BRITISH MEDICAL JOURNAL

LONDON SATURDAY NOVEMBER 30 1957

THE CLINICAL COURSE AND CORTICOSTEROID EXCRETION OF PATIENTS WITH RHEUMATOID ARTHRITIS DURING LONG-TERM TREATMENT WITH CORTICOTROPIN*

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It has been shown in controlled trials by the joint committee of the Medical Research Council and Nuffield Foundation (1954, 1955) and by the Empire Rheumatism Council (1955, 1957) that the average case of rheumatoid arthritis fares as well with aspirin as with cortisone. However, there are certain cases which remain active in spite of treatment with rest in hospital and salicylates or gold, and some of these we have treated with corticosteroids, a number of them continuously for six years.

In the early days we gave oral cortisone for preference, but owing to the shortage of supplies we sometimes used corticotropin (A.C.T.H.) as an alternative. When reporting to the Medical Research Council three years ago we found that we had then treated 50 cases with cortisone, and in only two had we been able to stop the drug on account of a remission; whereas of 42 who had received corticotropin we had been able to withdraw the drug in 12.

Treatment with cortisone, its newer analogues prednisone and prednisolone, or corticotropin is not infrequently associated with serious side-effects. The suggestion, therefore, that clinical remission occurred in more cases treated with corticotropin than with cortisone indicated that further observations might give valuable information, though the disadvantages of daily injection had to be accepted.

Since the original report of Hench, Kendall, Slocumb, and Polley (1949) on the clinical effects of cortisone and corticotropin, efforts have been made to discover methods of measuring adrenocortical activity. In 1950 Porter and Silber reported studies on urinary steroids, whilst in 1955 Appleby, Gibson, Norymberski, and Stubbs published a method of estimating total 17-hydroxycorticosteroids (17-(OH)CS) in urine which could be carried out as a routine laboratory procedure. Since this method is a measure of glucocorticoid metabolism it gives a quantitative indication of the total adrenal stimulation produced by corticotropin.

Selection of Patients.—This method has been applied, in conjunction with clinical observation, to severe active cases of rheumatoid arthritis which have failed to respond to classical methods of treatment. At the beginning of treatment the majority of these patients could no longer work or were compelled by their illness to take so much time off that they were anxious about the future. The women were unable to do their normal housework. Patients with tuberculosis, diabetes, psychoneurotic tendencies, or a history of peptic ulcer or severe dyspepsia were excluded.

We are reporting on 49 patients studied during the last two and a half years while on a long-term regime of self-administered corticotropin. In all these cases, which have been observed for at least six months, regular clinical and biochemical observations have been made.

Method of Study

By collaborating in a number of multi-centre controlled trials we have gained experience in the clinical assessment of rheumatoid arthritis. It has become clear that many of the tests generally used are too subjective and that the more complicated ones are not suitable when patients are studied at frequent intervals for months or years. For this study we have chosen two clinical measurements which can be done rapidly and which our experience has shown to be the most satisfactory of a large number tried.

Tenderness of selected joints to firm pressure is assessed in three grades: 1 point if the patients admit tenderness; 2 points if they wince; and 3 points when they refuse to allow the test to be repeated. The total points are divided by the number of joints tested to give an average "score" for tenderness.

Strength of grip is measured with an ordinary sphygmomanometer. The rubber blood-pressure cuff is rolled and inserted in a cloth bag measuring 6 by 3 in.

*This work has been aided by grants from the Dan Mason Research Foundation of the West London Hospital Medical School, the Empire Rheumatism Council, and the Medical Research Council.

(15 by 7.5 cm.): this bag measures 2 in. (5 cm.) in diameter when inflated to a pressure of 30 mm. Hg (Fig. 1). The patient squeezes the bag as hard as possible, and the average of three readings is recorded for each hand.

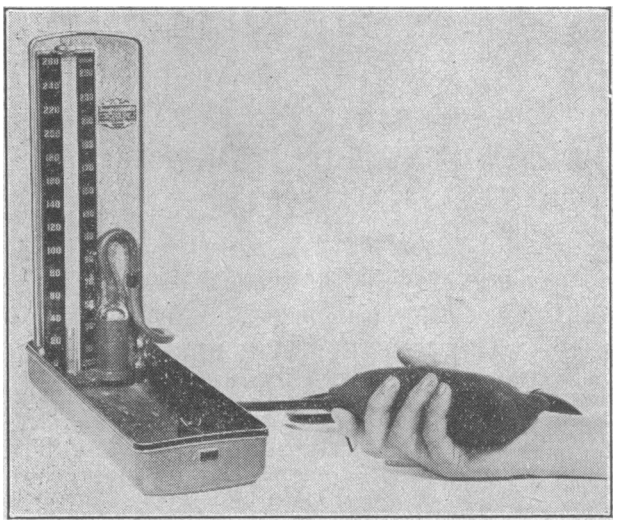

FIG. 1.—Grip test.

