either severe or moderately severe symptoms, while 86% of patients who received more than 1,000 protein nitrogen units as a maximum dose were either symptom free or had mild symptoms only.

3. It is concluded that in the treatment of ragweed hay fever there is a critical level of dosage above which one may expect to get good results and below which results are almost uniformly poor.

4. Factors preventing achievement of high dosage; irregular attendance at the office or clinic, large reactions at the injection site or constitutional reactions, have been outlined and means of preventing these have been discussed.

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THE MANAGEMENT OF MARIE-STRUMPELL SPONDYLITIS WITH SPECIAL REFERENCE TO LONG-TERM CORTISONE THERAPY*

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APPROPRIATE REST and adequate exercise remain the best form of treatment for Marie-Strumpell spondylitis. Before 1950, the only added treatment of proven value has been Roentgen therapy. This had failed to give as much or lasting relief as had been hoped. When cortisone appeared, its use was adopted as another adjunct to the basic program. Contrary to prevailing trends and for reasons to be given, study of a small number of patients was undertaken 2½ years ago, using cortisone intermittently rather than continuously. The results of this method have been satisfactory.

Selection of patients.—As a result of previous experience (in Shaughnessy Hospital), the impression was gained that most patients with rheumatoid disease tend to improve, or recover, if placed under ideal conditions for a sufficiently long period of time, even without specific treatment. Of more than 150 veterans of World War II with Marie-Strumpell spondylitis, some 35 had not, by 1950, achieved sufficient recovery to permit reasonably satisfactory wage-earning. Some of these 35 patients were badly disabled by deformities or by very severe persistent rheumatoid inflammatory activity and, with few exceptions, were not included. An economic factor, potential restorability to wage-earning, was the chief consideration in selecting this group of 11 male patients for long-term management with cortisone in order to test its practical value. Of the 11, four had been in hospital for some months before hormone therapy was started. The other seven patients, called in to hospital for treatment, were prevented from working full-

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time by active rheumatoid disease. It was felt that moderate subsidence of the inflammatory activity would permit all these patients to become economically self-sufficient. Although spondylitis was the primary disease in all, weight-bearing joints were involved in eight of the 11 patients and often shared equally with the back involvement in producing the total quantity of disability.

Plan of treatment.—All of these patients had previously had one or more similar hospital periods, without cortisone, without restoration of full wage-earning ability. The initial course of cortisone was given in the Shaughnessy Clinical Investigation Unit. Subsequent management was on an out-patient basis; at first at weekly intervals. Further cortisone was administered when necessary, usually without bringing the patient back in to Hospital.

(a) *Dosage.*—The standard dosage was 100 mgm. daily, given either intramuscularly or orally. Rarely was it necessary to increase, temporarily, the daily dosage to as high as 200 mgm. in order to obtain a satisfactory clinical response. Routinely, the supplementary courses ("booster") consisted of five or ten days of 100 mgm. daily given as one dose intramuscularly, or as 25 mgm. every six hours by mouth.

(b) *Duration of initial course.* — The initial course was intended to bring about maximal symptomatic remission. However, it was, nevertheless, terminated when, after substantial clinical gain, further improvement failed to occur on the maximum dosage tolerated well by the patient.

(c) *Indication for supplementary treatment.*— The short "booster" course was given whenever it seemed clinically necessary to maintain or retrieve the satisfactory remission. As a rule, increasing functional impairment rather than worsening of more objective criteria constituted the indication for re-treatment. We adopted this policy because most of the patients became fully employed and the primary objective of this project was to keep them at work. Each patient was re-treated according to the dictates of his own rheumatoid inflammatory process and no attempt was made to institute a uniform treatment-free interval between courses. Nor was the hæmatological picture reliable as an indication for re-treatment.

Results.—It is difficult to assess results by a rigid set of criteria in rheumatoid disease. This is especially true in spondylitis where spine and peripheral joints contribute variably in the disability. In these veteran patients, we have felt that the most important criterion was change in work capacity. Fig. 1 records these results. Degrees of work capacity were classified thus: Class 1—Complete work capacity with ability to carry on all usual duties without handicaps. Class 2—Work capacity adequate to conduct normal activities despite handicaps of discomfort or limited mobility of one or more joints. Class 3—Work capacity adequate to perform only little or none of the duties of usual occupation. Class 4—Largely or wholly incapacitated.

