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OBSERVATIONS ON PROLONGED CORTISONE ADMINISTRATION IN RHEUMATOID ARTHRITIS*

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In a preliminary study of the therapeutic effects of cortisone and other steroid substances in rheumatoid arthritis, certain methods of objective assessment by which relatively small clinical variations can be detected were described (Copeman *et al.*, 1950). The application of these methods to a further series of patients with active rheumatoid arthritis under treatment with cortisone for longer periods is the subject of the present report.

We have been mainly concerned in devising a suitable method of administration which will suppress the disease indefinitely and enable the patients to resume useful and independent lives, free from unpleasant side-effects. Haematological and metabolic changes occurring during routine administration of cortisone were investigated, and such side-effects as did occur in this small series were studied in detail.

Selection of Patients

The patients selected had suffered from active and undoubted rheumatoid arthritis for at least six months, and in most cases much longer, as shown by the clinical signs and a raised erythrocyte sedimentation rate. They were all regarded as "severe cases," since they could not carry out their normal occupation and had already become dependent on others. They described themselves as "crippled," though, since the joint changes as studied radiologically were often minimal, much of their disability was potentially reversible.

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Each of the 20 cases was observed for at least three months. Thirteen have been examined in detail by the methods of assessment previously described, with the addition of a finger-ring test (Hart and Clark, 1951), and concurrent metabolic studies. The remaining seven patients, who provided their own cortisone, were placed in the same clinical category, though they were submitted to a less extensive metabolic study. The length of study under continuous administration was as follows:

Months:	3	4	5	6	7	8	9	10	Total
No. of cases ..	1	3	4	3	6	1	1	1	20

Dosage Schedule

On the assumption that cortisone does not cure rheumatoid arthritis but only suppresses the disease (Hench, 1950), it was decided that as soon as the symptoms had been relieved adequately the dose should be lowered to a level at which this improvement might be maintained for a prolonged period without the appearance of undesirable reactions. Such a scheme has recently been favourably reported on by Boland (1951), who studied a much larger series for a longer period. Our dosage schedule therefore consisted of the following three phases: a period of initial high (suppressive) dosage; a period of gradual reduction of dosage; and a period of minimal (maintenance) dosage.

In most cases cortisone has been given by intramuscular injection during the first two periods (initial suppression and reduction of dosage). When the minimal maintenance level has been found the oral route was used. In this way we were able to compare the relative effectiveness of muscular and oral administration; furthermore, it was much more convenient for out-patients to take the compound by mouth.

Initial Suppressive Dosage

Two initial dosage schemes have been studied: (1) The "classical" method described by Hench, Kendall, Slocumb, and Polley (1949) in their original report—namely, 300 mg. on the first day, 200 mg. on the second, 150 mg. on the third, and subsequently 100 mg. daily; and (2) 100 mg. daily from the first day onwards. Doses of more than 100 mg. were divided into two injections, whereas 100 mg. and below was given once a day.

A daily dose of 100 mg. has been given until the patient has improved enough to lead a comfortable life and to have a reasonable prospect of returning to work. This level of improvement is assessed by the methods already described, which are based on disappearance of pain and tenderness and performance of functional tests (Copeman *et al.*, 1950). If possible, the patients leave the hospital for a day or two to test their functional capacity in their home surroundings.

Ten patients have been treated according to scheme 1 and 10 patients according to scheme 2. It is our impression that the lower dosage is sufficient and gives a smoother response, though there may be no measurable improvement for five to seven days.

"Boost" Dosage.—In our recent cases we have given a higher dose—200 mg. a day for 7 to 10 days—at the "comfortable" stage, which usually develops 14 to 21 days after treatment has begun, in order to obtain further improvement. Increasing experience with the "classical" initial dosage scheme has led us to the conclusion that, despite dramatic loss of pain and tenderness, patients who had often been "crippled" for months might be unable to take full advantage of the improvement owing to their prolonged relative immobility, and that they tended to develop pains due to muscular strain. By giving the "boost" dosage for a short time after the patients had been rehabilitated and had been free from pain for two weeks or more we frequently obtained a further gratifying degree of improvement.

Period of Gradual Reduction of Dosage

At a stage when the disease process seems to be satisfactorily under control the daily dose is reduced by 12.5 mg. (0.5 ml.) at a time. During this stage we find that careful methods of assessment are most important, as it is only in this way that the lowest maintenance dose can be found. The patient, knowing the dose is being reduced and fearful of relapse, will tend to exaggerate minor changes. Originally the dose was reduced every two or three days, but this proved to be too rapid, and dose reduction every five to seven days seems to be more satisfactory. The daily dose is raised by 12.5 mg. or more on changing over to oral administration, since, as other workers (Boland and Headley, 1951) have found, oral dose requirements are slightly larger. Eventually the oral dose is lowered in the same way as described for diminution of the intramuscular dose.

