CORTICOTROPHIN INTRAVENOUS INFUSION THERAPY IN RHEUMATIC CONDITIONS

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It has long been known that temporary improvement may be observed in rheumatoid arthritis during pregnancy and jaundice due either to obstruction or to hepatitis. Less effective remissions have sometimes been associated with febrile reactions induced by the administration of foreign proteins. Comparable alleviation has also occasionally been observed following surgical procedures. Finally it must be recognized that from the very nature of the disease spontaneous remissions unrelated to any specific therapy may occur. This potential reversibility was discussed by Hench (1949), who indicated retrospectively the reasoning which led to the experimental administration of certain adrenocortical and anterior pituitary hormonal compounds in rheumatoid arthritis. It was in September, 1948, that the now classical experiment of the administration of the adrenal cortical hormone (17-hydroxy-11-dehydrocorticosterone) compound E, or cortisone, to a patient with severe rheumatoid arthritis was undertaken. In 1949 Hench *et al.* reported the rapid and striking improvement in the clinical and other features of the disease from both cortisone and corticotrophin (A.C.T.H.). Later, confirmation of these results followed with the experience of other groups—Thorn *et al.* (1949), Markson (1949), Elkinton *et al.* (1949), Ragan *et al.* (1949), Spies and Stone (1949), and Spies *et al.* (1949) with corticotrophin; Boland and Headley (1949) with cortisone; and Freyberg (1950), Hench *et al.* (1950), Rosenberg (1950), and the speakers at the Seventh International Congress on Rheumatic Diseases at New York, 1949 (1952) (Freyberg, Boland, Rosenberg, Holbrook, and Bauer), with corticotrophin and cortisone.

In all these original reports the corticotrophin was administered by intermittent intramuscular injections. However, a new therapeutic technique of prolonged administration by slow intravenous infusions was later described by Gordon *et al.* (1950), Renold *et al.* (1951), Mandel *et al.* (1951), and Jelliffe *et al.* (1951). The results obtained by these authors in rheumatoid arthritis and other conditions were so rapid and impressive as to suggest a superiority over the usual method of administration. This new method then seemed to be promising as a means of utilizing small amounts of corticotrophin and achieving maximum results. In this respect, 10–25-mg. doses of the ordinary soluble preparations available, administered slowly by the intravenous route, were reported as more effective than 100 mg. daily in divided doses by intramuscular injections. Moreover, it might be argued that this procedure seemed to imitate more closely the natural method of secretion as compared with intermittent (six-hourly) injections.

This paper records our experience with corticotrophin administered by slow intravenous infusion in the treatment of rheumatic conditions, as employed by us since August, 1951, at a time when both this hormone and cortisone were scarce.

The investigation was carried out amidst the ordinary day-to-day working of a busy rheumatic centre. For ethical reasons all the usually accepted methods of treatment have had to be employed—rest, correction of anaemia and other general measures, application of physiotherapeutic procedures, including manipulation, plaster corrective and occupational therapy, and general rehabilitation regimes. The corticotrophin infusions have thus been only a part of the general therapeutic scheme. However, the type of improvement is characteristic enough to present no great difficulty in differentiation and assessment. Our prime endeavour, therefore, was to ascertain how far the employment of the technique in conjunction with other routine methods would augment the total rehabilitation of the patient. A stage has now been reached where sufficient experience has been obtained to enable us to form some conclusions on the place and value of this method of treatment in the general problem of the therapy and rehabilitation of rheumatic patients. We have had to concern ourselves not only with the immediate response of the patients to the course of treatment as recounted here, but, in addition, with methods of maintaining the initial effects where favourable, their duration, and the incidence of relapse. These features will be the subject of further observations and later report.

Material Investigated

Our observations have extended from August, 1951, until October, 1953. All patients admitted to the rheumatic unit were considered for treatment; after diagnosis no selection was made either for the administration of the hormone or in the analysis of results. Although we were mainly concerned with the effects in rheumatoid arthritis, a few other rheumatic conditions were treated—psoriatic arthritis, ankylosing spondylitis, osteoarthritis, "frozen-shoulder" syndrome, and a miscellaneous group consisting of "fibrositis," Paget's disease, rheumatic fever, palindromic rheumatism, psychogenic rheumatism, and Raynaud's syndrome.

Altogether 425 patients (involving 516 separate periods of admission) were treated; their allocation to the various diseases according to sex and age groups is indicated in Table I.