From the results (Fig. 1) it will be seen that four patients (D.M.L., C.W., T.W. and W.H.W.) showed marked improvement, an increase in work ability of two or more classes. Moderate

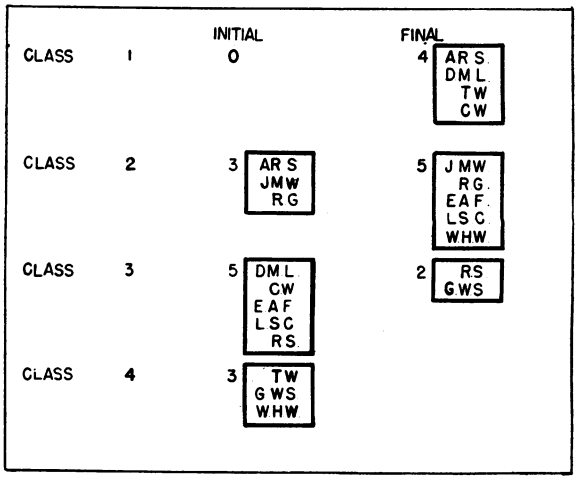

Fig. 1.—Results in the treatment of eleven patients with Marie-Strumpell spondylitis using intermittent cortisone, showing increase in work capacity.

improvement, an increase by one class, was shown by four patients (A.R.S., E.A.F., L.S.C. and G.W.S.) while three (J.M.W., R.G. and R.S.) showed little or no improvement.

Initially, four of the eleven were employed at part-time or light work, while at the present time ten are employed at full-time duties ranging from sedentary desk work to arduous manual labour.

Fig. 2 indicates the amount of cortisone given in the initial course and the length of time over which it was given. It shows the smaller "booster" courses, the route of administration and the interval between each. The duration of the period of observation and the total amount of cortisone given is listed at the left.

Change in physical examination.—Objectively none are worse. Those with marked increase in

work capacity show at least some measurable gain physically, with decreased inflammatory activity and improved range of movement.

Hæmatological effects. – During the longer initial course of cortisone the sedimentation rate tended to fall and to gradually rise again during the intervals between therapy. In only three cases (T.W., A.R.S. and E.A.F.) has the sedimentation rate remained consistently at a lower level than before starting therapy. The hæmoglobin and white blood count tended to rise during the initial course, only to fall gradually to the

Supplementary courses.—A rather surprising amount of symptomatic benefit was obtained from short, supplementary courses. So far as purely spondylitis symptoms were concerned, little difference between ½ gram in five days or one gram in ten days was noted. When active inflammation of weight-bearing joints was present, the ten-day booster course usually gave the better results.

Impairment of adrenal function —In the six patients whose urinary excretion of 17-ketosteroids was followed during the period of initial