The erythrocyte sedimentation rate is estimated by the Westergren method at monthly intervals.

Urinary Steroids.—Estimation of the urinary excretion of total 17-(OH)CS by Norymberski's method are done weekly throughout treatment and more often during the initial stages.

The collection of urine specimens by out-patients originally presented a problem. It was found impracticable for patients to bring a whole 24-hour specimen to the hospital each week. Therefore while in hospital for the start of treatment they are taught in the biochemical laboratory to measure a 24-hour specimen. When they leave hospital they are lent a litre-measuring cylinder and a number of 1-oz. (31-ml.) containers with wooden cases which can be posted. As nearly all these patients are now working they collect their specimens at the week-end, using small plastic bottles for urine collection when they go out during the day. An aliquot of the well-mixed specimen with a note of the 24-hour volume is sent by post to the laboratory each week. The accuracy of the 24-hour urine collection is checked by creatinine determinations.

Patients are admitted to hospital and treated only with rest in bed and adequate salicylates for at least a week. During this time daily urinary steroid estimations are carried out. If there is no improvement with rest, corticotropin is then started with the object of suppressing symptoms of active disease, abolishing tenderness, and substantially increasing the grip. In our experience this has always been accompanied by a rise in corticosteroid excretion.

Once symptoms are relieved and the initial adrenal stimulation is produced, we maintain a dose which will continue to suppress symptoms, whether this raises the corticosteroid excretion or not.

The average stay in hospital has been four weeks, and during that time the patients are taught to inject themselves daily with corticotropin by the subcutaneous route just as diabetics give themselves insulin. In this series it is estimated that 26,000 injections have now been self-administered without mishap.

After leaving hospital these patients attend as out-patients about once a month for clinical assessment and send a specimen of urine each week for steroid estimation to the laboratory.

Controls.—For controls, patients with rheumatoid arthritis on salicylates or gold were used. Fig. 2 shows that full salicylate dosage produces no increase in corti-

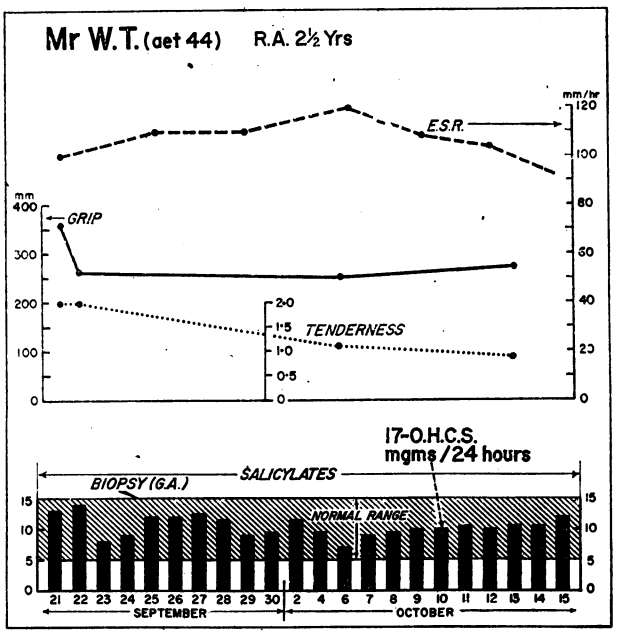

FIG. 2.—Daily 17-(OH)CS estimations during control period on salicylates.

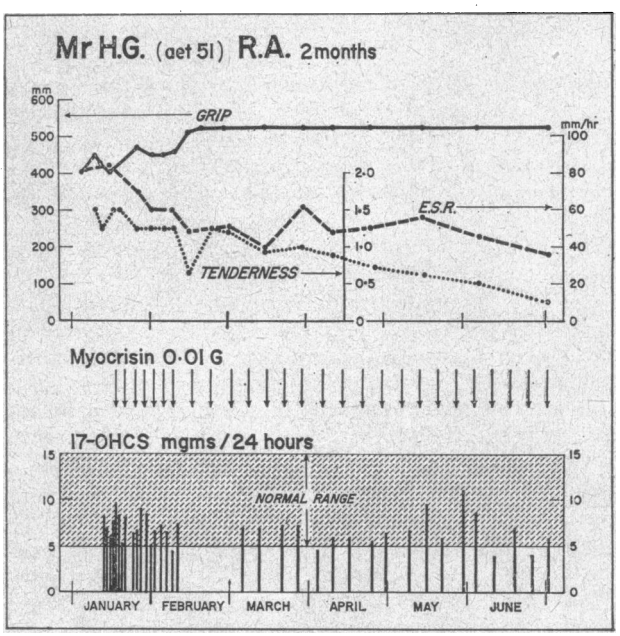

FIG. 3.—A six-months study with 17-(OH)CS estimations during gold therapy.