Maintenance Dosage

Because most cases of rheumatoid arthritis will require prolonged treatment with cortisone, as low a maintenance dose as possible must be found. Although this may need to be increased temporarily during periods of physical and mental stress, it will remain effective in most cases for prolonged periods without relapses occurring, and may even in some cases be further diminished as time goes on.

When the oral maintenance dose has been established the patient is discharged from hospital, encouraged to return to his normal duties, and asked to attend once a week for clinical and haematological assessment.

Oral Dosage.—The relative effectiveness of intramuscular and oral maintenance doses is subject to individual variations. In some cases the difference between the two is not more than 25 mg. a day. In at least one case (Case 7) the response seemed to be actually better when the drug was taken by mouth. In Case 6 it was impracticable to administer the drug intramuscularly as the patient was having a large dose of insulin at the same time. We have used "cortone" tablets in a few cases, but most of the oral administration has been in the form of the aqueous crystalline suspension produced for intramuscular injection, which is satisfactory except for its obnoxiously bitter taste, to which most patients become accustomed. We recommend that the dose should be measured accurately with a syringe into a spoon; in view of the tendency of the crystals to adhere to the sides of glass great care should be taken that none of the dose is wasted.

Clinical Assessment

The methods of assessment which we have previously described have provided a satisfactory means of controlling the dosage of cortisone. We now rely on them to a much greater extent than on metabolic or pathological investigations, including even the sedimentation rate. The methods as described are rather laborious for day-to-day clinical use, so that the full joint chart and set of functional tests are now completed only from time to time, six or seven representative joints and tests being chosen for day-to-day assessment.

Of the tests described, joint tenderness continues to correlate accurately with the clinical state. We are less impressed with the tests involving the study of the range of movement of individual joints—unless, as in the knee-joint, the range can be accurately measured between two fixed points—because the increase in range of movement is either too obvious to need measuring, or, if it is slight, measurements are not accurate enough to eliminate the error due to subjective bias on the part of the assessor.

We find the grip test particularly useful if the fingers, hands, or wrist-joints are involved. Similarly, the ring-size test is an accurate and objective measurement of the swelling in the interphalangeal joints.

Where stiffness is a prominent feature, tests involving speed of movement—for example, the speed with which the arms can be "flailed" or lifted vertically above the head in a fixed period of time, usually 15 seconds—are especially useful. Where the lower limbs are predominantly involved the rheumatoid "flop" disappears early in treatment and its study is of little use in assessing progress in the later stages; but the ability to stand on a chair without holding on, to kneel, and to lie on the ground and get up without help, or—in bedridden patients—the speed at which they can flex and extend their knee-joints, are all satisfactory tests.

In general it is important to choose the tests individually for each patient according to his particular disabilities. No single quota of tests can possibly be satisfactory if indiscriminately used.

Results

Of the 20 patients treated, improvement was graded as good in 12 cases (fully employed in normal work and able to undertake normal recreation and normal housework); fair in 5 cases (fully employed in light work—limited recreation and all but heaviest housework); and definite but poor in 3 cases (unemployable—limited physical activity—light housework).

Table I shows that cortisone treatment has enabled 17 of the patients chosen for this study to leave hospital and resume their previous work or, in the case of the women, carry out normal housework. In three patients the results were disappointing. In one (Case 4) we were unable to find a maintenance dose low enough to avoid adverse effects. In the other two (Cases 16 and 19) permanent joint damage was too severe for the patients to become independent of help.

In Case 1 cortisone appeared to induce a complete clinical remission which has lasted so far for eight months. In spite of this the patient has had a persistently raised sedimentation rate, suggesting that the condition is latent and not cured.

The maintenance dose necessary to keep a patient comfortable varies considerably from case to case, but the

requirements of any single individual fall within a small range —for example, 25 mg. We have not seen the type of case reported by Boland (1951), in which maintenance requirements fluctuated wildly and inexplicably. No case has so far become refractory on prolonged administration. We have not been able to determine any factors which will enable us to predict in advance whether a patient will need a high or a low maintenance dose. As our cases were chosen from those showing the disease in a highly active condition, though the permanent deformity was not extensive, we are unable to correlate dosage with the duration of the disease, but our results do not suggest that there is a significant relationship between dosage and the degree of activity of the disease as judged on a clinical and haematological basis.