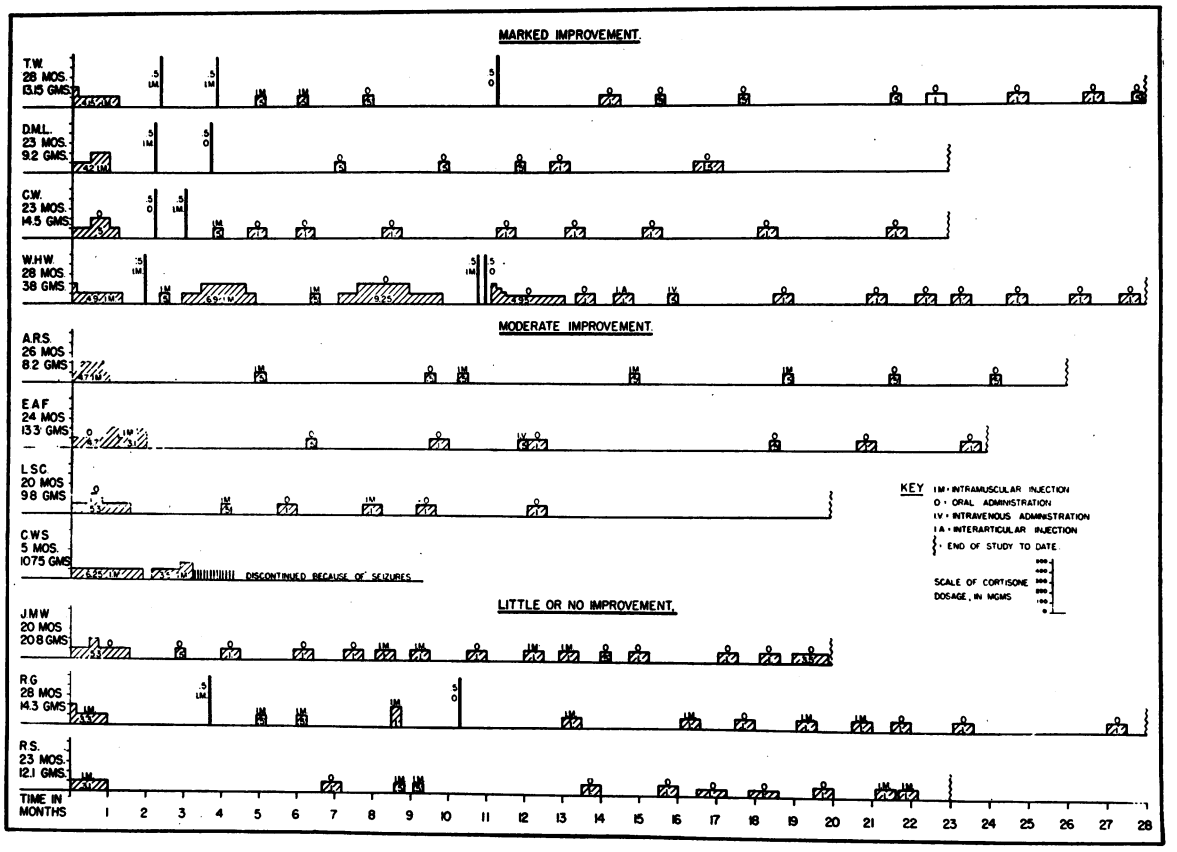

Fig. 2.—This figure records the total amount of cortisone used, the duration of the period of observation, the route of administration and the interval between courses.

former levels. The eosinophil count showed no consistent variation related to cortisone treatment.

No change in the blood electrolytes or serum protein was discernible.

Route of administration.—The route of administration of cortisone did not appear to have any relationship to the results since the same results were noted with both intramuscular and oral cortisone in most of the patients. Intravenous and intra-auricular routes in the same dosage gave similar results.

therapy, a change was observed consisting of a fall in the 17-ketosteroid level, which was more striking in those in whom the level was higher before treatment. This fall occurred in patients receiving both parenteral and oral cortisone.

The response to a single 20 mgm. intramuscular dose of ACTH (Thorne test) was established, before treatment, in a number of patients. Both eosinophil responses at four hours and 17-ketosteroid excretion over a six hour period after ACTH administration were measured. This information has been published[1] but, in summary,

it can be stated that a depressed response to ACTH for thirty days after the *initial* course parenterally, and twenty days when the oral route was used, was observed. Further studies are in progress to see whether the adrenocortical inhibition is correspondingly less with short courses of five and ten days.

Adverse effects. — These consisted of reactivation of well-controlled epilepsy during a long initial course in one patient, presumably due to hydration from salt and water retention.

While gastro-intestinal hæmorrhage occurred in two patients under treatment, there was no more reason to believe that this was due to the cortisone than to the aspirin compound consumed in the intervals between courses of hormone therapy. In one a new peptic ulcer was demonstrated by x-ray, while in the other, no such lesion could be found. Some retention of fluid occurred in two instances.

DISCUSSION

The intermittent rather than the continuous method of administration of cortisone was decided upon for the following reasons:

1. It was felt that the continuous use of an agent which resulted in the suppression of adrenocortical function might interfere with the spontaneous remission which, in the past, was encountered in a reasonable number of patients with rheumatoid disease.

2. To reduce the likelihood of the side-effects of continuous long-term administration. With the use of cortisone now on a wide scale, it has become apparent that a "tissue fastness" or resistance to cortisone develops in a good many patients in whom it is used continuously. This also we had hoped to avoid by using cortisone intermittently. We had also anticipated that following a "short burst" of cortisone, a return towards more optimal function of the adrenal cortex might occur.

After due consideration we adopted the change in work capacity or job performance as the main criterion for our evaluation of cortisone therapy in Marie-Strumpell spondylitis. The fact remains that all but one of these eleven patients are now working and this seems to us to be significant. Each patient had had previous admissions to hospital where basic, essential treatment had been employed, thus each had served as his own control.

The return of symptoms, with the cessation of cortisone, appeared to follow one of three courses: (1) Transient over-resurgence. (2) Rapid return of symptoms. (3) Slow return of symptoms. Over-resurgence was infrequent. Failure of cortisone, by this intermittent method of administration, would seem to be assured by a rapid return of symptoms. However, this was not invariably the case, as shown by the young man who had repeated, long courses over the first eighteen months, during which time he suffered a rapid return of symptoms on each occasion when cortisone was stopped. During the past ten months he has responded well to one gram supplementary courses with only a slow return of symptoms. Weight-bearing joints have been improved also by the concomitant use of compound F acetate* intra-articularly and he has now become self-supporting. If, after the initial course, the patient remains reasonably comfortable for three or four weeks without further cortisone, a good result may eventually be achieved.

As noted before, cortisone in these patients has been an adjunct to the basic program of treatment. Relief of pain made it much easier to provide emotional and physical rest. Exercise therapy was more successful. The physical gain obtained in the initial course was seldom lost when symptoms returned. Much of any such loss was quickly regained with the short supplementary courses. Cortisone proved to be a morale builder even in two of the three patients who were not materially benefited, for they could and do look forward to the comfort provided by the next brief course, though the effects were usually transient. The third patient was taken off cortisone because of persisting duodenal ulcer in the face of a poor response to treatment. Co-operation has been excellent and no one has asked that the treatment be stopped. These observations, together with the definitely improved work capacity of most of the group, influenced us in coming to the conclusion that there is merit in the intermittent technique of using cortisone at least in certain patients with Marie-Strumpell spondylitis.