costeroid excretion, which, though varying from day to day, falls well within the normal range. Fig. 3 shows a study of a patient who received weekly gold injections for six months; again there is no evidence of adrenal stimulation.

Observations.—Of the 49 patients on whom we have carried out regular corticosteroid estimations during treatment six have gone into remission, 35 are still having corticotropin therapy, one has died, and seven have stopped treatment, six because of side-effects and one because of the development of apparent resistance to corticotropin.

As already stated, we have adjusted the dosage of corticotropin to the clinical course of the disease whilst recording the corticosteroid excretion as an indication of resultant adrenal activity. In this respect our study differs from that of West (1957), who aimed to produce continuous adrenal stimulation with a daily 17-(OH)CS excretion of between 20 and 35 mg. and then studied the effect of this on the course of the disease.

Clinical and Biochemical Responses

Initial Response

Corticosteroid estimations were carried out from the start of treatment in 41 cases. In all these there has been a rise in 17-(OH)CS excretion concomitant with clinical suppression of the disease, as indicated by a significant diminution of joint tenderness, increase in the strength of the grip, and a fall in the sedimentation rate. The level, however, to which the corticosteroid excretion has been raised has varied a good deal, but it does not appear that a high level is necessary to achieve a clinical response. West (1957) states that elevation of 17-(OH)CS excretion by 50 to 100% above the pre-treatment level results in complete or partial suppression of symptoms and signs of disease activity. We have reviewed our observations in the light of this statement and agree with it, although in a few patients elevation of 17-(OH)CS excretion of this order has been accompanied by only slight but measurable clinical improvement. We have only once observed a favourable clinical response without a rise of 17-(OH)CS excretion at least 50% above the pre-treatment level: this was a patient whose excretion of 17-(OH)CS before treatment was unusually high (18 mg./24 hours) and who showed a good clinical response to corticotropin when it rose to 21 mg./24 hours.

Long-term Treatment

Most patients appear to need continuous but usually only slight adrenal stimulation (as evidenced by a raised 17-(OH)CS excretion) to maintain clinical suppression. On a constant dose of the same batch of corticotropin there is a general tendency for 17-(OH)CS excretion to fall off after a few weeks, and this is associated, as a rule, with clinical relapse. This apparent acquired resistance to corticotropin is a relative one; an increase in dose, sometimes by as little as 5 units, or a change of batch, results in a further rise of corticosteroid excretion and resumption of clinical improvement. Since we have been using biochemical control we have only once seen almost complete resistance to corticotropin. This was in a patient who, after responding satisfactorily for seven months, relapsed severely in the face of intense emotional stress and failed to show any significant clinical or biochemical response to several potent preparations of corticotropin in doses up to 30 units every six hours.

Less frequently than the development of partial resistance to a given batch of corticotropin, we have observed an apparent increased sensitivity, with a rising 17-(OH)CS excretion, although the dose remains constant. The significance of this pattern of adrenal response is yet to be elucidated.

These variations in adrenal response to corticotropin during long-term treatment (Fig. 4), and the variation in strength between batches, discussed below, mean that fairly frequent adjustments of dosage may be necessary to maintain clinical suppression without causing excessive adrenal stimulation. It is possible to achieve this, and even after several months' treatment we have found that the pattern of clinical and biochemical response remains the same. We also agree with West (1957) that the clinical suppression of disease activity associated with a given level of corticosteroid excretion does not diminish during long-term treatment. This is in contrast to our experience with cortisone, where not infrequently clinical suppression diminishes although side-effects persist.