TABLE I.—*Results*

Case No.	Age and Description	Clinical Assessment and Duration of Disease	Initial Dose High or Low	Maintenance Dosage (mg.)		Result
				I.M.	Oral	
1	Married woman aged 50. Housework	Rheumatoid arthritis 2 years Unable to run house or carry anything for 11 months. Walked 100 yards with difficulty. Wakened every night by pain	High	37·5	37·5	After 3 weeks' administration was able to return home and lead a normal life, including housework. Cortisone gradually reduced, and stopped after 6 months. No signs of relapse 7 months after suspending administration
2	Unmarried woman aged 55. Company secretary	R.A. 4 years. Unable to work for 2½ years. Walked ½-mile slowly. Continually wakened by pain Large synovial swellings on dorsum of both wrists and knees	High, and "boost" dose of 200 mg./day for 4 days on 98th day and 5 days on 134th day	75	70	Able to resume full-time secretarial work 6½ months after starting administration. Successfully ran her own flat for 4 months. This patient was found dead in her flat on 8/8/51, having been at work the previous day. Necropsy (Dr. Keith Simpson) revealed a massive intracerebral haemorrhage
3	Married woman aged 34. Housework and 3 children	R.A. 16 months. Light cooking; nothing else. Wakened ½-hourly by pain for 2½ years	High, and "boost" dose of 200 mg./day for 13 days on day 101	75	87·5–100	Able to lead a completely normal life, including housework, care of children, shopping, while under administration. Knees relapsed rapidly whenever dosage was cut to below her maintenance dose; the rest of her joints retained their improvement
4	Married woman aged 38. Housework and child	R.A. 20 months. Unable to dress herself or do housework for over a year. Could shuffle only 300 yards. Had not slept well for 18 months. Could not get into a bath	High, and "boost" dose of 200 mg./day for 6 days on day 40 and 7 days on day 84	75	100	Able to run her home and look after her child and do light gardening. Administration suspended because of side-effects. Rapid relapse
5	Married woman aged 46. Housework and child (Figs. 1 and 4)	R.A. 5 years. Rapid deterioration in last 3 months. Able to do only very light housework. Continually wakened by pain	Low	62·5	80	Can lead a normal life as a housewife
6	Army officer aged 31. Married	R.A. 2½ years Partly bedridden; with great difficulty could walk 30 yards. Unable to dress or climb stairs. Wakened for 6 months nightly by pain	Low	75–100	75–100	Starting training as a telephone operator. Can travel independently
7	Married woman aged 34. Housework	R.A. 9 years. Permanent flexion deformity in one knee. Could walk only 100 yards. Unable to dress herself or get into a bath. Unable to run her home	High, and "boost" dose of 200 mg./day for 10 days at day 14	100	100	Can carry out all domestic duties except those involving kneeling; runs her home by herself, which she has not been able to do for years. Able to go out visiting and to theatres
8	Married woman aged 40. Housework	R.A. 2 years. Could walk only ½ mile very slowly. Unable to do her own hair for 5 months. Could not get into bath or climb stairs	Low, and "boost" dose of 200 mg./day for 10 days at day 21	100	100	Symptomless on high dose, but gets side-effects. Comfortable but not symptomless on lower dose
9	Married man aged 44. Superintendent water inspector (Fig. 2)	R.A. 12 years. Rapid deterioration in last 2 years. Unable to work	High	50	62·5	Has returned to full employment. Work involves much travelling, walking, stair-climbing. Completely free from pain and tenderness
10	Unmarried woman aged 32. Clerk	R.A. 5½ years. Unable to work for the past 18 months. Could walk only ¼ mile slowly and with a limp. Could not get into a bath	Low, and "boost" dose of 200 mg./day for 15 days on day 14	25		Apart from her wrist-joints, which are permanently deranged, she can lead a normal life. Can do only light clerical and housework because of her wrists
11	Married woman aged 38. Housework and child	R.A. 26 months. See Case 4. Entire relapse within month of stopping treatment. On objective tests was significantly worse than on previous occasion	Low	100	100	Can do housework and look after child, light gardening, and shopping. Still discomfort on overexertion
12	Married man aged 34. Civil servant	R.A. 9 months. Could only dress himself slowly and incompletely. Had not slept well for 9 months. Unable to climb stairs or get into a bath	Low, and "boost" dose of 200 mg./day for 13 days on day 16	62·5	75	Returned to work. No pain or analgesics. Able to dress completely at normal speed. Sleeping well
13	Married woman aged 37. 3 children. Housework and 1 child to look after	R.A. 4½ years. Cannot dress herself. Help required to do stairs. Wakened by pain during the night	High	50	50	Able to do housework and take part in family life—dancing a little and light gardening
14	Married woman aged 59. Household duties	R.A. 8 months. Febrile. Swelling and pain in interphalangeals, wrist, knees, and feet. Confined to bed with pain	Low	75	50	Free from pain and able to live a slightly restricted but normal life
15	Business man aged 46	R.A. 6 years. Had to give up attending his business. Could barely walk	High	75	50	Walks slowly with some pain, but can get to his work
16	Business man aged 50	R.A. 10 years. Could get about only with difficulty; in constant pain	Low	50	50	Can walk without a stick. Some permanent deformity in hands. Can work only part-time
17	Unmarried woman aged 41. Schoolteacher	R.A. 3 years, interfering intermittently with her work as a teacher. Faced with possibility of permanent inability to continue working	,,	50	50	Able to return to work
18	Married woman aged 27. Housework and 2 children	R.A. 9 years. Gradual deterioration in last 3 years. Barely able to look after herself and children. Unable to do housework. Walked with a stick	,,	62·5	75	Able to lead a normal life
19	Unmarried woman aged 35. Independent means	R.A. 9 years. Ankylosis of right knee. Chair-bound	High	50	50	Able to walk without sticks. Less rest pain
20	Business man aged 66	R.A. 1 year. Practically bedridden and able to attend to his business only intermittently	,,	100	100	Able to return to work after 2 months