TABLE I.—Different Diseases Treated

Disease	No. of Patients		Age Groups (Years)											
			20-29		30-39		40-49		50-59		60-69		70+	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Rheumatoid arthritis ..	90	239	5	19	15	43	26	56	33	77	10	39	1	5
Psoriatic rheumatism ..	—	4	—	—	—	—	2	—	1	1	—	1	—	—
Spondylitis ..	7	6	1	1	4	2	1	—	1	1	—	2	—	—
Osteoarthritis ..	4	44	—	1	—	—	2	—	2	12	2	19	—	10
Frozen shoulder ..	5	8	—	1	—	—	1	2	2	5	1	—	1	—
Miscellaneous* ..	3	15	—	3	1	3	—	1	1	5	1	3	—	—
Total ..	109	316	6	25	20	48	28	63	39	101	14	64	2	15
	425		31		68		91		140		78		17	

* Fibrositis, psychogenic rheumatism, Raynaud's syndrome, Paget's disease, rheumatic fever, palindromic rheumatism.

The rheumatoid arthritis group was the largest, comprising 90 males and 239 females—329 in all. A detailed description of these patients is presented in Tables II and III. The age groups most affected were 40–49 years (82 patients—26 males and 56 females) and 50–59 years (110 patients—33 males and 77 females). The duration of the disease was two to five years for 79 patients (23 males and 56 females), five to ten years for 88 patients (23 males and 65 females), and ten to twenty years for 76 patients (19 males and 57 females). Only 30 patients (10 males and 20 females) had the disease for less than one year.

TABLE II.—*Rheumatoid Arthritis. Functional Capacity Before and After Therapy in Relation to Age Groups*

Age Group (Years)		Class								Total				
		I		II		II +		III -				III		IV
		M	F	M	F	M	F	M	F	M	F	M	F	M
20-29	Before	—	—	—	2	3	5	—	7	2	4	—	1	} 5 19
	After	—	7	—	9	—	1	—	—	2	—	—	—	
30-39	Before	—	—	2	4	1	8	8	13	2	16	2	2	} 15 43
	After	2	13	11	16	1	11	—	2	1	1	—	—	
40-49	Before	—	—	3	5	8	8	7	19	7	18	1	6	} 26 56
	After	4	10	16	25	5	13	1	3	—	4	—	1	
50-59	Before	—	—	—	2	5	11	14	31	13	19	1	14	} 33 77
	After	2	9	20	32	9	16	1	11	1	7	—	2	
60-69	Before	—	—	1	3	2	1	3	17	3	13	1	5	} 10 39
	After	—	2	6	13	2	13	1	7	1	3	—	1	
70+	Before	—	—	—	—	—	—	—	1	1	1	—	3	} 1 5
	After	—	—	—	—	—	1	1	—	3	—	—	1	
Total	Before	—	—	6	16	19	33	32	88	28	71	5	31	} 90 239
	After	8	41	58	95	17	55	4	23	3	20	—	5	

TABLE III.—*Rheumatoid Arthritis.—Functional Capacity Before and After Therapy in Relation to Duration of Disease*

Duration (Years)		Class								Total			
		I		II		II+		III-				III	
		M	F	M	F	M	F	M	F	M	F	M	F
-1	{ Before After	— 1 10	— 9 6	3 2	3 2	2 2	11 2	5 —	4 —	— 1	{	10	20
1-	{ Before After	— 3 5	3 8 11	— 7	3 —	7 1	13 —	5 1	1 —	2 —		{	12
2-	{ Before After	— — 14	2 15 18	8 5 15	10 5	15 3	8 5	16 5	7 —	1 3	{	23	56
5-	{ Before After	— 2 5	1 17 35	4 16	8 3	11 16	8 4	22 —	6 1	21 4		{	23
10-	{ Before After	— 2 4	— 5 13	2 6	2 6	3 6	5 1	13 1	6 8	8 1	{	15	32
Over 15	{ Before After	— — 3	— 4 12	1 3	3 9	2 3	14 10	3 —	17 5	8 3		{	7
Total	{ Before After	— 8 41	6 58 95	19 17 55	33 55	32 4 23	88 23	28 3 20	71 20	5 — 5	{	90	239

In the rheumatoid arthritis group the duration of inpatient treatment varied from one to sixteen weeks. The usual periods were two to four weeks for 122 patients (22 males and 100 females) and five to eight weeks for 115 patients (22 males and 93 females). Only 25 patients (7 males and 18 females) were admitted for longer than twelve weeks. In the above group of 122 patients gold had previously been administered to 60 (9 men and 51 women), and in the group of 115 patients to 56 (8 men and 48 women). In the whole rheumatoid arthritis group of 329 patients, 165 (44 males and 121 females) had received previous gold therapy. Readmission for further infusion therapy on account of relapse was considered necessary on one or more occasions for 59 patients. This must not be regarded, of course, as the full relapse proportion.

