plays no part in that response. On the contrary, the rats with denervated adrenals which have been given insulin in a dose well tolerated by normal rats are severely hypoglycaemic, comatose, or convulsing, so that we are in fact submitting the denervated animals to a much severer test instead of observing them and their controls under comparable conditions of stress. Equal depletion of adrenal ascorbic acid may actually constitute a diminished responsiveness of the denervated rat which is able to mobilize its A.C.T.H. only through the hypoglycaemia and not through the secretion of adrenaline as well. The results obtained on rats with denervated adrenals were confirmed in rats completely deprived of both adrenal medullae.

The second suggestion for a common factor releasing A.C.T.H. under all conditions of stress has been made by Sayers and Sayers (1947). Their hypothesis is as follows: in stress there is accelerated utilization of cortical hormones by the tissues, and therefore a low blood level of these hormones. This low level acts as a stimulus to the pituitary, which releases A.C.T.H. Conversely, output of A.C.T.H. is repressed when the level of circulating cortical hormones is high. This has been proved experimentally (Ingle, 1938; Sayers and Sayers, 1945) by showing that injection of cortical hormone inhibits the secretion of A.C.T.H. during stress. The stimulating effect of lack of hormone is much more difficult to demonstrate and has, so far, not been established.

Though we can be certain, therefore, that increased availability to the tissues of cortical hormones will check adrenocortical activity, we cannot be sure that lack of hormone will increase it by causing secretion of A.C.T.H. At present, however, this view is at least a good working hypothesis. It raises a number of further questions: is a low level of circulating cortical hormones the only stimulus which will induce the pituitary to give off A.C.T.H.? How does the role of adrenaline fit into the picture? Does it, too, like other forms of stress, act by increasing the utilization of cortical hormones in the tissues? Further, where are the receptors sensitive to low levels of circulating cortical hormones? Sayers and Sayers pictured them in the anterior lobe itself. For emotional stimuli, however, and for adrenaline, the work of de Groot and Harris (1950) and of Hume and Wittenstein (1950) suggests receptors in the hypothalamus. Does the whole control of A.C.T.H. secretion lie in the hypothalamus? To all these questions we can only guess the answers. And rather than by speculating, I should like to end by discussing a purely practical problem.

Conclusion

Shortage of cortisone and of A.C.T.H. has prompted the search for a treatment of rheumatoid arthritis which will stimulate the pituitary of the patient to secrete enough A.C.T.H. to obtain clinical improvement comparable to that achieved in the Mayo Clinic by injecting exogenous hormones. Insulin has been repeatedly tried, and, according, for example, to a recent report from the Oxford Regional Rheumatism Research Unit, with encouraging success (Kersley *et al.*, 1950). American authors, however, who gave insulin together with cortisone, had less convincing results (Henderson *et al.*, 1950), and Hench stated in a recent lecture at Edinburgh University that in the Mayo Clinic no benefit had been obtained from the combined use of insulin and cortisone. This apparent disagreement is easily explained in the light of the experiments referred to above, in which injected cortical hormones were shown to inhibit the pituitary response to stress. By giving the insulin along with the cortisone, the physician defeats his own ends, because he prevents the very release of

A.C.T.H. which presumably constitutes the beneficial action of insulin in rheumatoid arthritis. Insulin can be expected to have the desired effect only if allowed to act without a simultaneous check on the action of the anterior lobe. In this instance, the fact that cortisone was probably not available to the British workers has proved to be of unexpected benefit to their patients.

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OBJECTIVE ASSESSMENT OF IMPROVEMENT IN RHEUMATOID ARTHRITIS

BY

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Hench (1949) has shown that most of the manifestations of rheumatoid arthritis are potentially reversible. The introduction of cortisone and A.C.T.H. has further shown that reversal can be induced by these hormones, and that many features of rheumatoid disease can be influenced within a few hours of their administration (Hench *et al.*, 1950). In prolonged and intensive courses these changes can be observed by clinical examination and by simple tests of function as shown originally by Hench and other workers in America and more recently by Copeman *et al.* (1950) in this country; and indeed Hench considers that the patient's own assessment of his degree of improvement is one of the more reliable indices of progress. Subjective improvement and simple clinical examination are, however, both very susceptible to psychological factors, and in less experienced hands these methods have led to many false claims of which those made for deoxycortone acetate and ascorbic acid by Lewin and Wassén (1949), LeVay and Loxton (1950), and others are recent examples. These difficulties have been well illustrated by the work of Quin, Mason, and Knowelden (1950).