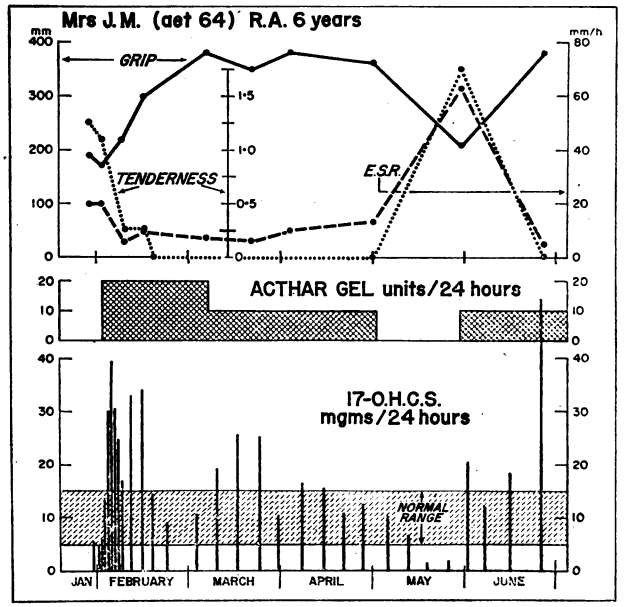

FIG. 4.—Correlation between 17-(OH)CS output and clinical response.

Variation in Strength of Batches of Corticotropin

The variation in strength between different batches of the same preparation of corticotropin is a practical difficulty in long-term treatment. We suspected this variation early in our work with corticotropin, but were unable to confirm it until biochemical control became available.

Fig. 5 shows the type of variation which can occur. This woman had been having corticotropin for four years without biochemical observations but with satisfactory suppression of symptoms until she changed to batch N.34110. There was immediate and severe relapse. The steroid excretion at that time indicated little adrenal stimulation. On another batch (P.80001), in the same dosage, immediate suppression of symptoms occurred with marked adrenal stimulation. It also brought side-effects, mooning and acne, but even in

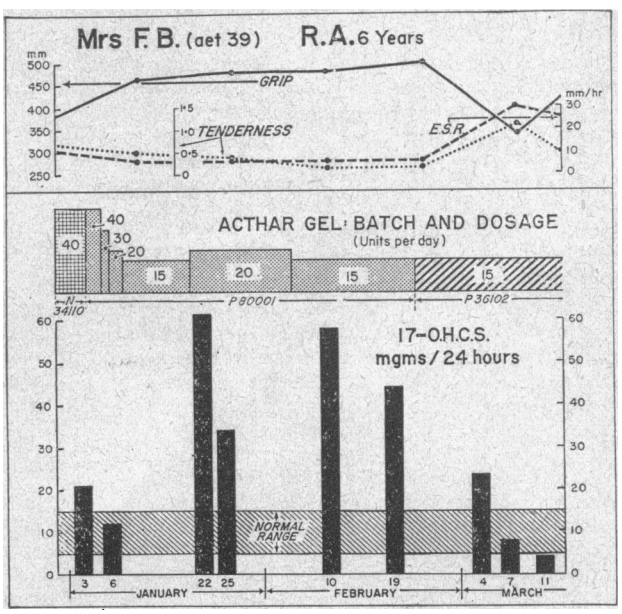

FIG. 5.—Variation between different batches.

half the dosage it produced three times the steroid excretion of the previous batch. This is not an isolated example of batch variation. We have found that 17-(OH)CS excretion in patients shows general agreement on the relative potency of individual batches. In the case of some of the earlier "highly purified" preparations this variation was due to rapid deterioration during storage, which has now been overcome. It should also be appreciated that the "official" method of assay (ascorbic acid depletion in rats) has wide limits of error, and the permissible limits of accuracy of labelled strength are 50 to 200%; but it is probable that variations of the order of 80–125% are detectable when using corticotropin clinically, especially when the aim is to produce only relatively slight adrenal stimulation.

Remission of Disease

Six of the 49 cases treated with corticotropin in the last two and a half years have gone into remission. The drug has been withdrawn and it has not proved necessary to recommence it.

We have come to recognize a clinical and biochemical pattern in those patients who go into remission (Fig. 6). In all cases there has been a good clinical response to adrenal

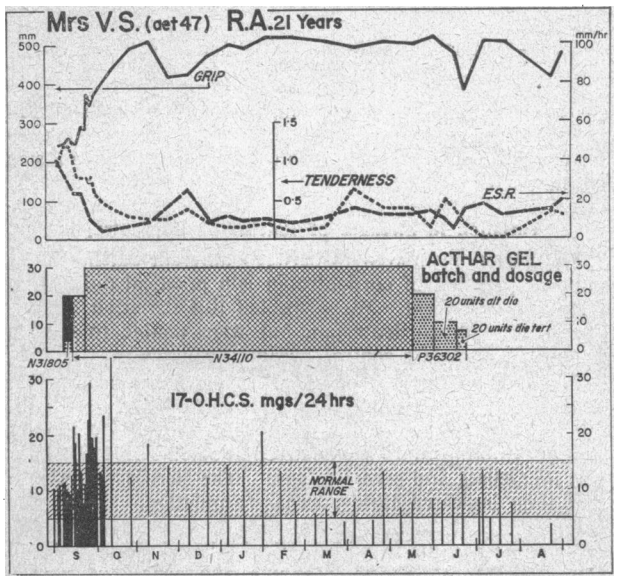

FIG. 6.—Clinical and biochemical pattern when the disease goes into remission.