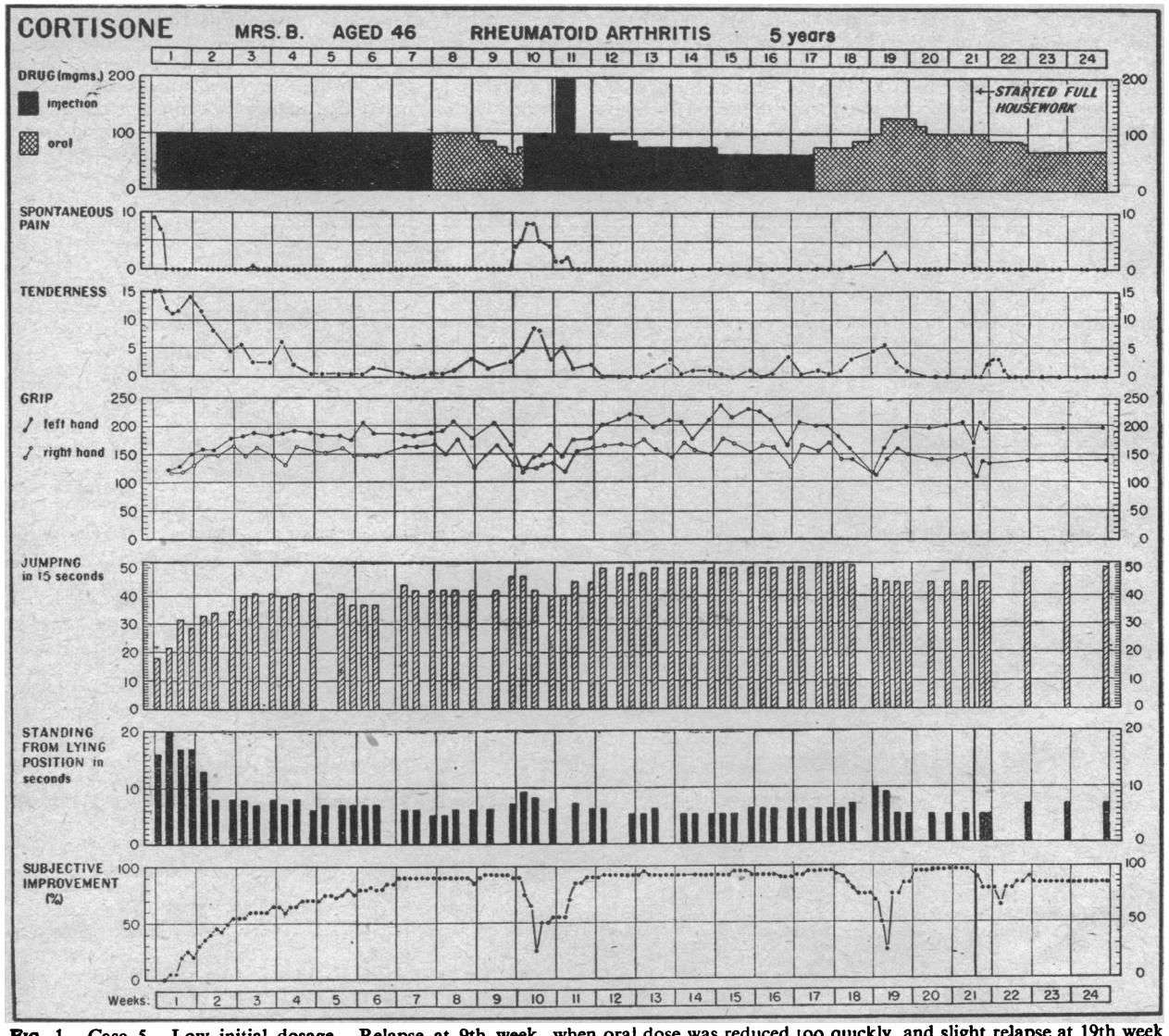

FIG. 1.—Case 5. Low initial dosage. Relapse at 9th week, when oral dose was reduced too quickly, and slight relapse at 19th week after changing to oral therapy in insufficient dosage.

Side-effects

Our series has been notable so far for the absence of serious side-effects, and in only Case 4 have they been severe enough to cause us to stop administration of the drug. Table II summarizes all the side-effects observed. In nearly every case they were slight, and might have been ignored but for the alarming reports which have been published by other observers.

