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RHEUMATIC DISEASES IN THE U.S.A.*

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Clinics and Hospital Facilities for Rheumatic Diseases

The publication in 1949 of a survey of research on rheumatic diseases in the United States by a committee of the National Research Council provided ample evidence that the rheumatic diseases constituted a major social and economic problem. In its final report the committee says that the most common cause of chronic illness in the United States is the group of rheumatic diseases. They estimated that some 7,500,000 Americans suffer from arthritis or some other form of rheumatism, and that 30,000,000 people, counting the families of arthritics, are concerned with the medical, social, and economic aspects of this problem. In 1939, 97,200,000 days of work were lost as a result of rheumatism, amounting to a financial loss of \$500,000,000 a year. The estimated yearly cost of medical care was \$100,000,000.

In 1949 there were only 65 specially endowed beds for arthritic patients in the United States as opposed to 100,000 free beds for patients suffering from tuberculosis. There would appear to have been little change in the position since the time of the committee's report. It was found that in the majority of hospitals visited clinics have been established, staffed by physicians with a special interest in rheumatic diseases, but few beds are available for patients in need of hospital care. As a rule patients are referred to these clinics from the medical out-patient department or from the medical and surgical services of the hospital for consultation. A proportion remain under the care of the clinic for treatment, the remainder being returned to the referring service. In the case of patients requiring in-patient care, admission to beds in the general medical wards is arranged, and treatment is carried out along the lines indicated by the physician in charge of the rheumatic clinic. Responsibility for these cases, however, is borne by the visiting physician to whose ward they have been admitted.

Few of the physicians who have made a special study of rheumatic diseases have direct charge of beds. This arrangement arises from the belief held by most physicians in America that the chronic rheumatic diseases form an integral part of the field of general medicine, and that their segregation in special wards or units would

be a retrograde step, leading to undue specialization on the part of doctors in charge of such units, to their detriment as general physicians. Experience in Britain would suggest that from the point of view of the arthritic patient there is a real need for a limited number of such special units, where the problems of treatment can be studied and research carried on under unified control. It must be borne in mind, however, that the development of such units in America presents a much more difficult problem on account of the high cost of hospital care and the limited number of free beds. In a number of the teaching hospitals State grants are available which enable selected patients to be admitted for long-term study and treatment. Twenty such State beds are available in the Massachusetts General Hospital, Boston, in the arthritis service directed by Dr. Walter Bauer.

An exception to the general rule is the Robert Breck Brigham Hospital, Boston, where some 30 beds are available in the public wards for rheumatic patients. Even in this specially endowed hospital, rising costs have led to a reduction in the number of beds, and there are few non-paying patients even in the public wards. Application for admission to this hospital is made by the patient's own doctor, who gives details of the clinical and financial status of the patient. Patients are followed up after discharge in home service clinics run by the eight physicians on the visiting staff. This hospital provides a very complete service for rheumatic patients, including orthopaedic and surgical care, and it appears to be the only institution of its kind in America.

Arthritis and Rheumatism Foundation

Mention must be made at this point of the Arthritis and Rheumatism Foundation, which was incorporated in 1948 with the following purposes: "To formulate and carry out a national program of research and education in the rheumatic diseases in order to discover the causes and to develop methods of prevention. To promote on the local level more effective methods of diagnosis for sufferers, more facilities for treatment and for training physicians in rheumatic diseases. To provide systematic re-training and rehabilitation for those disabled by rheumatic diseases."

By 1950 eighteen Chapters of the Foundation had been organized throughout the nation and appeals for funds successfully launched. In New England considerable progress has been made by the Chapter in organizing

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a programme of information for physicians, in the form of lectures and clinical demonstrations and the distribution of scientific literature; in the award of clinical fellowships to doctors practising in more remote districts to enable them to pursue special studies at a teaching centre for three months to a year; in providing financial support and professional service to arthritis clinics in country districts; and in aiding patients to obtain admission to hospital. The activities of the New England Chapter are guided by a whole-time medical director, who is advised by a medical and scientific committee. If Chapters in other States are meeting with a similar degree of success, the activities of the Arthritis and Rheumatism Foundation will do much to better the lot of sufferers from rheumatism in the States, who might otherwise experience considerable difficulty in obtaining early and adequate treatment.