Treatment

The great majority of our patients received the Armour Laboratory preparation "acthar," others the Organon, Wilson, or Crookes Laboratory material; some patients received preparations from two different laboratories according to the availability of supplies. With the usual precautions the ordinary (intramuscular) powdered hormone was dissolved in sterile normal saline (about 2 ml.), which was injected into the manufacturer's rubber-capped phial (for the Organon hormone sterile water had to be employed, as this particular material was supplied diluted with sodium chloride). The corticotrophin solution was then transferred to the infusion flask containing the vehicle. Nearly two-thirds of the patients received a total quantity of one litre of fluid in each infusion, the remainder one pint (568 ml.). After preliminary trials with various vehicles, the final choice was normal saline. More than one-half of the patients received infusions with normal saline as the vehicle.

In the beginning blank infusions were administered for control and comparison in some cases. No benefit was obtained by the patients from such administrations. In fact, the difference was apparent to them as well as to us through the absence of certain trivial but well-recognized accompaniments of the corticotrophin infusions.

Variations were made in the amount of corticotrophin in the infusions ranging from 25 mg. down to 5 mg. in an attempt to find the optimum dose for maximal clinical effect. We observed clinical responses with low dosages, such as 5 mg. Eventually, in view of variations in individuals, as well as possibly in material, 20 or 25 mg. was regarded as the standard dose, administered in one litre of normal saline. The entire 425 patients treated received a total of 1,490 infusions, and the total amount of corticotrophin used was no more than 28.12 g. Of the 1,231 infusions administered to the rheumatoid arthritis group of 329 patients, 738 infusions each contained a 20-mg. dose of corticotrophin and 229 a 25-mg. dose.

During any one admission the number of infusions administered to a single patient varied from 1 to 11; the total dosage of corticotrophin ranged from 10 to 227.5 mg. The most usual practice was to administer three infusions; actually this was the procedure in nearly one-third of the admissions.

As there was some experimental evidence that infusions prolonged beyond eight hours were more effective in terms of adrenocortical stimulation, variations were also made in the duration of administration. In a few instances the administration was prolonged even up to 72 hours. On the whole, the patients tolerated this well. A few permitted themselves little sleep or movement in their desire not to disturb the needle and connexions; some became apprehensive about the successful delivery of the drip during such lengthy periods. Further, these prolonged drips often resulted in local venous thrombosis. When all these factors were taken into account the optimum period was considered to be 18 to 24 hours. Thus, in actual practice, of the 1,231 infusions administered to the rheumatoid arthritis group, 507 were of this duration; 484 were of shorter and 240 of longer duration.

Second and subsequent infusions were given according to the individual response and the possible tendency to early relapse. The usual number of clear days intervening between the cessation of one infusion and the beginning of the next was six (four to seven). The duration, frequency, and number of infusions given were individualized according to the aims of treatment in relation to the particular problem presented by each patient. The necessity for administration of another infusion was thus indicated by (1) an obvious decrease in the beneficial effect obtained by the previous infusion, or (2) the desire to continue therapy until no further real benefit was obtained, or (3) in some cases an attempt to obtain amelioration, if possible, in a residual refractory joint. It will be appreciated that, no matter how much relief of pain and freedom of movement is obtained from an infusion, repair and re-education of atrophied muscles necessarily require some considerable time. Thus this therapy must be complemented by physiotherapeutic and rehabilitation procedures, which in turn are facilitated by reinduction of a waning remission.

In the early stages efforts were made to minimize the most frequent complication—local venous thrombosis—first by the change of glucose-saline to saline as the vehicle, and secondly by the addition of heparin to the infusion solution. This latter procedure resulted in flocculation; as heparin readily unites with protein compounds, it was then felt that an undesirable chemical interaction might have occurred, and the method was abandoned. Later, however, Linquette *et al.* (1952) apparently successfully added heparin, 200–400 mg., to each infusion. Recently heparin has been added to the infusion material without any apparent *in vitro* reactions. As indicated above, we now routinely use normal saline as the vehicle. Local thrombotic complications are now much less frequent.