Injection Abscesses.—Cortisone acetate is prepared in a microcrystalline suspension which forms a depot at the site of the injection. The injections are painless if they are placed deeply in the intramuscular tissue. An abscess may start from injection into the superficial fat, from an intramuscular haematoma, or from imperfect skin sterilization. The onset is insidious, with mild local pain but no constitutional disturbance. This failure of constitutional response can be most misleading, and in our early cases caused us to delay incision until a large amount of pus had accumulated, with considerable necrosis of the gluteal muscles. If recognized in time we have found that most of these abscesses can be satisfactorily dealt with by aspiration of the pus through a wide-bore needle and local replacement by the appropriate antibiotic.

Rounding of the Face.—This complication occurred in five cases. In two the patient was having a "boost" dose of 200 mg. a day when it appeared. In these cases it con-

TABLE II.—*Side-effects*

Case No.	No Side-effects	Injection Abscess	Rounding of Facies: Mild / Moderate / Severe	Decreased Carbohydrate Tolerance	Fluid Retention Causing Oedema	Spontaneous Bruising	Menstrual Irregularities	Paraesthesia and Enlarged Submandibular Glands	Comments	Treatment Suspended Because of Side-effects
1										
2	*	*								
3		*				*	*			
4		*	*				*			*
5		*								
6			*	*	*					
7			*		*	*		*	Oedema on high dose only	
8			*					*		
9	*									
10		*					*			
11		*	*							
12	*									
13	*									
14	*									
15	*									
16	*									
17							*			
18	*				*					
19		*								
20										
Total	8	7	3 mild, 2 mod.	1	4	2	4	2		1

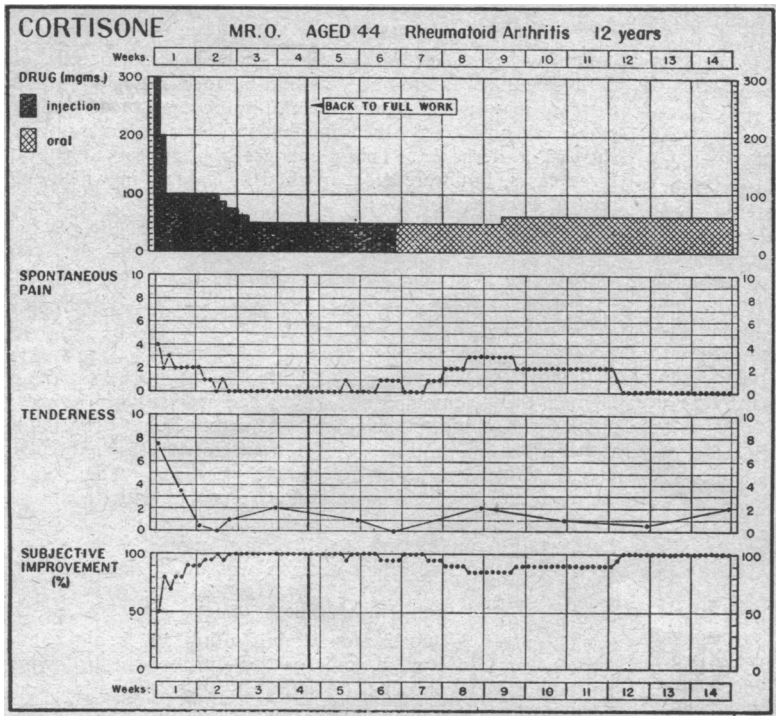

FIG. 2.—Case 9. Previous improvement with A.C.T.H. and relapsed to 50%. High initial dosage and adequate suppression of arthritis at oral maintenance dosage of 62.5 mg. a day.

sisted of a mild degree of "moon face"; there were no supraclavicular pads, no dorsal hump, no striae, and no acne, but one of the patients subsequently developed an excess of fair fine hair on her cheeks and lips. The third case (Case 6) developed a rounding of the face in association with a significant degree of water retention. Case 4 developed a "moon face," supraclavicular pads, and a small dorsal hump, but no other manifestations of Cushing's syndrome. As it was impossible to control this patient's arthritis on a lower dose and as she objected on cosmetic grounds, treatment was suspended. The nature of the "moon face" in Cushing's syndrome is not properly understood, nor is its significance in cortisone and A.C.T.H. therapy. From our brief experience with these substances it would appear that a "moon face" may occur in the absence of any other manifestation of Cushing's syndrome and is therefore merely of aesthetic concern to the patient.

Carbohydrate Tolerance.—No patient developed persistent glycosuria during treatment, but ketone bodies were occasionally found, in some cases without glycosuria. Case 6, however, had been rendered diabetic by a previous course of high-dosage A.C.T.H. therapy. (This case is to be reported in detail later.) When cortisone treatment was started he was insulin-sensitive and the diabetes was well controlled with 12 units (P.Z.I. and soluble) given once a day; but cortisone rendered him insulin-insensitive for a time, though his urine is now sugar-free on 104 units of insulin a day. It was considered justifiable to continue treatment in spite of the insulin resistance, as he was responding so well and would have become totally crippled had cortisone treatment been stopped.