Interest in Chronic Rheumatism

The advent of cortisone and A.C.T.H. has done much to arouse interest, both lay and medical, in chronic rheumatism in the United States, and considerable sums of money are now available for research. It is felt, however, that, owing to the structure of hospital organization and the rising cost of in-patient treatment in the States, there are too few beds available for severely affected patients requiring more detailed study and prolonged treatment. The administration of cortisone by mouth has proved very effective in the suppression of symptoms even in severely incapacitated patients. Oral cortisone is now available on prescription throughout the country, and it is felt that its indiscriminate use on an out-patient basis may temporarily obscure the need for more adequate provision of hospital accommodation for the rheumatic diseases. The limitations and risks of long-term cortisone therapy will be discussed later, but it may be said at this point that the hopes aroused by the first reports of its use in rheumatoid arthritis, that an effective means of controlling the disease had become available, have not been confirmed by experience gained during the past two years.

In comparing the state of affairs in Britain with that in the United States, it is felt that the development of a limited number of special units in connexion with teaching hospitals and universities under the control of full-time physicians, which is taking place at present in Britain, is on the right lines. In the States there is as yet no evidence that such a policy is likely to be developed, for the reasons given above, although the activities of the Arthritis and Rheumatism Foundation will undoubtedly improve the facilities for the diagnosis and treatment of the rheumatic diseases.

A.C.T.H. and Cortisone in the Rheumatic Diseases

Since the report by Hench and his colleagues in the Mayo Clinic of the dramatic suppression of symptoms following the administration of compound E (cortisone) or adrenocorticotrophic hormone (A.C.T.H.) to patients suffering from rheumatoid arthritis a vast literature on the subject has accumulated. No attempt will be made to review the innumerable papers that have appeared in medical journals since 1949. It will suffice to state that the original claims have been fully substantiated by many workers all over the world. That overdosage effects of greater or lesser significance appear sooner or later in about 50% of cases was made clear by Hench in his original and subsequent papers.

The object of the present inquiry was to ascertain the opinions of experienced physicians who had been using the

hormones for the past two years on their ultimate place in the treatment of the rheumatic diseases. This question was discussed in detail with many workers, and, although considerable divergence of opinion exists both on the therapeutic value of A.C.T.H. and cortisone and on the mode of action of the adrenal steroids, an attempt will be made to review the position as fairly as possible.

First, it is universally agreed that neither A.C.T.H. nor cortisone has any curative action in disease, although in certain self-limiting conditions symptoms may apparently be completely suppressed until the disease has run its natural course—for example, in acute rheumatic fever. It is also agreed that, if high doses of either hormone are required for any length of time, overdosage effects will eventually appear. Withdrawal of either hormone is followed in most cases by a return of symptoms. In a smaller proportion of cases cessation of the administration of cortisone is followed by the severe and prolonged "post-cortisone withdrawal syndrome," which will be discussed later. With these general considerations in mind, experience of the use of the hormones in rheumatoid arthritis will be considered in more detail, as a large number of cases have now been studied in those centres where long-term trials have been run. The majority of patients have received cortisone by parenteral injection, or, more recently, by mouth, as the injection of A.C.T.H. four times daily renders its use a much less practical procedure outside hospital.

Long-term Use of Cortisone in Rheumatoid Arthritis

Rheumatoid arthritis varies in its clinical course. In the earlier stages of the disease spontaneous remissions are not uncommon, but most cases relapse and run a subacute or chronic course over many years. The rapid suppression of pain and restoration of mobility and function which followed the administration of cortisone demonstrated for the first time that symptoms could be effectively controlled even in the active stages of the disease. It was natural to think that a really effective method of treatment had become available in a disease which had previously proved singularly resistant to all forms of therapy. Experience has shown, however, that various overdosage effects may complicate the picture during prolonged administration of cortisone. Their incidence is high when the daily dose is 100 mg. or more. Under 50 mg. a day these effects become much less common. Unfortunately, only a small proportion of patients derive significant benefit in the lower dose range (25–50 mg. daily).