In the beginning, because of the fear of sodium retention and oedema, restriction of salt in the diet was enforced, but later, when this procedure was relaxed, no untoward effects were observed. A full generous diet was allowed to all patients, unless suffering from obesity.

Attempts have been made to maintain improvement achieved by the corticotrophin drip method by the subsequent employment of certain other measures—for example, intermittent injections of adrenaline in oil or hyperdureic adrenaline, gold compounds, or long-acting corticotrophin compounds, oral administration of para-aminosalicylic acid, sodium salicylate, or phenylbutazone, and in some instances frequently repeated corticotrophin infusions or cortisone. These procedures are still being studied and modified, and it is hoped that the results will be reported later.

Accompaniments, Side-Reactions, and Complications of Therapy

In a total of 1,490 separate infusions no serious complications have arisen. On three occasions a moderately severe reaction took place, consisting of feelings of malaise and coldness, shivering, and pyrexia. This may have been due to impurity of the particular preparation in its protein content. Subsequently infusions were successfully given to these patients. More recently, a patient experienced a similar but very mild reaction with one particular preparation, but an alternative preparation of different manufacture was satisfactory.

The most annoying complication of the technique was the development of local venous thrombosis. Following multiple infusions this resulted in increasing difficulty. In advanced deformed and difficult cases, where repeated courses of treatment might be desired, it could be the limiting factor so far as the intravenous route was concerned. Full use therefore had to be made of the small veins on the dorsum of the hand in some cases. On one or two occasions it was necessary to resort to the venesection technique or to a subcutaneous infusion with the aid of hyaluronidase. The possibility that both corticotrophin and cortisone may alter the coagulability of the blood has received consideration by others. Rawls (1951), in a large series of patients treated with ordinary corticotrophin or cortisone, found the incidence to be 3%. Ragan (1952) and Chatterjea and Salomon (1954) also have drawn attention to the development of thrombo-embolic phenomena. During corticotrophin or cortisone therapy, Cosgriff *et al.* (1950) and Cosgriff (1951) observed an increased coagulability of the blood, which persisted for several weeks after withdrawal. However, the work of Smith *et al.* (1950) and McGraw *et al.* (1952) suggested two opposing coagulation effects; while Fahey (1951), and more recently Sussman *et al.* (1954), found no alteration in blood coagulability.

Oedema, production of hypertension, aggravation of existing hypertension, alteration in facial contour, and changes in mineral metabolism were not encountered. Abdominal cramps occurred in one patient during two successive infusions, but not in other patients receiving material from the same batch. At least three patients with a definite dyspeptic history were treated without ill-effect; one had had a partial gastrectomy, and one suffered from cardio-spasm.

Mild glycosuria during the day of the infusion and sometimes part of the following day was often noted. No permanent disturbance of sugar tolerance was observed; indeed, we have applied the method to known diabetic arthritides without any particular troubles other than some slight modification of insulin dosage for a day or two.

Certain other accompaniments were often reported—a temporary feeling of fullness or tightness in the frontal and temporal regions of the head, a “salty” parched taste in the mouth, and feelings of heat and flushing, especially of the face and extremities, often with sweating, and lasting several hours during the infusions. A feeling of hunger some hours after the start of the administration was frequently mentioned. All the patients took their meals well,

and all but the very apprehensive generally slept well while the infusions were running.

We have had no experience of the development of potassium deficiency. Muscle weakness, fatigue, or paraesthesiae which would indicate such a complication were not complained of by the patients. Blood potassium serial estimations and electrocardiograms would be helpful if a particularly long course of frequent high-dosage infusions was contemplated.

In summary it may be said that the method has been found safe. There has been no hesitation in its use when this was justified by the rheumatic condition. It has been withheld only in extreme cases of congestive cardiac failure. Hypertension, diabetes mellitus, and impaired renal function have not been regarded as contraindications. Signs of hypercorticism were never induced. In this respect it may be noted that only after daily infusions in doses of 5 to 20 mg. for periods of 6 to 25 days, yielding total dosages of 68 to 500 mg. of corticotrophin, did Cohen and Sulman (1954) find mooning of the face in five out of eight patients. Early signs of hypercorticism were observed by Mandel *et al.* (1951), who also employed daily drips in a similar dose range and total corticotrophin amount. It will be observed that our total dosage range was much smaller than that employed by either of the above groups, and, moreover, was administered intermittently in fewer infusions spread over a longer period of hospital admission.