Fluid Retention Causing Oedema.—Fluid retention causing temporary oedema has occurred in four cases. In Cases 7 and 8 it developed while the patient was on the "boost" dose of 200 mg. a day and soon disappeared when the dose was reduced. In Cases 6 and 20 it was controlled by moderate salt restriction in the diet.

Psychic Effects.—Possibly because our patients were chosen, among other things, for their mental stability and intelligence, we have not encountered any serious psychic effects. Some of them complained temporarily of mild exhaustion and apathy. Two complained of a feeling of tension and quick temper while on the high dosage; one complained for a short period of a feeling of unreality. There has been an absence of pathological euphoria, and in no case was insomnia a prominent symptom. Some of the patients complained of transient morning headaches, which may have been associated with mild psychological symptoms already described.

Spontaneous Bruising. — Two patients developed a mild spontaneous bruising. This is a classical feature of Cushing's syndrome. Robson and Duthie (1950), however, have observed that cortisone increases capillary resistance, in which case bruising would not be expected to occur.

Menstrual Irregularities.—The intervals between menstrual periods increased slightly in four cases without other symptoms. In Case 4 menstruation ceased after the second month of treatment, and amenorrhoea persisted until after treatment was suspended on account of the development of a "moon face," to which the patient objected on aesthetic grounds.

Oral Paraesthesia and Enlarged Submandibular Glands.—Cases 7 and 8 developed paraesthesia in their tongue and cheeks. Case 7 developed small buccal ulcers which disappeared without treatment. Case 8 has developed bilateral swelling of her submandibular glands. They are not painful, but are associated with a dryness of the mouth.

Steroid Metabolism Studies

A large number of estimations were carried out during cortisone administration. These are too voluminous to publish in detail, and the following is a summary of the main findings.

Corticoids.—The pre-treatment values of urinary formaldehydogenic steroid excretion in four cases were below the normal range for the method—namely, 0.4–1 mg./24 hours. On treatment with cortisone (100 mg./24 hours) a small increase into the normal range was observed. A further increase to levels exceeding the normal range was noted when the daily dose of cortisone was increased to 200 mg.

17-Ketosteroids.—In the seven cases studied, pre-treatment levels of 17-ketosteroid also tended to be at the lower limit of the normal range. The inception of treatment in all

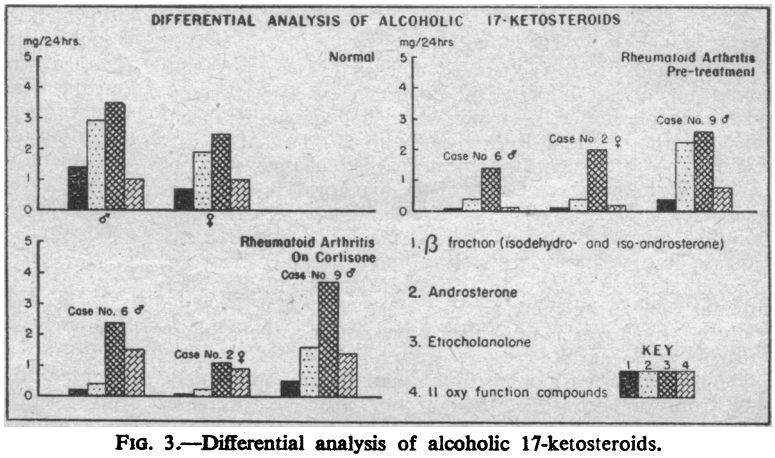

FIG. 3.—Differential analysis of alcoholic 17-ketosteroids.

cases investigated was associated with an initial fall in 17-ketosteroid excretion. On prolonged administration those cases having a relatively high pre-treatment 17-ketosteroid output continued to excrete reduced amounts, while in those cases with a low pre-treatment output excretion rose above pre-treatment levels. In the three cases in which a differential analysis of 17-ketosteroids was attempted (Fig. 3) there was an increased excretion of steroids with the 11-oxy-function—possibly catabolic products of the administered cortisone. In two of these cases, and in others not reported here, the ratio of etiocholanolone/androsterone excreted was significantly raised compared with normal subjects, although this is not necessarily of particular significance to rheumatoid arthritis (Robinson and Goulden, 1949). In no case was the raised etiocholanolone/androsterone ratio restored to normal during the treatment with cortisone; on the contrary, there was a further relative and absolute increase in etiocholanolone in two cases.

Haematological Investigations

Three cases were investigated in detail (Nos. 5, 6, and 9), including observations on all types of cell in the peripheral blood and bone marrow, and serial readings of the sedimentation rate.

Peripheral Blood

Haemoglobin and Erythrocytes.—In all three cases an increase in reticulocytes was noted during the second week of treatment, and this was followed by a rising haemoglobin and red-cell count until normal levels were reached. At the same time the cells showed a full complement of haemoglobin, and microcytosis, if it had been present, disappeared.

