capacity from 1 to 5 as in the M.R.C./Nuffield Trials:
Grade 1 = Physically "normal" for age and sex.
Grade 5 = Bedfast and completely helpless.

Fig. 2 shows the changes in these indices in the various groups and the mean monthly doses employed. Mean haemoglobin levels and mean white blood counts did not differ significantly. The subjective estimates went slightly in favour of triamcinolone. The assessments of functional capacity remained unchanged for the prednisolone group, but improved a little in the triamcinolone group. What may be of significance is that three of the five triamcinolone patients who showed a very definite improvement relapsed in the last 2 months. Other observations made are set out in Table III.

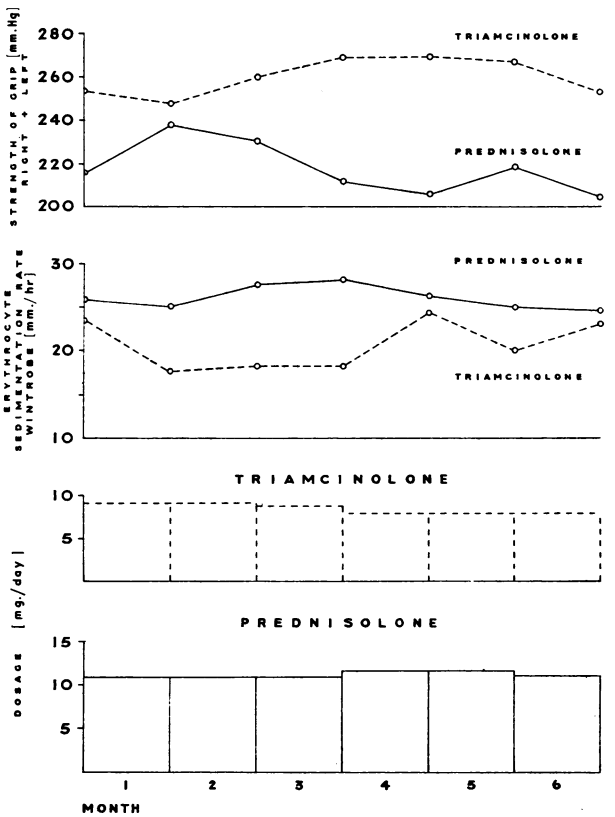



Fig. 2.—Mean monthly dose, erythrocyte sedimentation rate (Wb), and strength of grip (right hand plus left hand) for triamcinolone and prednisolone patients. The previous mean dose of prednisolone for each group is shown in Table I. The maximum grip allowed for each hand was 260 mm. Hg.

TABLE III

CHANGES IN CERTAIN CHARACTERISTICS BETWEEN WEEK 0 AND WEEK 24 IN TWO GROUPS OF PATIENTS WHO HAD HAD PREVIOUS PREDNISOLONE THERAPY

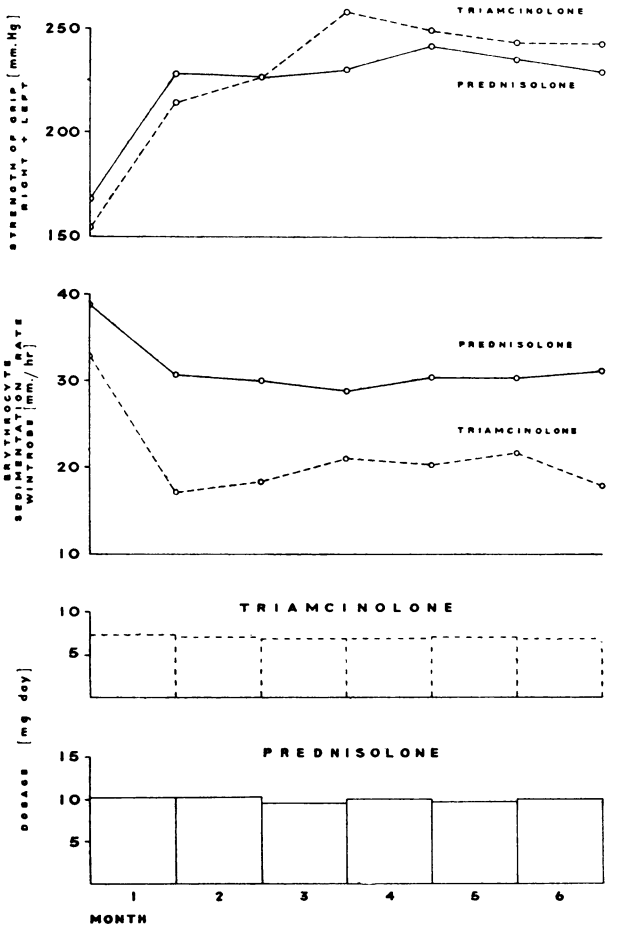
| Observation | Drug | Changes Seen |
|---|---|---|
| Weight (kg.) | Prednisolone<br>Triamcinolone | Rise from 64·5 to 66·4<br>Fall from 63 to 60 |
| Mean Blood Pressure (mm./Hg) | Prednisolone<br>Triamcinolone | 147/90 to 150/90<br>149/89 to 148/89 |
| Appetite | Prednisolone<br>Triamcinolone | 1 up; 1 down<br>1 up; 5 down |
| Dyspepsia | Prednisolone<br>Triamcinolone | 10 at start } Slightly less in each group<br>8 at start } |
| Sleep | Prednisolone<br>Triamcinolone | 2 more; 2 less<br>2 more |