stimulation with a fall of the sedimentation rate to the normal range. Continued adrenal stimulation has been necessary for variable periods to maintain clinical suppression; eventually, however, the expected fall in 17-(OH)CS excretion after a period on a constant dose of one batch has not been accompanied by clinical relapse, and we have been able to withdraw corticotropin gradually.

Withdrawal Effects

One of the main problems encountered in the treatment of rheumatoid arthritis and other diseases with cortisone and the newer oral steroids is the danger of distressing general symptoms which accompany the relapse of the arthritis when the drug is withdrawn. These symptoms, which are due to involution of the adrenal cortex, include profound fatigue, asthenia, hypotension, dizziness, and muscular weakness, possibly with fever. During the course of this study, in testing the strength of a variety of batches and preparation of corticotropin, we have often changed patients abruptly from a strong batch giving adrenal stimulation (17-(OH)CS>30 mg./24 hours) to a weak batch giving no apparent adrenal stimulation (17-(OH)CS<10 mg./24 hours), but although we have seen severe relapse of the arthritis on these occasions there have seldom been any general symptoms. Neither have we seen general symptoms when the corticotropin has been withdrawn during a remission, though this has always been done slowly.

We can only speculate on the reasons why withdrawal of corticotropin should be so much easier than that of cortisone. At first sight it would appear that the tendency to suppress endogenous hormone production would be common to both forms of therapy. There is, however, one factor which may be significant in this respect: even with the long-acting corticotropin preparations the effect of an injection lasts only about 12 hours, so that with daily injections adrenal stimulation, and therefore presumably suppression of endogenous corticotropin production, is intermittent.

Pregnancy

We have been able to study one patient who had corticotropin throughout her pregnancy. This is worth recording, as in a search of the literature we have been unable to find a similar report.

Mrs. B. aged 39, who had had two previous normal pregnancies, the last eight years earlier, was injecting herself with corticotropin with adequate suppression of arthritic symptoms and was leading a normal life. In April, 1956. she became pregnant, and it was noted that there was marked adrenal stimulation with a daily excretion of 65 mg. of 17-(OH)CS. We attempted to withdraw corticotropin in June because of a tendency to hypertension, but a severe clinical relapse occurred with a drop in steroid excretion, and the drug had to be restarted. However, during the last four months of pregnancy satisfactory clinical suppression was achieved with a dose of only 5 units per diem as compared with the 15 units she had required before pregnancy. A normal premature female child was delivered by caesarean section at about eight and a half months. Following the birth there was a rapid relapse of the arthritis which made necessary a rise in the corticotropin dosage. Some four weeks after delivery a marked increase in adrenal stimulation occurred, culminating in a steroid excretion of 116.7 mg. per diem, which then fell slowly to the previous level on the same dose (Fig. 7).

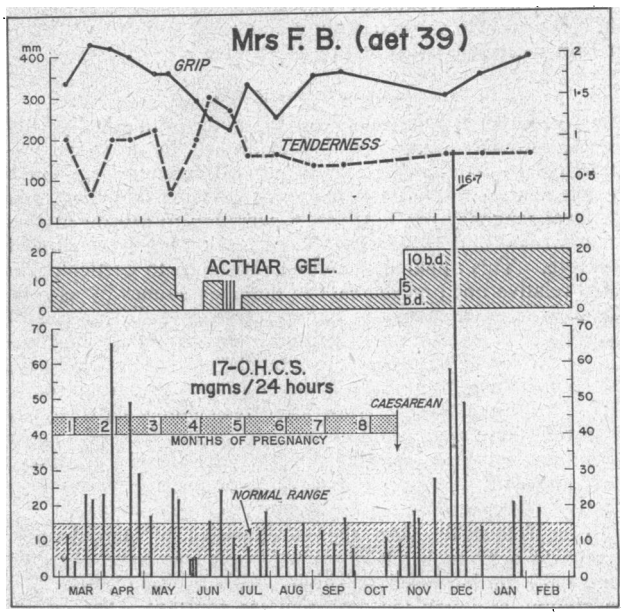

FIG. 7.—17-(OH)CS output followed throughout pregnancy.