Scheme of Analysis of Results

In our recognition of the importance of using some generally appreciated standards by which judgment could be passed on the therapeutic efficiency of the technique, we decided to employ, with a slight modification, the scheme recommended by the American Rheumatism Association (Steinbrocker *et al.*, 1949) so far as the cases of rheumatoid arthritis were concerned. Thus, according to this scheme there has been recorded the anatomical stage (which rarely was altered), the activity, and the assessment of the functional capacity before and after treatment. It is, of course, well recognized that a considerable degree of functional improvement may occur and yet the anatomical stage of the disease remain unaltered. It is therefore the induced remissions and the improvement in pain, stiffness, mobility, and hence the functional capacity, which have been of most interest to us.

Briefly, the anatomical stages were delineated by the following criteria: in Stage I (early), no destructive changes, radiologically; in Stage II (moderate), radiological evidence of osteoporosis with or without slight subchondral bone destruction, slight cartilage destruction, and limitation of joint mobility without deformities; in Stage III (severe), radiological evidence of cartilage and bone destruction and osteoporosis and joint deformity; and in Stage IV (terminal), fibrous or bony ankylosis. While the rheumatoid process usually advances to an approximately similar degree in multiple joints, sometimes two or more stages may exist in different joints in the same patient. It has been recommended that the stage should be determined by the state of the worst joint. We have modified this in so far as one advanced single joint—for example, an ankylosed interphalangeal joint—or a terminal condition of certain joints in a patient requiring treatment because of active, less advanced, but progressive arthritis in other joints has not determined the anatomical stage for the patient as a whole.

For the classification of functional impairment, the American scheme has been modified by the division into three subgroups (II, II+, and III-) of Class 2 (functional capacity adequate to conduct normal activities despite the handicap of discomfort or limited mobility of one or more joints). The classification utilized in this investigation was therefore as follows:

Class I.—Complete functional capacity, with ability to carry on all usual duties without handicaps.

Class II.—Functional capacity adequate to conduct normal activities despite handicap of discomfort or limited mobility of one or two joints.

Class II+.—Functional capacity adequate to conduct most or all of the usual duties and activities with considerable discomfort or limited locomotor ability of joints.

Class III-.—Functional capacity adequate to conduct some of the normal duties with considerable discomfort or limited locomotor activity of joints or ability to carry out some handwork with little or no locomotor ability (for example, kneeling, climbing) or fair locomotor activity with little or no handwork.

Class III.—Functional capacity adequate to perform only little or none of the duties of usual occupation or self-care.

Class IV.—Largely or wholly incapacitated, with patient bedridden or confined to wheel-chair, permitting little or no self-care.

Some of the basic features, of which full details are given in Tables II and III, may now be summarized. Of the total 329 rheumatoid arthritis patients, 120 (32 males and 88 females) were graded as Class III- and 99 (28 males and 71 females) as Class III. In the age groups 40 to 49 years 26 patients (7 males and 19 females) were in Class III-, and 25 (7 males and 18 females) in Class III; and in the age group 50 to 59 years, 45 patients (14 males and 31 females) were in Class III-, and 32 (13 males and 19 females) in Class III.

In the 2 to 5 years' duration group, 23 patients (8 males and 15 females) were in Class III-, and 23 (7 males and 16 females) in Class III; and in the 5 to 10 years' duration group, 30 (8 males and 22 females) and 27 (6 males and 21 females) were in Class III- and Class III respectively.

Results

Where benefit accrued from the treatment, the majority of the patients experienced a striking improvement after the first infusion, which subsequent infusions maintained with little or no increase; however, as indicated above, recovery and repair of atrophied muscles show a relatively slow progress, and the maintenance of the improved status is necessary for rehabilitation. Some few others showed gradually increasing benefit from a succession of infusions. A few patients who had shown no improvement with intramuscular administration of the hormone derived benefit following infusions.