The mechanism of action of cortisone in rheumatoid disease is still a matter of speculation. It is unlikely that the beneficial effect is related to the suppression of adrenal function. It would seem more reasonable to suppose that the

*Compound F was supplied by Merck & Co. Ltd., through the courtesy of Dr. J. H. Laurie.

activity of the rheumatoid process is dampened by cortisone which, perhaps, inhibits tissue response to the etiological agents. Following cessation of cortisone therapy, the disease process takes a variable length of time to be rekindled. The reason for this variation is unknown but may depend upon such factors as the intensity of the provoking stimuli and the rather nebulous quality known as host resistance. This concept seems to fit most of the clinically observed features. It has the advantage of recognizing the natural history of remission and exacerbation in the untreated condition and it served as a useful premise that resulted in our relatively satisfactory effort to employ cortisone intermittently at a time when its continuous use was universally advocated.

SUMMARY AND CONCLUSION

The intermittent use of cortisone in the treatment of a small number of patients with Marie-Strumpell spondylitis has proved an important adjunct to the basic program of treatment. Ten of eleven patients showed improved work capacity that can be attributed to the use of cortisone intermittently by short supplementary courses, over a period of twenty-four to thirty months.

The authors wish to thank Dr. M. M. Baird, Director of Medicine, Shaughnessy Hospital and the nursing and technical staff of the Clinical Investigation Unit for their assistance throughout this investigation.

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CASE REPORTS

PURPURIC ERUPTION DUE TO "SEDICIN"

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IN AUGUST 1952, Dr. J. R. E. Morgan of Peterborough referred to me two patients with bizarre, widespread purpuric eruptions. These eruptions in each case started on the feet and legs, spread to the thighs and later to the buttocks, lower trunk and forearms being most pronounced below the knees. The eruption resembled that described many years ago by Schamberg[1] as a peculiar, progressive, pigmentary dermatosis. In each case, however, the eruption had spread much more rapidly than in typical cases of Schamberg's disease. Morgan discovered that each patient had taken Sedicin prior to and during the course of the eruption. Following withdrawal of the drug, the skin gradually returned to normal.

Sedicin is a patent medicine sold by druggists without prescription and advertised widely in the daily press as a "safe remedy for insomnia and to relieve nervousness". It is acetyl-diethyl-bromo-acetyl urea and is an open chain ureide closely related to Sedormid and to the barbiturates. Joron, Downing and Bensley[2] report two deaths from Sedormid, in both of which there was marked central nervous system depression prior to death. They also report three other fatal cases in two of which there was cerebral purpura. The statement is made that Sedormid produces purpura even in small doses but there is no clear evidence that related ureides cause it.

The following case is briefly reported, together with a photograph of her feet and ankles, to show the type of eruption present.

A white female patient, aged 62, was first seen September 29, 1952. An eruption had started on her feet in July. This had spread to her legs, thighs, abdomen, buttocks and finally to her arms. There was mild pruritus. Because of the two previous patients who had eruptions produced by Sedicin, this patient was carefully questioned regarding the taking of medicine. She purchased Sedicin without prescription and took one tablet each night for one week in July, then increased to two tablets each night because she did not sleep well, and finally to three tablets. Following three tablets at bedtime she stated that she "felt stupid" the next day. She had taken three boxes of Sedicin prior to being seen.

The eruption developed after she started taking the Sedicin and became rapidly worse. The patient had applied various topical remedies to the skin without relief and it was becoming so pronounced and extensive that she was alarmed about it. On examination she appeared to be in excellent general health.

Involving the areas of skin mentioned previously there was a brownish red eruption, most pronounced on feet, ankles and knees and least pronounced on arms. The eruption consisted of patches of discrete and confluent, small macules which had a slight scale and in which there were minute hæmorrhages appearing like dots of cayenne pepper. There was also some brownish pigmentation about the small macules. The mouth and throat appeared normal. Capillary resistance test was normal.

Laboratory investigation.—Urinalysis, normal. Leucocyte count, 9,600. Bleeding time, 1 minute 35 seconds (normal). Coagulation time, 5 minutes 40 seconds (normal). Differential leucocyte count: neutrophiles 61.6%; eosinophiles 1.8%; lymphocytes 30.2%; endothelials 6.4%.

The patient was immediately advised to discontinue the use of Sedicin and all similar or related hypnotics and sedatives. The eruption began to fade within a few days