In most of the American series of cases some 50% have shown side-effects of one kind or another. The significance of these effects varies. Some are of little importance and are readily accepted by patients for a time without complaint—for example, mild oedema due to salt retention, rounding of the face, increased hair growth, striae, acne, disturbance of menstruation, nervousness, mild depression, headaches, dizziness, blurring of vision, tachycardia, exhaustion, insomnia, obesity due to increased appetite. In long-term administration, however, the persistence of one or more of these minor effects may so disturb the patient as to necessitate withdrawal of the hormone. Other effects are more serious. Signs of intercurrent infection may be masked. Although there is no clear evidence that cortisone inhibits the production of antibodies, it may lower the resistance of the tissues to invasion by pathogenic organisms and their toxins. This may be directly related to its ability to inhibit or suppress inflammatory reactions which are likely to form an important part of the body's defence mechanism. Cases have been reported in which such inhibition of the symptoms of infection have had serious consequences, and this constitutes one of the real hazards of cortisone therapy.

Activation of quiescent tuberculous lesions has occurred. Massive haemorrhage from the gastro-intestinal tract and perforation of peptic ulcers have been reported from several centres. In older patients fractures of the long bones and collapse of vertebral bodies constitute a real risk. Thrombo-

phlebitis, pulmonary infarction, coronary thrombosis, and major psychotic episodes are among the other less frequent but more serious complications which may occur. In the individual case which has previously been adequately controlled the underlying disease process may become more acute, and symptoms may reappear which necessitate an increase in dose from a safe to a more dangerous level. Warning of such an event may be given by an increase in sedimentation rate or a rise in circulating eosinophils, although this occurs in a fairly high proportion of long-term cases without recurrence of symptoms. In other cases a progression of the damage in the joints has been demonstrated radiologically when symptoms have remained under adequate control. It would appear, therefore, that, although pain and stiffness may be abolished with a corresponding increase in functional activity, the disease process may not be completely arrested. Under these circumstances increased function, unrestrained by pain, may cause further articular damage, the effects of which may be appreciated only at a later date.

Complications of Cortisone Withdrawal

If the administration of cortisone has to be stopped for any of the reasons given, or because of financial considerations, a significant proportion of cases suffer from what has come to be described as the "cortisone withdrawal syndrome." Symptoms may appear within a few days of withdrawal or be delayed for a week or two. These patients complain of profound weakness and exhaustion, generalized aching pain and stiffness in joints and muscles—no longer relieved by the usual doses of analgesics, made worse by activity and relieved by sleep—anorexia, mental depression, and weight loss. Similar symptoms occur after partial adrenalectomy in Cushing's disease, but do not appear to be directly related to suppression of the adrenal cortex. The electrolyte pattern may be normal and the response to A.C.T.H. adequate long before symptoms disappear, which may be a matter of weeks or even months. Excretion of 11-oxysteroids may be within the normal range. A possible explanation may be that the tissues become conditioned to a high level of circulating steroids, and symptoms arise as a result of a relative deficiency. This view is confirmed to some extent by the fact that withdrawal symptoms rarely appear unless cortisone has been given for several months. When this syndrome is accompanied by an acute exacerbation of the rheumatoid process the adverse effect on the patient's physical and mental condition may be very severe.

A much rarer complication of cortisone withdrawal has been the appearance, in several cases of rheumatoid arthritis, of the signs and symptoms of disseminated lupus erythematosus or periarteritis nodosa. None of these cases have as yet been reported in the literature, but several have been examined personally, and the case records of others have been studied. This may be further evidence in support of the possibility that in certain instances cortisone may render the tissues more vulnerable to some unknown tissue-damaging agent which may be present in the collagen group of diseases. Too much significance should not be attached to these clinical observations at this stage, but certain experimental evidence would seem to point in the same direction.