It would clearly be advantageous to have methods of studying rheumatoid arthritis which would provide some more sensitive and measurable indices of improvement, and if these methods were delicate enough to give a reliable index of the response to single injections of cortisone or A.C.T.H. they would provide a means of comparing the responses of a variety of unknown substances with known standard active and inert preparations all in the same patient. It would also be possible to study the responses of different patients to a single standard active injection, and to compare the responses in the same patients at different stages of the disease, thus providing much valuable information.

Methods of Study

Certain features of rheumatoid arthritis seem to be suitable for detailed study.

Joint tenderness is characteristic of active rheumatoid disease, and this can be estimated clinically by squeezing a joint with the hands or fingers. It can, however, be more accurately assessed by compressing a joint between sponge-rubber cushions and recording the pressure at which pain is first experienced. The small joints of the hand, particularly the proximal interphalangeal joints so often involved in rheumatoid arthritis, are most suitable for this purpose. In the apparatus used the joints are compressed from back to front, the fingers resting on a fixed rubber cushion and being compressed by a second rubber cushion of 1.5 cm. diameter carried on a spring-loaded piston. To avoid errors due to temperature of the kind described by Kellgren, McGowan, and Hughes (1948) the hand can be kept in a water bath at 35° C. With this apparatus pain is produced in the fingers of normal subjects only when pressure exceeds 6–8 kg. In the fingers of patients with active rheumatoid arthritis pain is produced with pressures ranging from 0.25 kg. upwards, depending on the severity of the disease, and in these patients the end-point is clearly defined, readings being reproducible to within 0.25 kg. With this technique a number of joints can be tested and an average figure obtained.

Weakness of grip, often extreme, is another frequent finding in rheumatoid arthritis. This feeble grip probably results from a combination of muscular weakness, joint pain and stiffness, and flexor tendon inefficiency produced by rheumatoid tendinitis and by the painful and impacted nodules described by Kellgren and Ball (1950). As the grip could be inhibited by local pressure on painful areas a method originally suggested by Dr. H. S. Barber was evolved. A canvas-and-rubber bag was constructed of suitable size for holding in the hand, and when connected with a mercury manometer and inflated with air to a pressure of 10 mm. Hg the bag moulds itself to a deformed or

stiff hand, and by asking the patient to squeeze it the power of grip can be measured by the height reached by the mercury column. The average of three grips with each hand is recorded, the figure accepted on each occasion being the highest which the subject can attain with slow steady pressure and sustain for a period of two or three seconds. Using this technique, normal subjects can always produce a pressure in excess of 300 mm. Hg, whereas patients with rheumatoid arthritis give readings usually varying between 30 and 200 mm. Hg, according to the severity of the disease, and in these patients readings are usually reproducible to within 5 mm. Hg.

Circulatory disturbances are another feature of rheumatoid disease. Local warmth is usually found over actively diseased joints, and a plethysmographic technique was therefore devised for measuring blood flows in involved knee-joints. The plethysmograph was constructed on the general lines described by Lewis and Grant (1925) and by Barcroft and Edholm (1943). The knee segment is placed in a thermostatically controlled water bath at 35° C., the knee being separated from the water by a sleeve of latex rubber held in close contact with the skin by water pressure, and cuffs are placed immediately above and below the segment, the lower occluding cuff being inflated to above arterial pressure before and during readings and the upper collecting cuff being raised rapidly to venous pressure when readings are made. The patient wears standard clothing and lies supine with the head resting on one pillow. The room is maintained thermostatically at 18° C. With this technique it was found that blood flows in normal knees varied between 1 and 2 ml./100 ml./min., while in actively involved rheumatoid knees blood flows varying from 3 to 20 ml./100 ml./min. were found.

Although the joints in rheumatoid arthritis are warm the extremities, particularly the fingers, are often abnormally cool and may display Raynaud-like phenomena. Skin temperatures were therefore recorded by thermocouples on the finger-tips during the conditions of standard exposure used for the measurement of knee blood flow.

FIG. 1.—Joint-pain, grip, and eosinophil readings in three types of rheumatoid arthritis patient on a basic hospital regime of bed-rest and without treatment.

Eosinophil depression in the circulating blood following the administration of cortisone and A.C.T.H. has been widely described, and throughout these studies eosinophils were counted at appropriate intervals. The method originally described by Dunger (1910) was used and was found to be satisfactory if precautions were taken in mixing and in time of counting.