The Leucocytes

Eosinophils.—The administration of cortisone resulted in a diminution of 60–70% in the number of circulating eosinophils in all cases. In two cases this effect was obtained in the first 24–48 hours, but in the third case the lowest level was not reached until the fifth day. In two cases the eosinophils "escaped" to levels much above the original in two to four weeks. This phenomenon was also observed in five other patients treated with cortisone on whom eosinophil counts were performed but which were not studied in detail. In Case 9 the eosinophils returned transitorily to their original level—the marked and sustained increase noted in the other cases not being present.

Total Leucocytes.—In all cases the total count rose and a leucocytosis was observed at some stage. This contrasts with the low normal or subnormal level before treatment. The neutrophil granulocytes showed the most spectacular rise, but the lymphocytes and monocytes showed some small increases also. A lymphopenia was not observed at any stage.

Blood Platelets.—The changes in the blood platelets were not so dramatic as in the leucocytes. Generally speaking, the count appeared to follow the granulocytes—rising and falling with the level of these cells.

The Bone Marrow

The bone marrow was studied in each case by repeated sternal punctures. Initially, the bone marrow showed some increase in plasma cells—a fact which had previously been noted by Hayhoe and Robertson-Smith (1951). After the beginning of treatment the most marked change was an increase in the number of cells of the marrow. This increase in number applied to all types of cells, but particularly the granulocytes. The number of plasma cells appeared to decrease, but this was probably a relative rather than an active diminution due to an increase in the number of the other cells. In the most anaemic case (No. 6) a marked erythroid hyperplasia was also noted during the second week of treatment.

The number of eosinophils in the marrow varied considerably from time to time, though they probably decrease slightly at first but later increase.

The Plasma Volume

During treatment all patients showed some degree of fluid retention as studied by fluid-balance estimations and increase in weight. In Case 6, pitting oedema of dependent parts was noted. At the same time plasma-volume studies showed a decrease. These changes were observed in all three cases, but were most marked in Case 6, in which the results were as follows:

Date	Plasma Volume	Hb	P.C.V.
16/4/51	3·6 litres	60%— 8·7	29%
27/4/51	2·0 ,,	80%—11·6	38%
8/5/51	2·0 ,,	86%—12·5	40%
12/6/51	2·2 ,,	87%—12·6	40%
21/6/51	2·4 ,,	88%—12·8	41%
13/9/51	3·5 ,,	90%—13·0	40%
29/9/51	3·5 ,,	88%—12·8	39%

It will be seen that, initially, during the period of rapid change the haemoglobin and packed-cell volume showed similar variations to the plasma volume. But, as the latter returned to its normal level rather slowly, the red cells, etc., had increased and no change was seen. The period of maximum oedema appeared to coincide with the minimum plasma volume. At the same time serum potassium levels fell from 19 mg. to 10.6 mg. per ml.—the lowest level being reached when oedema was at its height.

Effect on Serum Antibodies

The effect of cortisone administration on serum antibodies was also studied, and for this purpose the following antibodies were chosen: (1) naturally occurring alpha and beta antibodies, one or both according to the group of the case; (2) antistaphylococcal toxin titres; (3) Rose's differential agglutination titre; and (4) antistreptolysin O titre.

Among the first three groups of antibodies studied no significant change in titre was noted in any case. In two cases no change in the antistreptolysin titre was observed, but their titre was low at the beginning of treatment. In the third case (No. 6) the titre was high before treatment and the level fell from 700 units to 300 units per ml. at the end of the period of observation.

The Sedimentation Rate

Both Wintrobe and Westergren techniques were used. There did not seem to be any great difference between them, but the impression gained was that the Wintrobe was probably the more sensitive. In rheumatoid arthritis treated with cortisone, it must be emphasized that the actual level of the sedimentation rate does not appear to be of great importance, particularly in the case of the Westergren method. Thus cases which are clinically active and with numerous manifestations of the disease may have sedimentation rates only slightly above normal levels. Further, cases which are clinically progressing favourably may show a raised figure.

In this short study it was noticed that there seemed to be some correlation with the clinical condition if the general trend was noted. Thus cases which are deteriorating show a rising rate and cases improving show at first a falling rate which later flattens out and remains more or less steady, though sometimes at a figure greatly in excess of the conventional "normal." On the results so far, it would appear that the trend, rather than the absolute level, is much more significant, and if this is noted it is capable of giving some indication of the progress of the case. But the clinical assessment still remains the most important, as an intercurrent infection may raise the sedimentation rate quite independently and possibly without affecting the arthritic condition.