TABLE IV

CHARACTERISTICS OF TREATMENT GROUPS AT START OF TRIAL

| Drug | | Prednisolone | Triamcinolone |
|---|---|---|---|
| Number of Patients | | 8 | 9 |
| Sex | Male | 2 | 2 |
| | Female | 6 | 7 |
| Mean Age (yrs) | | 40 | 50 |
| Range (yrs) | | 27-53 | 34-66 |
| Mean Duration of Rheumatoid Arthritis (yrs) | | 3 | 5 |
| Range (yrs) | | ¼-11 | ½-20 |
| Mean Grip at Start of Trial (mm./Hg) Right/Left | | 84/83 | 88/66 |
| Range (mm./Hg) | | 55/48-155/125 | 30/20-170/110 |
| Mean Erythrocyte Sedimentation Rate (Wb) at Start of Trial (mm./hr) | | 39 | 33 |
| Range (mm./hr) | | 22-56 | 19-55 |
| Mean Functional Capacity* | | 2·75 | 3 |

* Gradings of functional capacity are as in Table II. Grade 3 = Unemployable and able to do only a limited amount of light housework.




(2) *Efficacy of Triamcinolone without Previous Corticosteroids.*—In the second trial, conducted in the same way but with patients who had received no previous corticosteroid therapy, seventeen patients were assessed monthly for 6 months. Table IV (above) shows the characteristics of the groups at the start.

Table V (opposite) shows certain changes in the characteristics between Week 0 and Week 24.

Fig. 3 depicts the monthly mean dose, erythrocyte sedimentation rate, and strength of grip.

Subjective changes were correlated with the change in erythrocyte sedimentation rate, the triamcinolone group showing a greater reduction in morning stiffness and more overall benefit. Although these patients

Fig. 3.—Mean monthly dose, erythrocyte sedimentation rate (Wb), and strength of grip for triamcinolone and prednisolone patients. All had been receiving analgesics before the trial began.

TABLE V

CHANGES IN CERTAIN CHARACTERISTICS BETWEEN WEEK 0 AND WEEK 24 IN TWO GROUPS OF PATIENTS WHO HAD HAD NO PREVIOUS CORTICOSTEROID THERAPY

| Drug | Prednisolone | Triamcinolone |
|---|---|---|
| Erythrocyte Sedimentation Rate (Wb) (mm./hr) | 39→32 | 33→18 |
| Hb (g./100 ml.) | 13·3→14·1 | 12·1→14·6 |
| Total Leucocyte Count | 8,400→8,700 | 8,000→8,600 |
| Functional Capacity | 2·75→2·25 | 3→2 |
| Strength of Grip (mm. Hg) | 84/83→112/119 | 88/66→116/125 |
| Weight (kg.) | 60→63 | 59·3→58·6 |
| Blood Pressure (mm. Hg) | 133/79→135/85 | 134/79→136/85 |

failed as a group to gain weight, four reported increased appetite and none reported a loss of appetite. The incidence of dyspepsia in each group was low.

(3) *Triamcinolone and Steroid-Induced Hypertension.*—Another trial was made to assess the effect of triamcinolone upon the blood pressure of patients who had become hypertensive during previous corticosteroid therapy. Freyberg, Berntsen, and Hellman (1958) found that the hypertension "often decreased" after triamcinolone administration.

Nine of our patients who had received prednisolone, or cortisone followed by prednisolone, for several years were transferred to triamcinolone and their blood pressures were recorded monthly. The mean blood pressure of the group before corticosteroid therapy was 135/80 mm. Hg; during the 6 months before the change to triamcinolone the diastolic blood pressure of each patient had risen to or exceeded 100 mm. Hg at least on one occasion. Fig. 4 shows the mean blood pressure and corticosteroid dose for the 6 months before and after the change over. No fall was observed during triamcinolone therapy.