Biochemical studies were also made during the prolonged courses of A.C.T.H. and on numerous other occasions. Detailed observations were made of the E.S.R., of a modified Rose's differential agglutination test (Ball, 1950), and of urinary uric acid and creatinine excretions. Electrolyte balance studies were undertaken by Professor R. Platt, of the University Department of Medicine, and 17-kestosteroids and cortin-like substances were measured by Dr. Hain and Mr. Bassil, of the University Department of Obstetrics. The well-known changes which accompany A.C.T.H. administration were observed, but these results will not be discussed here, as they do not appear to contribute to the present discussion.

Selection of Patients

These methods of study were applied to hospital in-patients suffering from rheumatoid arthritis in whom disability was judged to be mainly due to active reversible disease. The patients studied all had multiple joint involvement with radiological signs at least of osteoporosis; other stigmata of rheumatoid disease, such as constitutional disturbance, raised sedimentation rate, nodules, tendon lesions, and lymphadenopathy, were also present. These patients were placed on a basic hospital regime of rest in bed, during which drugs were not given. Daily or twice-daily measurements were made, and the results compared with daily standard clinical assessments of functional capacity and of

FIG. 3.—Knee blood flow and finger-tip temperature readings in a patient on 12.5 mg. of A.C.T.H. 8-hourly for 10 days.

joint pain, swelling, and range of movement. Three types of patient were identified, and an example of each type is recorded in Fig. 1.

Patient J.S. showed a steady improvement in all readings from day to day, and her subsequent progress and clinical assessment confirmed that she was going into spontaneous remission on rest in bed. Patient J.K. showed marked fluctuations in all readings from day to day, and these fluctuations were more pronounced than those revealed by standard clinical assessment. Patient W.B. showed only small fluctuations from day to day, and at the end of a week there had been little change in her measurements, and no change had been recorded in her general clinical assessment.

Patients of this last type, with active disease as defined above, were considered to be relatively stable but potentially reversible cases of rheumatoid arthritis and were selected for special study.

Results of Studies

Having selected patients of the type described it was necessary to determine if the methods used were sensitive enough to demonstrate the effects of a single dose of an active hormone. To eliminate psychological factors patients were told that they would receive a series of injections, most of which would be inactive, and in fact injections of normal saline or other inert substances were given at frequent intervals, and studied with equal intensity. The detailed effects were observed of single injections of 25 mg. of A.C.T.H. in six patients, of 5 mg. of A.C.T.H. given eight-hourly for 72 hours in four patients, of 12.5 mg. of A.C.T.H. given eight-hourly for 10 days to two patients, and of 200 mg. of cortisone acetate given in a single injection to five patients.

After a single injection of 25 mg. of A.C.T.H. (see Fig. 4) improve-

FIG. 2.—Knee blood flow and finger-tip temperature readings in a patient on 5 mg. A.C.T.H. 8-hourly for 72 hours.

ments occur in joint tenderness and grip, rising to a maximum in between six and eight hours, then falling, often to a rebound level within 24 hours, and returning to around the original level within 48 hours. During this period the circulating eosinophils are depressed, the maximum depression occurring between four and six hours after injection, preceding by about two hours the changes in joint tenderness and grip. The knee blood flow shows a diphasic response, a variable initial increase at six hours being followed by a rapid decrease between 8 and 12 hours. The skin temperature shows no change. If 5 mg. of A.C.T.H. is given eight-hourly for 72 hours the joint tenderness and grip improve more slowly, rising to a maximum at the end of this period, and the eosinophils become moderately depressed and remain so throughout the period. The knee blood flow, after showing an initial increase at the end of six hours, decreases to a lower level by the end of the period, and this decrease is accompanied by a rise in skin temperature on the finger-tip (Fig. 2). When 12.5 mg. of A.C.T.H. is given eight-hourly for 10 days these changes become very large. There is complete remission in joint tenderness up to normal levels, the grip becomes much improved, and the eosinophils remain greatly depressed throughout the course. Knee blood flow decreases steadily over the period following an initial increase, and finger-tip skin temperature rises and remains high (Fig. 3). After stopping these repeated injections the changes observed do not return to their original level in 48 hours but may remain at a new level for days or weeks.

With a single injection of 200 mg. of cortisone acetate (see Fig. 4) a slower series of responses occur, presumably due to slowness of absorption. Joint tenderness and grip show no tendency to improve for at least eight hours, and then rise slowly to a maximum in between 24 and 48 hours. The eosinophil depression is maximal at about 24 hours.

Knee blood flows have not shown the initial increase found with A.C.T.H., but decrease to a lower level in between 24 and 48 hours. One of the five patients tested with cortisone gave no response and was afterwards shown to be also refractory to A.C.T.H. During this series of observations no significant deviations in the curves were produced by injections of normal saline and other inert substances.