Discussion

It is apparent from this series of cases that the manifestations of active rheumatoid arthritis can be suppressed by the administration of cortisone. We have not encountered any case in which rheumatic symptoms are resistant to adequate doses of cortisone, and we have been impressed by the consistency of the clinical

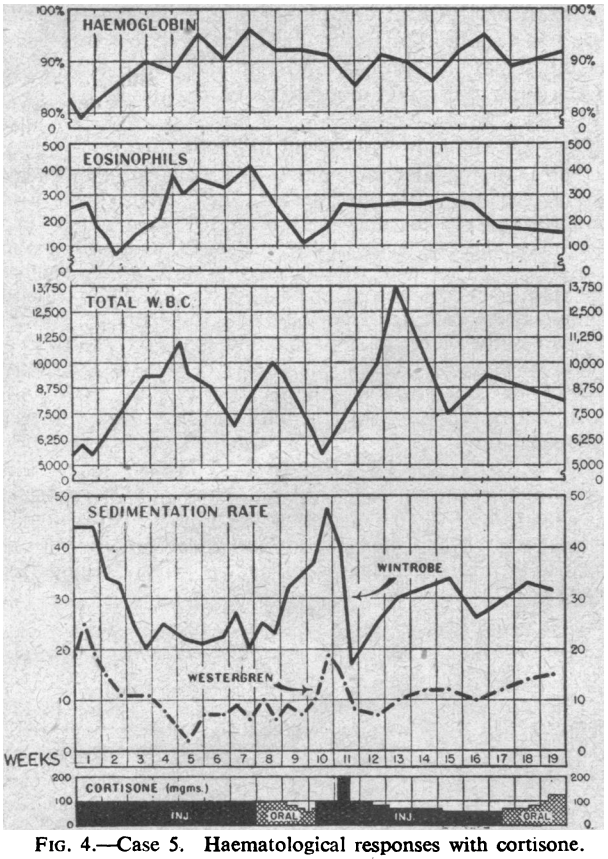

FIG. 4.—Case 5. Haematological responses with cortisone.

response as compared with the variability of the metabolic and other effects of cortisone (Browne, 1951). Where permanent damage is absent or moderate patients can eventually be returned to their own work, or to some form of lighter work, and women will be able to undertake most household duties. However, in almost every case administration has to be continued indefinitely to maintain this suppressive effect, although it seems likely that in the occasional case—for example, Case 1—cortisone can precipitate a remission of symptoms of considerable duration, and we have seen and heard of other such cases.

The success of cortisone treatment depends upon careful selection of cases and is much influenced by the difference between the suppressive dose and the "toxic" dose. This varies greatly from patient to patient and cannot be predicted in any given case.

Where the margin is large, as for example in Case 3, cortisone administration is both simple and highly satisfactory; where it is small (Case 4) it may be extremely difficult to achieve and maintain the balance between the control of symptoms and the incidence of undesirable side-effects.

Nevertheless we are of the opinion that there is a tendency at the moment to attach too great significance to mild side-effects, such as facial rounding and slight irregularity of the menstrual cycle. For instance, the incidence of side-effects reported by Ward *et al.* (1951) was 63% of 21 cases treated by 75 mg. or more of oral cortisone daily, though all these side-effects were reversible and none necessitated the discontinuance of treatment. The preoccupation of many observers with these mild side-effects reminds one of a house-proud woman overconscious of a speck of dust which the visitor has not noticed.

It would appear from our series that no single-cell type of blood investigation is of much value as a method of controlling treatment. Indeed, the changes observed in the blood all appear to be secondary to the general effect of the drug on the body as a whole—the changes in the blood being indirect. Apart from the first few days of treatment, eosinophil counts are unreliable and their level would seem to have little or no bearing on the clinical progress of the case. The remaining blood changes, if viewed as a whole, may, however, give some indication. The sedimentation rate is of some help, but even here it is the general trend rather than the absolute level which must be noted. Any sustained or sharp increase heralds deterioration in the clinical condition. Any marked and sustained fall in the erythrocyte, leucocyte, or haemoglobin levels, particularly that of the granulocytes, coincides or precedes a clinical deterioration, but the correlation is not absolute and is in the nature of a pointer—a danger signal. The clinical assessment still remains the best and most reliable guide to progress.

The discovery of this form of treatment emphasizes the importance of the early diagnosis of rheumatoid arthritis. It is probable that the results achieved in our series, in which we purposely excluded very early cases, could have been further improved—on a lower dosage and therefore with fewer side-effects—if earlier cases without joint damage had been selected. Cortisone will have little effect where extensive joint damage is present, and may be dangerous in view of the high dosage required to obtain a small amelioration of symptoms.

Until the significance of cortisone's side-effects is more fully understood, our aim should be to maintain the patient in a state in which he remains reasonably comfortable. We do not consider it advisable to attempt to suppress the symptoms of rheumatoid arthritis completely when this requires a high maintenance dosage.

Summary

Twenty selected cases of active rheumatoid arthritis have been studied during prolonged cortisone administration and have been separately assessed from the clinical, haematological, and metabolic aspects.

In 17 cases the patient has been enabled to return to previous work or household duties.

In only one case has it been possible to stop administration.

Certain methods of dosage have been assessed and side-effects have been studied.

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