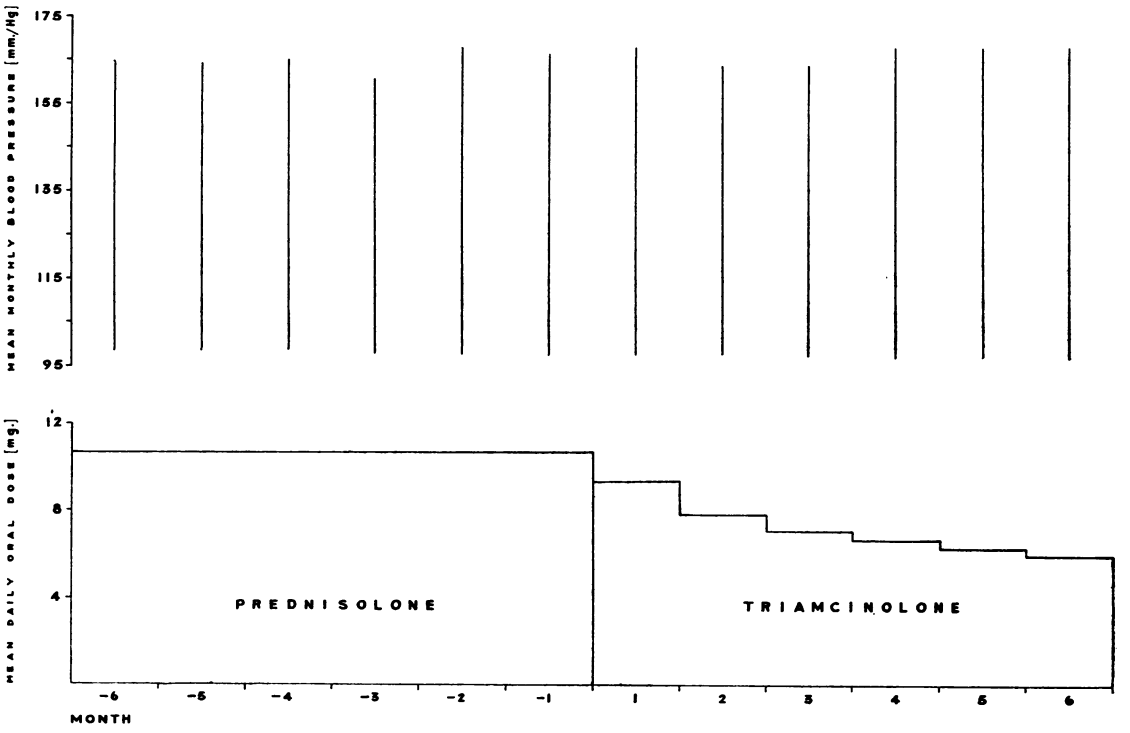



Fig. 4.—Mean blood pressure and corticosteroid dosage at monthly intervals before and after the transfer from corticosteroids to triamcinolone of nine patients whose blood pressure had risen during prolonged corticosteroid therapy.

## Discussion

As no corticosteroid yet developed cures rheumatoid arthritis, we are at present concerned with finding the cortisone analogue that in prolonged use provides the most benefit without adding disease to disease. So far no new analogue has proved, in therapeutic doses, to be free from unwanted metabolic effects. This being so, it is essential that in therapeutic trials dose levels should be chosen that can be maintained safely for long periods. The varied opinions held by those who speak from experience about the value of different corticosteroids in the treatment of rheumatoid arthritis show how important it is that the trials should be "controlled".

(1) The interpretation of the first trial reported above depends upon whether 8 to 9 mg. triamcinolone are equivalent to 11 to 12 mg. prednisolone in the production of unwanted metabolic effects. No precise tally can be made of these effects when they are mild, as in this trial. Our impression is that 9 mg. triamcinolone is certainly not less productive of unwanted effects than 12 mg. prednisolone. Both amounts are at the upper limit of what we consider a safe therapeutic dose. In our opinion the findings justify the statement, in answer to the first question, that the change from prednisolone to triamcinolone has not resulted in a renewed response of the type seen when prednisolone replaces cortisone in a 1 to 5 ratio.