From this series of observations it was clear that with all these active agents grip and joint tenderness improved rapidly and eosinophil counts fell. The circulatory changes were interesting but more complex, the initial change in knee blood flow being either an increase or a decrease with single injections, and with repeated injection an eventual decrease in joint blood flow associated with a rise in finger-tip skin temperature. It was felt that this variable initial response precluded the use of joint blood-flow measurements as indicators of responses to single injections and that further studies would be needed to demonstrate their significance.

With the use of these techniques it was decided to make a preliminary survey of some substances claimed to be effective in rheumatoid arthritis, and simultaneously to determine if consistently positive results were obtained with substances of known potency. Suitable patients were selected by the methods already described, and they were told that they would be receiving a series of injections or tablets, most of which would be ineffective; but all patients received at least one injection of A.C.T.H. to demonstrate that they were in fact capable of responding, and at least one injection of normal saline to demonstrate any psychological response. In many instances also the observer did not know what substance had been given. An example of one experiment is shown in Fig. 4, in which the effects of 4.8 mg. of an A.C.T.H. peptide from the chemical and

FIG. 4.—Effects of 4.8 mg. of A.C.T.H. peptide compared with those of cortisone, saline, and A.C.T.H.

biochemical laboratories at Cambridge University were compared with 25 mg. of the original A.C.T.H. from which it had been prepared, with 200 mg. of cortisone acetate, and with normal saline. The magnitude and type of response to this A.C.T.H. and its peptide are very similar, and in this case biological assays in the Cambridge Laboratories had suggested that 4.8 mg. of this peptide fraction should be equivalent to 25 mg. of the original A.C.T.H., which had a potency 1.93 times that of the Armour standard L.A.1A.

In suitable patients studies of this kind continued over prolonged periods showed that without special therapy small fluctuations occurred in grip, in joint tenderness, and in circulating eosinophils, but these random fluctuations were small and often in opposite senses, improvement in grip being accompanied by deterioration in joint tenderness while the eosinophils fluctuated independently. With cortisone and A.C.T.H. fluctuations were always larger and in the same sense, a fall in eosinophils being accompanied by improvement in both grip and joint tenderness. It is clearly desirable to summate these fluctuations after giving them each a comparable weighting. As a standard the response six hours after a single injection of 25 mg. of A.C.T.H. has been taken. In 10 patients to whom the dose was given the average increase in grip was 26 mm. Hg, the average increase in pressure required to produce joint pain was 1 kg., and the average fall in eosinophils was 77% of the original count (see Table). Defining each of these as a unit of fluctuation, the scatter diagrams in Figs. 5 and 6 have been constructed. Fig. 5 represents the result of adding together units of fluctuation in joint tenderness, grip, and eosinophil counts, and each point represents this total fluctuation in one patient during the period stated in

TOTAL FLUCTUATIONS IN GRIP, JOINT TENDERNESS & EOSINOPHILS

FIG. 5.

to cause eosinophil fluctuations, and Fig. 6 has been similarly constructed, each point representing the summation of fluctuations in joint tenderness and grip only. Since the average deviation six hours after 25 mg. of A.C.T.H. is by definition 3 units in the case of Fig. 5 and 2 units in the case of Fig. 6, interrupted lines have been drawn in at half these values to represent the mid-point between absent response and average response.

In commenting on these results, it is clear that A.C.T.H. given in any of the three doses tested and cortisone given in single injections produce deviations which are outside the limits of chance deviations occurring on blank days or deviations associated with inert injections. The only exceptions are the ringed observations, all four of which occurred in the one refractory patient already mentioned. Apart from the active peptide (also illustrated in Fig. 4) the only substance so far used which produced significant deviations was aspirin, and of the 10 patients tested three appeared to be sensitive and seven insensitive. It is perhaps of interest that this sensitive group showed an eosinophilia in response to aspirin—a phenomenon we have also observed in four cases of acute articular rheumatism of rheumatic fever type. The group labelled steroids includes two compounds supplied by the Chemistry Department of this University, Δ^5 -cholene-3 β -25-diol and 17 α -allyl testosterone. The peptide fraction which gave no response was subsequently found to be inactive by rat assay at the Cambridge laboratories. The column labelled A.C.T.H.-Z3 contains results of preliminary trials with a new preparation of A.C.T.H.

Fluctuations in 10 Patients Measured 6 Hours After 25 mg. of A.C.T.H.