Euphoria was a feature induced in most patients. We regarded this as a valuable contribution in the rehabilitation of a patient previously depressed and apathetic. Relief of joint pain and tenderness were obtained with resulting ease of movement. In some cases the actual increase in the range of movement was not great, but the ease of movement, the resulting feeling of satisfaction, and the recognition of what was still functionally possible in the diseased joints were of extreme importance in the encouragement of the patients, the improvement of their outlook, and the simultaneous development of a physiotherapy regime. Other important features were the sense of increased physical well-being, improvement in appetite, and the dissipation of malaise.

Experimental confirmation of the effect on the peripheral circulation was obtained. The resting digital circulation, as indicated by serial skin temperatures, was increased, and the previously sluggish induction of peripheral vasodilatation in the thermal response test of indirect heating was improved following a corticotrophin infusion (Beattie and Woodmansey, 1953).

As might be expected in rheumatoid arthritis, in general the anatomical status of the patient was not notably altered. At most an occasional patient might be assessed as passing from one stage only to the one above. An alteration in the anatomical stages occurred 25 times among females and 11 times among males—a total of only 36.

In rheumatoid arthritis the greatest alteration occurred in the functional capacity. The detailed assessments before and after treatment are presented in Tables II and III with reference to age groups and duration of disease respectively. The overall improvement in the functional assessments can be appreciated from Fig. 1 and Table IV. No patient was designated as of Class I status functionally before treatment, but attainment of this class occurred in 15% of the whole group. An elevation after treatment up to Class II or I was

obtained in 57% of the whole group. Improvement of some degree was obtained in 89% of cases. Both males and females showed a similar response. Patients previously treated with gold reacted in a similar manner to those who had not had this therapy (Fig. 1).

Owing to the absence of selection of patients it was not possible for the results to be assessed in sufficient detail

FIG. 1.—Change in functional capacity after treatment. The number of cases in the various classes previously treated with gold is indicated by the broken line, both in the shaded portion (before treatment) and the unshaded portion (after treatment) of the histogram.

TABLE IV.—Rheumatoid Arthritis. Alteration in Functional Capacity Per Class

Class Before Treatment	Class After Treatment											
	I		II		II+		III-		III		IV	
	M	F	M	F	M	F	M	F	M	F	M	F
I { M — F —												
II { M 6 F 16	1	7	5	9								
II+ { M 19 F 33	3	11	15	18	1	4						
III- { M 32 F 88	3	15	23	48	5	25	1					
III { M 28 F 71	1	8	14	19	8	22	3	12	2	10		
IV { M 5 F 31			1	1	3	4		11	1	10		5
Total	8	41	58	95	17	55	4	23	3	20	—	5

in the ordinary way, so that the attempt was undertaken by means of simple scoring, before and after treatment of each particular group as a whole. For this purpose tables of assessment and treatment data already compiled were utilized. The six functional classes—I, II, II+, III-, III, and IV—were allocated the arbitrary values of 6 to 1 respectively; the scores of each group before and after treatment were obtained from the product of the class values and the numbers in the classes; an improvement factor was represented by the difference in the scores before and after treatment, and this could be expressed as a percentage improvement factor. The fact that a group showed improvement does not, of course, imply that every member of the group improved by the same amount, but it does allow some comparison to be made between unselected groups.

Analysis along these lines showed the greatest improvement where the disease had been present for less than one year, with a gradual decline as the duration increased, but a further marked rise in improvement in cases of over 15 years' duration (Fig. 2). This latter effect may be related to the possibility that the disease at this time tends to be burnt out and that pain, soft-tissue stiffness, and apathy may be the cause of poor functional capacity. On the other hand, all age groups showed fairly comparable improvement (Fig. 3). For the functional classes as a whole, previous gold therapy did not affect the responses.

Again, using the simple scoring method, we investigated certain features regarding the infusions. Where the average duration of the infusions was about 18 to 24 hours the

response appeared to be maximal, and there was not much evidence of further improvement when the time was increased. There did not seem to be any clear evidence of greater improvement the larger the total amounts of corticotrophin administered. Increasing the overall average concentration above 0.9 mg. per hour did not result in increased efficacy. Further, there was no real evidence that increasing the number of infusions beyond three produced any better results. So far as the scoring figures go, they tend to support our clinical impression that the maximum effect was

FIG. 2.—Improvement in functional capacity in relation to duration of disease.