(2) The second trial, which was for rheumatoid arthritic patients who had not previously received corticosteroid therapy, showed the triamcinolone group at a considerable advantage when the mean dose levels were 7 mg. triamcinolone and 10 mg. prednisolone. We were not surprised at the marked improvement seen in the triamcinolone group, but had expected to see more improvement in the prednisolone group. A comparison of the characteristics of the groups at the beginning of the trial did not suggest that the prednisolone group were likely to run a less favourable course. Some readers may be surprised at the relatively small overall improvement in the prednisolone patients in view of the common saying that 60 to 70 per cent. of rheumatoid arthritic patients improve on any form of treatment. The reason for the apparent discrepancy lies in the fact that the patients we have treated with corticosteroids were not representative of rheumatoid patients as a whole but were drawn from the 5 per cent. in whom the disease appeared to be running a severe course. This trial was made to help answer the second question. If it is agreed that the doses used were the maximum safe doses for each steroid, the answer must be that triamcinolone was more effective; but it may be that the small number of patients studied does not justify this conclusion. This second trial is being continued in the hope that it will contribute to an answer to the third question.

(3) The third trial was designed to study the effect of triamcinolone on cortisone- or prednisolone-induced hypertension. Our failure to confirm the observations of Freyberg, Berntsen, and Hellman (1958) was caused, we think, by our use of a smaller dose of triamcinolone. When the original 2-mg. tablet was replaced by the 4-mg. tablet, two of our hypertensive patients received a daily dose of 16 instead of 8 mg. The blood pressure of both patients fell markedly, only to climb back to the hypertensive levels as the dose was gradually reduced to 8 mg. In the first two trials there was no significant change in the blood pressure in either group. It will be necessary to follow triamcinolone therapy for much longer than 6 months before it can be decided whether this analogue will or will not induce hypertension. It is, of course, only a minority of patients who develop hypertension during prolonged cortisone or prednisolone treatment. When prednisolone replaced cortisone it was suggested that with less salt retention there should be less hypertension, but this did not prove to be the case.

The only other "side-effect" encountered in these trials that calls for special comment was loss of weight.

It will be seen that, in the first trial, the triamcinolone patients lost, on average 3 kg. in 6 months. This loss was approved by most patients and in the majority the fall in weight appeared to have stopped by the sixth month. In the trial with previously untreated patients there was a mean fall of 0·7 kg. in the triamcinolone patients, none of whom had experienced a decrease in appetite. Some, of course, began with poor appetites. Such a group of rheumatoid arthritic patients would be below their normal weight at the start of therapy and we should expect their weight to *rise* as the disease subsided. There have been a number of reports of gross weight loss and also of muscle wasting in patients treated with triamcinolone. The fact that we have not seen such changes may be due to the moderate dose level that we have used, nevertheless, the losses in weight that we *have* seen cannot be dismissed as necessarily harmless.

*Dexamethasone.*—The three questions proposed at the beginning of this paper will have to be answered for dexamethasone (16-methyl 9α fluoro prednisolone). Our own trial of this very interesting hormone in patients habituated to prednisolone

therapy is collapsing through our inability to obtain, in some patients, an anti-rheumatic effect without inducing an uncontrollable weight gain. It is not possible to study these cortisone analogues without constantly speculating as to the factors that determine their diverse properties and potencies. It seems to one of us that differences in the protein-binding in the plasma of these hormones plays some part. Another factor, of more importance, concerns the mechanism in different tissues, and in different sites within these tissues, that determines the concentration of physiologically-active hormone available within the cells. Alterations in the configuration of the hormones appears to affect such concentrations from site to site in different degree. The physiological effects that follow no doubt depend upon the function of the particular tissue concerned.


## Summary

Four controlled trials of cortisone and prednisone have been reviewed and some related data added.

Three trials of triamcinolone are reported:

**Trial 1.**—To assess the value of changing therapy from prednisolone to triamcinolone, 31 rheumatoid arthritic patients were studied who had been receiving prednisolone for from 1 to 3 years. They were allocated at random to continue with prednisolone or change to triamcinolone. The doses used, a mean of 11·5 mg. prednisolone and 8·5 mg. triamcinolone, were, in our opinion, at the upper limit of safety for prolonged administration for each hormone. The patients in each group were assessed at monthly intervals for 6 months. It was concluded that the slight apparent advantage gained by the triamcinolone patients was not such as to suggest that triamcinolone will favourably affect the course of rheumatoid arthritis when prednisolone has ceased to do so.

**Trial 2.**—Seventeen rheumatoid arthritic patients, who had not previously been treated with corticosteroids and who were deemed to belong to the 5 per cent. of rheumatoid arthritics in whom the disease runs a severe course were allocated at random to receive prednisolone or triamcinolone. The mean doses used were 10 mg. and 7 mg. respectively. These patients were studied in the same way as those in the first trial. The results showed a definite advantage for the triamcinolone patients. Over a 6-month period the doses used did not give rise to serious side-effects.