The diminished requirement of corticotropin during the later months of pregnancy fits in with the recognized tendency to clinical remission of arthritis during this time, and with the evidence of increased adrenal activity described by Bayliss (1955). The severe relapse when corticotropin was stopped during the fifth month, however, shows that the natural increase in adrenal activity was not of itself sufficient to produce suppression of the disease. We have no explanation to offer for the sharp rise in 17-(OH)CS excretion in the post-natal period.

Side-effects

All but three of these 49 cases showed side-effects, if only of slight degree, at some time during treatment. The incidence of these is shown in the accompanying Table. In the majority of cases these side-effects have not been severe and have not influenced treatment. We have, however, had one death from haematemesis ascribable to corticotropin—discussed below—and have stopped treatment because of side-effects in six cases. The predominant features which made this necessary were: osteoporosis with pathological fracture in one case, androgenic effects in two cases, chemosis in one case, fluid retention in one case, and mental disturbance in one case.

Incidence of Side-effects

	Women (33)	Men (16)	Total (49)
Hypertension (diastolic pressure 100 mm. Hg or above)	9	5	14
Weight increase (7 lb. (3·2 kg.) or more above normal weight)	11	5	16
Oedema	11	4	15
Moon-face	25	7	32
Chemosis	2	3	5
Pigmentation	9	6	15
Androgenic effects (acne, hirsuties, menstrual disturbance)	21	4	25
Glycosuria	4	1	5
Osteoporosis	1		1
Dyspepsia, peptic ulcer, haematemesis		2	2
Mental disturbance	2		2

We have observed certain trends in the incidence of side-effects at different levels of adrenal stimulation; these are discussed below.

Hypertension.—All patients have shown some rise of blood pressure when the 17-(OH)CS excretion has risen significantly above the normal range. When the excretion has been between 25 and 35 mg./24 hours about 15% of patients have shown a rise of the diastolic pressure to 100 mm. Hg, and when the excretion has exceeded 40 mg./24 hours the proportion has risen to about 45%. As a rule these rises in blood pressure are transient and closely parallel the corticosteroid excretion. We have not seen chronic hypertension arise in this way, but in a few cases, when a high corticosteroid output has been maintained for two to three weeks, the hypertension has persisted after a reduction in dose of corticotropin has brought the 17-(OH)CS down to a lower level, and the blood pressure has then fallen only gradually over a period of weeks or months.

Glycosuria.—As with the blood-pressure responses, some patients have shown transient glycosuria when corticosteroid excretion has been high. One patient developed a true "steroid diabetes": this was a man who showed evidence of marked adrenal stimulation when he was given what proved to be a very powerful batch of corticotropin. Despite rapid reduction of the dose, his 17-(OH)CS excretion rose from 40 to 105 mg./24 hours over a period of five weeks. It then fell to about 80 mg., but after a further three weeks he developed glycosuria, with polyuria and thirst, and a glucose-tolerance test showed a diabetic type of curve; corticotropin was withdrawn, and with the fall in 17-(OH)CS excretion glucose tolerance gradually reverted to normal, although there was a significant time-lag. Characteristically, at no time was ketonuria detected.

Fluid Retention and Weight Increase.—All patients have put on some weight while having corticotropin, but many of them were underweight when treatment was started, and we have taken an increase of 7 lb. (3.2 kg.) or more above their normal weight as being excessive. Improvement of appetite almost always follows effective corticotropin administration, and many patients have to be warned to watch their weight. The majority are able to maintain a normal weight without any drastic dietary restriction, but in about 20% strict measures are necessary. On the whole it is this group which shows a tendency to fluid retention. these side-effects appear to be due to individual susceptibility rather than adrenal over-stimulation, and almost without exception are apparent as soon as the daily 17-(OH)CS excretion rises above 15 mg. (the upper range of normal values). In these cases where fluid retention is easily produced we have found acetazolamide useful in permitting corticotropin therapy to be continued.

Moon-face and Chemosis.—Mooning of the face is a feature so common with all forms of corticosteroid therapy that it can hardly be called a side-effect. It is quite independent of fluid retention. With similar levels of adrenal stimulation it appears to occur much more readily in women than in men, and is often detectable when 17-(OH)CS excretion rises only just above the upper limit of normal. In five patients in this group we have observed conjunctival congestion and oedema in association with severe mooning. We have not seen this feature with other forms of corticosteroid therapy even when mooning has been very marked. This chemosis has developed in all five cases when 17-(OH)CS excretion has been raised above 45 mg./24 hours, but has tended to persist for some weeks after the excretion has fallen to 20 mg. or even lower.