Patient	Eosinophil % Change	Pain Threshold Change (kg.)	Grip Change (mm. Hg)	Eosinophil Unit Change	Pain Threshold Unit Change	Grip Unit Change	Total Fluctuations
H.J.	-100	+0.9	+25	+1.3	+0.9	+1.0	+3.2
A.J.	-74	+0.7	+25	+1.0	+0.7	+1.0	+2.7
J.E.	-90	+2.1	+25	+1.2	+2.1	+1.0	+4.3
R.K.	-72	+1.9	+52	+0.9	+1.9	+2.0	+4.8
E.M.	-98	+1.5	+40	+1.3	+1.5	+1.5	+4.3
D.S.	-90	+0.9	+10	+1.2	+0.9	+0.4	+2.5
R.S.	-82	+0.8	+25	+1.3	+0.8	+1.0	+2.9
M.W.	-25	+0.2	+2	+0.3	+0.2	+0.1	+0.4
K.M.	-86	+0.6	+45	+1.1	+0.6	+1.7	+3.4
W.B.	-52	+0.4	+15	+0.7	+0.4	+0.6	+1.7
Total	-769	+9.8	+264				
Average fluctuations = 1 unit	-76.9	+0.98	+26.4				

the left-hand column. The whole diagram represents the results of trials on 18 patients, each patient having been given at least one known active injection, one control injection, and one or two trial injections on the general plan shown in Fig. 4. Certain substances could not be expected

TOTAL FLUCTUATIONS IN GRIP & JOINT TENDERNESS

FIG. 6.

The spread in deviation from 1.5 to 4.5 units among the active substances is largely due to variations in individual sensitivity, and underlines the necessity for establishing the degree of sensitivity and for comparing drugs in the same patient at times not far separated.

Discussion

From the data presented it is clear that the response of rheumatoid patients to substances with cortisone-like or A.C.T.H.-like activity can be measured with some accuracy. Small single injections allow the patient to return to his original level in 48 hours, but repeated injections often cause prolonged changes in the patient's condition after they have been discontinued. Thus, provided that only single injections are given, the responses in a single patient may be used to compare the potencies of different preparations of these hormones, and unknown substances may be rapidly evaluated by comparison with A.C.T.H. or cortisone of known potency. Apart from such practical considerations, a study of these responses in different patients and at different stages in the disease process may produce some further information about the role of adrenocortical activity in rheumatic diseases.

The mechanism of the interesting changes induced by cortisone and A.C.T.H. in joint blood flow and in finger-

tip skin temperature also requires further investigation both in the normal and in patients with the more severe Raynaud-like syndromes which are found in a variety of rheumatic and peripheral vascular diseases.

Summary

Sensitive and reliable methods for studying some of the features of rheumatoid arthritis have been evolved. These include measurements of joint tenderness and the power of grip as well as plethysmographic studies of knee blood flow.

In suitable patients these methods can be used to study in detail the response to single injections of cortisone or A.C.T.H., and the responses to these substances have been compared with those obtained from inert control injections, and with other substances of unknown potency.

In rheumatoid arthritis knee blood flow is raised while the finger-tips remain abnormally cold. Administration of A.C.T.H. and cortisone reverses these changes, the knee blood flow falling towards normal while the finger-tip temperature rises.

When more cortisone and A.C.T.H. become available much useful information may be gained by studying the responses to standard doses in different patients, and in the same patient at different stages in the disease process.

Much of the A.C.T.H. used in these studies was donated through the kindness of Dr. W. Tindall, of Messrs. Organon Ltd. Cortisone and other A.C.T.H. were supplied through the courtesy of the Medical Research Council. The A.C.T.H. peptide was provided through Professor A. R. Todd, F.R.S., and Professor F. G. Young, F.R.S., of Cambridge University. The Δ^5 -Cholene-3 β 25-diol and 17 α -allyl testosterone were supplied through Professor R. E. Jones, of the University of Manchester. Thanks are due to Dr. R. Moore, who made many of the routine clinical assessments, and particularly to Dr. J. H. Kellgren for advice and criticism throughout.

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A two years' antimalarial campaign began in British Honduras in May, with the help of a grant of \$22,000 from the United Nations Children's Emergency Fund (U.N.C.E.F.). Malaria is endemic and a principal cause of sickness, being responsible for up to 20% of hospital admissions and 9% of certified deaths in the colony; and it is hoped that by spraying every single house twice a year with 5% emulsion of D.D.T. in xylol, and by distributing free prophylactic "paludrine" to selected schools as well as using the well-known routine measures, the great success achieved in similar campaigns in Cyprus and British Guiana will be repeated here.