FIG. 3.—Improvement in functional capacity in relation to age groups.

practically obtained by one infusion of 18 to 24 hours' duration (containing 20 to 25 mg.). However, other factors, such as the poor condition of the muscles and pain, necessitated continuance of the infusion therapy while the appropriate remedial treatment proceeded. There was also some indication that the best interval between infusions was three to six days.

With regard to the other conditions treated, certain features are of interest. In two of the four cases of psoriatic arthropathy a dual remission was obtained, although the skin condition responded more slowly than the arthritic. In the other two cases the skin condition was resistant and the improvement in the arthritis was much less marked. Ankylosing spondylitis also showed some response. A remission occurred in two cases and considerable alleviation in seven others. An attempt was also made in osteoarthritis to apply the functional classification; considerable improvement was obtained in 25 patients, and 9 more were rendered symptom-free. Thus, in all, 34 out of 48 patients showed a favourable response to therapy. Of the 13 cases of the frozen-shoulder syndrome, six, all of whom were of the early acute type, showed complete or nearly complete relief. The response in the more chronic type was much less satisfactory.

Discussion

Apart from the initial classification of our material as shown in Table I, no further subdivisions of the rheumatoid arthritis group were attempted. As Sclater (1942-3) pointed

out, rheumatoid arthritis can no longer be described as predominantly a disease of young females, and the condition in about half the cases may start in joints other than the fingers and wrists. Further, Cecil and Kammerer (1951) found that in the aged (over 60) the condition does not essentially differ from that in the younger age groups. Our experience is in agreement with these views.

In all age groups and in both sexes satisfactory improvement was often obtained. The response in the older age group was especially gratifying. In fact, there was not much alteration in response in relation to the different age groups. However, at this stage we have not been able to say why some patients failed to respond. This lack of response did not appear to be related to any obvious clinical feature such as age, onset, acuteness, rapidity of development, or any other easily recognizable clinical feature.

Our clinical observations in this series, when compared with our previous experience of intermittent intramuscular injection therapy for these conditions, have confirmed the initial reports of Mandel *et al.* (1951) and Renold *et al.* (1951) regarding the superiority of the infusion technique in respect of the rapid and often striking symptomatic relief produced. The later reports of Linquette *et al.* (1952) and Prosiegel *et al.* (1953) have also produced similar evidence.

The duration of the disease in the past has been regarded as of importance in the determination of response to the usual lines of treatment. Sclater (1942-3) noted the steady anatomical deterioration with increasing duration, while the reports of others—for example, Cecil and Archer (1926), Steinbrocker (1946), and Short and Bauer (1948)—have indicated the more easily obtained and more satisfactory response of early cases. On the contrary, we have found that while there is a gradual decline in improvement with increasing duration, yet in cases where the disease has existed for a long time—over fifteen years—considerable functional improvement has been obtained. As indicated above, this latter effect may be associated with a burnt-out state of the disease at this duration and major disability resulting from pain, soft-tissue stiffness, and apathy.

It has not been possible to make a comparison between our present results in this short-term in-patient study of rheumatoid arthritis and those presented in our previous long-term out-patient survey with gold salts (Hartfall and Garland, 1935, 1936; Hartfall *et al.*, 1937). In the latter investigation the present newly adopted mode of classification was not used, and since then there have been changes in the social status of hospital patients as well as a greater realization of the importance of intensive rehabilitation.

It seems that corticotrophin does little or nothing to alter the established anatomical status of rheumatoid arthritis, except perhaps in the earliest stages. Applied to early cases, it may in some circumstances arrest and apparently induce suppression of the disease, at any rate temporarily. In most cases it appears to be a valuable method of producing alleviation of the symptomatic disabilities, of procuring maximum co-operation from the patient by indicating potentialities for improvement still resident in the body, and of promoting the early and intensive initiation of a rehabilitation regime. Quite apart from its use in the early, moderate, and severe cases in good anatomical and physical condition, there is a place for it in the more advanced and even crippled cases. In the latter, the main purposes are to reduce pain and induce euphoria. It is thus a valuable means of obtaining in some cases a quick and sometimes a striking temporary suppression of symptoms which may allow increased mobility and other forms of maintenance treatment, including a more rapid and more thorough development of a physiotherapeutic regime.

As a means of initiating a rapid response in any acute or subacute exacerbation the method has been very useful. We have employed it as a preliminary to some other form of maintenance therapy such as a phenylbutazone or chrysotherapy regime.