Androgenic Effects.—We have found that evidence of androgenic overactivity is very common in women receiving corticotropin. Of the 33 women in this series, 21 showed some side-effects of this kind, although in the majority they were not severe. Acne was the commonest manifestation, especially in younger women, but hirsuties was not uncommon and menstrual disturbances occurred quite often; out of 21 women who gave a history of more or less regular menstruation, 13 experienced some definite irregularity whilst on treatment. In premenopausal women these androgenic effects often occurred when the 17-(OH)CS excretion was raised only slightly above the normal range—that is, to 15–25 mg./24 hours—and there appeared to be individual susceptibility. As a rule androgenic effects were not apparent until the patient had received an effective dose of corticotropin for at least three weeks. In two women it proved to be impossible to produce suppression of the disease without causing severe acne, and corticotropin had to be abandoned on this account. In one of these, 17-ketosteroid as well as 17-(OH)CS estimations were performed, and it was found that corticotropin was causing an almost equal excretion of each. In men and post-menopausal women acne and hirsuties (and loss of scalp hair in women) have been much less common and have been seen only when the 17-(OH)CS excretion has been at least moderately high, usually above 35 mg./24 hours.

Pigmentation.—This is presumed to be due to impurity of the corticotropin preparations, and one would therefore not expect any close relationship between its occurrence and 17-(OH)CS excretion. It might be anticipated that difference in melanophore-stimulating activity could be detected between different batches of corticotropin, but we have not observed this. As with the androgenic side-effects, there appears to be considerable variation in individual susceptibility, and usually pigmentation is not noticeable until adrenal stimulation has been maintained for two to three weeks.

Dyspepsia, Peptic Ulcer, and Haematemesis.—We have been impressed by the absence of dyspepsia when using corticotropin rather than oral steroid therapy. A few patients who had complained of dyspepsia of flatulent type before starting treatment had some persistence when on corticotropin, especially if they became rather "over-stimulated" and felt "blown-out." In two cases, however, symptoms of this type cleared up after starting corticotropin. We are thus generally in agreement with West (1957), who states that none of his 66 long-term patients having corticotropin had any dyspepsia. One of our patients had very mild dyspepsia for a short time and subsequently perforation of a duodenal ulcer. As mentioned above, one patient died after severe haematemesis. He was the patient who developed "steroid" diabetes after prolonged adrenal over-

stimulation, and this aspect of the case has been discussed. Withdrawal of corticotropin to control the diabetes resulted in severe relapse of his arthritis, so it was restarted in small dosage. Although he then proved to be very sensitive, as shown by a rapidly rising 17-(OH)CS excretion, the glycosuria did not recur. Three weeks later he had severe and persistent haematemesis. As the bleeding did not cease, surgical treatment was undertaken, but at operation no ulcer or bleeding-point could be found. A partial gastrectomy was performed, but haemorrhage continued post-operatively and he died. At necropsy no definite bleeding-site could be identified, but the whole upper intestine appeared to be thinned and oozing blood diffusely.

Conclusion.—There seem to be certain broad patterns in the occurrence of side-effects. Some, such as fluid retention and androgenic effects, depend largely on individual susceptibility and often occur with only slight adrenal stimulation. Others, such as hypertension and glycosuria, occur only with higher levels of 17-(OH)CS excretion and are usually transient, but if overstimulation is not soon checked there may be a considerable time lag between the subsequent fall of 17-(OH)CS and reversal of these side-effects. Androgenic effects are common in women of menstrual age and occur with much lower levels of adrenal stimulation than in men or older women ; these side-effects and also pigmentation are not apparent for two to three weeks after the rise in 17-(OH)CS excretion, but persist for several weeks after the level has fallen to normal.

Summary

Since the anti-inflammatory effects of cortisone and corticotropin in rheumatoid arthritis were first reported the main work in both the clinical and the biochemical fields has been on oral steroids.

Our interest in corticotropin was originally stimulated by the finding that, after using it for three years as an alternative to cortisone, six times as many patients had gone into remission. This observation has not been confirmed in the subsequent series reported here.