**Trial 3.**—Nine patients who had become mildly hypertensive during cortisone and prednisolone therapy were given triamcinolone instead; the mean blood pressure did not alter in the 6 months before and after the change in therapy.


One of us (H.F.W.) is the holder of a part-time research fellowship of the Nuffield Foundation. We also wish to thank Lederle Laboratories for a generous supply of Triamcinolone (Ledercort).

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## Essais des analogues de la cortisone dans le traitement de l'arthrite rhumatismale

RÉSUMÉ

On passe en revue quatre essais thérapeutiques contrôlés de la cortisone et de la prednisolone et on ajoute quelques données pertinentes. On relate trois essais de la triamcinolone:

*Essai I.*—Pour évaluer la triamcinolone par rapport à la prednisolone administrée antérieurement, on étudia 31 malades atteints d'arthrite rhumatismale et traités par la prednisolone pendant 1 à 3 ans. On les assigna au hasard à deux groupes: l'un qui continua à recevoir de la prednisolone et l'autre qui fut transféré à la thérapie par triamcinolone. Les doses employées (11,5 mg. de prednisolone et 8,5 mg. de triamcinolone en moyenne) furent, à notre avis, à la limite supérieure de sécurité pour l'administration prolongée de chaque hormone. Dans chaque groupe, les malades furent évalués tous les mois pendant 6 mois. On conclut que le léger avantage apparent de la triamcinolone ne fut pas suffisant pour affecter favorablement l'évolution de l'arthrite rhumatismale quand la prednisolone avait cessé d'agir.

*Essai II.*—On étudia 17 malades atteints d'arthrite rhumatismale et censés appartenir à ces cinq pour cent des rhumatisants chez qui la maladie suit une évolution très sévère. Aucun d'entre eux n'avait reçu de corticostéroïdes auparavant. On les assigna au hasard à recevoir soit de la prednisolone soit de la triamcinolone. Les doses moyennes furent 10 mg. et 7 mg. respectivement. Les malades furent évalués de la même manière que dans le premier essai. Les résultats accordèrent un avantage défini aux malades à la triamcinolone. Les doses employées pendant 6 mois ne produirent pas d'effets secondaires sérieux.

*Essai III.*—Chez neuf malades, chez qui la tension artérielle avait monté un peu pendant le traitement par la cortisone et la prednisolone, on substitua la triamcinolone; la tension artérielle moyenne ne changea pas pendant 6 mois qui précédèrent ou se succédèrent au changement thérapeutique.

## Ensayos de los análogos de la cortisona en el tratamiento de la artritis reumatoide

SUMARIO

Se pasan en revista cuatro ensayos terapéuticos controlados de la cortisona y de la prednisolona y se añaden algunos datos pertinentes. Se relatan tres ensayos de la triamcinolona.

*Ensayo I.*—Para valorar el cambio terapéutico de la prednisolona a la triamcinolona, se estudiaron 31 enfermos con artritis reumatoide tratados con prednisolona por uno a tres años. Estos enfermos fueron repartidos al azar en dos grupos: uno que siguió con prednisolona y el otro que fué tratado con triamcinolona. Las dosis empleadas (11,5 mg. prednisolona y 8,5 triamcinolona en promedio) aproximáronse, a nuestro juicio, a los límites superiores de seguridad para la administración prolongada de cada hormona. En ambos grupos los enfermos fueron valorados cada mes durante seis meses. Se llegó a la conclusión de que la pequeña ventaja aparente de la triamcinolona no fué suficiente para afectar favorablemente la evolución de la artritis reumatoide, cuando la prednisolona había cesado de actuar.

*Ensayo II.*—Se estudiaron 17 enfermos con artritis reumatoide, perteneciendo aparentemente a aquel cinco por ciento de los reumáticos en que la enfermedad sigue una evolución muy severa. Ninguno de ellos había recibido corticoesteroides anteriormente. Se les asignó al azar al tratamiento sea con prednisolona, sea con triamcinolona. Las dosis medias fueron de 10 mg. y de 7 mg. respectivamente. Los enfermos fueron valorados del mismo modo que en el primer ensayo. Los resultados fueron netamente mejores en los enfermos tratados con triamcinolona. Las dosis empleadas durante seis meses no produjeron efectos secundarios serios.

*Ensayo III.*—Triamcinolona fué administrada a nueve enfermos en los cuales la tensión arterial había subido algo durante un tratamiento previo con cortisona o prednisolona. No se observó cambio alguno de la tensión arterial media en estos enfermos seis meses antes o después de cambiar el tratamiento.