A useful field of employment has been to cover orthopaedic procedures, including manipulation for the breaking down of adhesions and for the correction of deformity.

In conjunction with cortisone therapy its use has been threefold: as a preliminary to routine cortisone maintenance to bring the patient under control quickly, from time to time to gain additional symptomatic improvement during the cortisone therapy, and to re-stimulate the pituitary-adrenocortical mechanism in those who seem to be losing ground on a dose hitherto nearly adequate to control symptoms.

With regard to the other conditions treated, it may be mentioned that in the few cases of psoriatic arthropathy the uncertain skin and joint responses observed were similar to those reported by Boland (1950a) and Hench *et al.* (1950) with ordinary corticotrophin therapy.

In osteoarthritis there may be theoretical arguments against the successful employment of corticotrophin (usually lack of inflammatory changes). We have treated 48 cases of osteoarthritis, and it seems clear that improvement has resulted. It may be, of course, that this has occurred in cases in which there has been some local superadded severe painful (inflammatory) condition, perhaps with accompanying effusion. We have no doubt that in painful osteoarthritis consideration should be given to the use of corticotrophin even if only as a temporary symptomatic therapeutic expedient. Dale (1950), Bauer (1950), and Dale and Amil (1953) have all noted a definite improvement following ordinary corticotrophin therapy in this condition.

In ankylosing spondylitis the method may be extremely valuable, the drips being interspersed in the course of a more prolonged therapeutic and rehabilitation plan. Infusion therapy has also been used by us in conjunction with deep x-ray therapy. Boland (1950b), McEwen and Bunim (1950), and Hart (1952) have found ordinary corticotrophin to be a potent weapon for short-term treatment of acute painful episodes in spondylitis. West and Newns (1954), however, thought that prolonged adrenal stimulation was justified only in the most severe cases.

In the acute cases of the frozen-shoulder syndrome with severe pain, occasionally a striking and rapid improvement is achieved, permitting the earlier initiation of a physiotherapeutic regime and sometimes producing an early termination of what is often a lengthy rehabilitation. In the more chronic cases with severe fixation or tissue calcification the results are usually poor and disappointing, and even when used before and after manipulation the results have not been impressive. Stein *et al.* (1953) were impressed with the acceleration of recovery when intravenous corticotrophin or an intramuscular long-acting preparation was used after manipulation.

About the small group of miscellaneous conditions we do not propose to make any definite comments except to say that we have not been successful in the relief of pain and stiffness in Paget's disease, but have had beneficial results in fibrositis and psychogenic rheumatism. From our general experience in cases with poor peripheral circulation we feel this technique might be useful in cases of Raynaud's syndrome.

In conclusion, it may be emphasized that there can be no doubt regarding the enhancement of the therapeutic effect when corticotrophin is administered by intravenous infusion. Moreover, a response can apparently be obtained upon occasions when no benefit has previously resulted from ordinary intramuscular administration. Further, there is a great economy in the material used and the labour involved when the regular intramuscular injections are superseded by the spaced intravenous infusions. There has also, upon analysis of our results, been confirmation of our clinical impressions that the more prolonged effusions of 18 to 24 hours were of greater efficacy; that there was no indication for dosages per infusion greater than 20 to 25 mg. or concentrations greater than 1 mg. per hour; that in general there was nothing to be gained by many frequently repeated infusions, the maximal effect being gained by the first few infusions; and that three to six days was a satisfactory interval period between infusions.

Summary

The application of a technique for corticotrophin therapy in rheumatic conditions by spaced intravenous infusions has been described.

The procedure has been found safe, economical, and free from side-effects such as hypercorticism, sodium retention, or permanent disturbance of carbohydrate metabolism.

Observations are recorded on the effects of this therapy, in conjunction with routine general supportive, physical, and rehabilitation regimes, on 425 patients.

The results obtained in the different conditions treated are presented: rheumatoid arthritis, 329 patients (90 males and 239 females); psoriatic arthropathy, 4 females; ankylosing spondylitis, 13 patients (7 males and 6 females); osteoarthritis, 48 patients (4 males and 44 females).

In the rheumatoid arthritis group, improvement of some degree was obtained in 89% of cases, and maximum improvement to complete functional capacity in 15% of cases.

The indications for the employment of this therapy and its value as part of the programme for rehabilitation in rheumatic conditions have been briefly considered.

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