However, we have learnt that treatment of severe rheumatoid arthritis with self-injected corticotropin (A.C.T.H.) over long periods is a practical procedure, and when used with biochemical estimations has certain advantages over oral cortisone and its newer analogues. These advantages are : (1) The level of adrenal stimulation produced by corticotropin can be estimated by measurement of the total urinary excretion of 17-hydroxycorticosteroids (17-(OH)CS). This can be done for out-patients by the method described. (2) When corticosteroid excretion is seen to fall the dose of corticotropin can be raised before severe clinical relapse occurs. (3) When the corticosteroid excretion is seen to rise it is possible to reduce the dose of corticotropin before excessive adrenal stimulation occurs.

We have studied 41 patients with the help of biochemical estimations from the beginning of treatment. In every case suppression of activity with a fall in sedimentation rate followed the administration of corticotropin in a dose which proved sufficient to raise the urinary excretion of 17-(OH)CS by a significant amount. In 23 cases the excretion was doubled, and in 17 it was increased by more than 50%. We have not seen a single case where clinical suppression of the disease was not accompanied by a significant increase in corticosteroid excretion.

After the initial response, dosage has had to be adapted to the fluctuation of the disease activity, or the development of an altered sensitivity to the hormone. We have observed that it has not been necessary to maintain a high level of adrenal stimulation in order to obtain continued clinical improvement ; and that adequate clinical and biochemical response can be maintained for years with only minor adjustments of steroid dosage. The occurrence of remission is recognized if at any time during a period of satisfactory clinical response a fall in the patient's 17-(OH)CS excretion is noted, without any concurrent relapse of the disease. One of the difficulties in the use of corticotropin is the variation in the strength of batches. This is a matter which is being explored continuously by the manufacturers, and a constant standard will undoubtedly be achieved in time.

We have observed that the more severe side-effects such as hypertension and glycosuria occur only when a high level of hydroxycorticosteroid excretion has existed for some weeks and that they are reversible. Androgenic side-effects, particularly acne, occur commonly in women before the menopause with only slight adrenal stimulation. We are impressed with the absence of dyspepsia in our patients. Only one developed peptic ulceration, whereas in 83 consecutive cases treated with oral steroids during the last five years 13 have developed gastric or duodenal ulceration. If corticotropin is withdrawn, relapse of the arthritis will follow, but this is not accompanied by the distressing general symptoms which attend the withdrawal of cortisone and other oral steroids.

We consider that biochemical control during long-term treatment of severe cases of rheumatoid arthritis with corticotropin results in a more accurate and less dangerous dosage regime than was formerly practicable. If a simple method were devised for testing the urinary corticosteroid excretion within a fairly wide range it would bring this additional method of control into the realm of routine clinical medicine.

A method of controlling dosage is described and discussed with reference to long-term treatment with biochemical estimations. It seems that the use of steroid therapy in a severe case of rheumatoid arthritis will probably not alter the basic course of the disease ; the satisfactory suppression of the inflammatory element will, however, enable the patient to regain independence and live a normal life.

We would like to thank Professor F. G. Young, F.R.S., and Dr. P. M. F. Bishop for their advice and help. The corticotropin used for this study was partly provided by the Ministry of Health, and supplies were also given to us by the following firms: Crookes Laboratories Ltd. and Organon Laboratories Ltd., of England; Armour Laboratories and Wilson Laboratories, of the United States; and Nyegaard and Co. A/S, of Norway.

REFERENCES

Appleby, J. I., Gibson, G., Norymberski, J. K., and Stubbs, R. D. (1955). *Biochem. J.*, **60**, 453.
Bayliss, R. I. S. (1955). *Brit. med. J.*, **1**, 495.
Empire Rheumatism Council (1955). *Ann. rheum. Dis.*, **14**, 353.
—— (1957). Ibid., **16**, 277.
Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F. (1949). *Proc. Mayo Clin.*, **24**, 181.
Medical Research Council and Nuffield Foundation (1954). *Brit. med. J.*, **1**, 1223.
—— (1955). Ibid., **2**, 695.
Porter, C. C., and Silber, R. H. (1950). *J. biol. Chem.*, **185**, 201.
West, H. F. (1957). *Ann. rheum. Dis.*, **16**, 322.

The five-hundred-thousandth microscope to be made by the firm of Ernest Leitz was presented last month to Dr. Paul A. Weiss, head of the department of developmental biology at the Rockefeller Institute, New York. In 1907 the firm gave Robert Koch their 100,000th microscope ; the 150,000th went to Paul Ehrlich in 1912 ; the 200,000th to Martin Heidenhain, histologist, in 1921 ; the 300,000th to Ludwig Aschoff in 1930 ; and the 400,000th to Gerhard Domagk in 1949.