A Conservative Attitude

The accumulated experience of the use of cortisone in rheumatoid arthritis during the past two years in America has led physicians to adopt a much more conservative attitude towards its routine employment. It is no longer regarded as a substitute for other forms of treatment. It has been found that only in about one-third of the patients started on treatment can a useful suppressive effect be maintained at a dose level which causes no undue disturbance. Complete suppression of symptoms is no longer aimed at. The dose is adjusted to control pain and stiffness to an extent which will enable a reasonable functional level to be maintained. The hormone is used as an adjunct to

other forms of treatment which by themselves have failed to restore a useful degree of function. The basic regime of general supportive measures, physiotherapy, gold, and rest splints is tried for several months before cortisone is prescribed, and is continued along with cortisone. The presence of significant articular damage will limit the value of the hormone, and preference is shown for early cases in which the pathology is still potentially reversible and in which a smaller dose will suffice.

The high initial suppressive doses (200–300 mg. daily) are no longer used in many centres, including the Mayo Clinic, because it has been found that patients who have experienced complete relief in the early stages of treatment find it difficult to accept even a partial return of symptoms when the dose is lowered to a safe maintenance level. This has led to difficulty in controlling the dose level in out-patients, who may occasionally obtain additional supplies at high cost from black-market sources. The disappearance of the initial euphoria may also cause psychological disturbance both in the patient and in his relatives. The more general practice is to start with between 50 and 75 mg. daily and adjust the dose up or down during the first weeks of treatment. In those patients in whom the useful dose is unduly high, treatment can be stopped before troublesome side-effects appear. Many methods of administration have been tried—intermittent and continuous courses of cortisone alone, cortisone combined in various ways with A.C.T.H., both continuous and intermittent, reduction of the frequency of administration to once, twice, or thrice weekly, low continuous maintenance dose with occasional booster doses, and so on, but no technique has been evolved to date by which satisfactory control can be maintained in all cases without side-effects. Individuals vary widely in their requirements, and alterations in dose may often be necessary in the same patient.

Precautions in Use

Oral cortisone is now the most commonly used form. Rapid absorption from the alimentary tract takes place, and tablets (25 mg.) are given three or four times a day, preferably after meals; otherwise the rapidity of absorption may cause nervousness and inability to concentrate. The dose by mouth is generally the same as that given by intramuscular injection, although in a few patients more is required to produce the same effect by the oral route as was previously obtained by injection. Cortisone is now available in a form which can be given by intravenous injection, and trials of this preparation are under way at the present time. It was hoped that, given by this route, the effect might be more prolonged. These hopes have not been fulfilled. The therapeutic effect is good, but is not sustained.

Cortisone has been given in combination with various other substances, such as gold, para-aminobenzoic acid, ascorbic acid, insulin, oestrogens, and testosterone. No definite conclusion can be reached at the present time, but on the whole such combinations have been disappointing. Claims have been made on behalf of insulin and para-aminobenzoic acid, but these require confirmation. The administration of oestrogens may minimize side-effects, especially in post-menopausal women. Negative nitrogen balance can be corrected by testosterone, but this is seldom necessary in patients who are not on a restricted diet. Restriction of salt and the administration of potassium chloride may correct disturbances of the electrolytic balance. Antibiotics should be used in adequate doses when infection is suspected in a patient receiving cortisone. These various precautions, combined with close clinical supervision, render the use of cortisone less hazardous, but it has become clear that the use of the hormone in the long-term control of the symptoms of rheumatoid arthritis is not as yet a practical procedure. The approach must still be experimental, as has been repeatedly emphasized by Dr. Philip Hench.

If further evidence be produced to show that its effect is only to suppress symptoms, leaving the underlying disease process unchecked, then the attitude of the medical profes-

sion towards its use in inflammatory diseases of unknown aetiology may have to be revised. In rheumatoid arthritis in particular, in which marked increase in the functional use of the affected joints follows the administration of cortisone, the possibility that articular damage may be increased rather than reduced must receive careful consideration. The answer to this question can come only from detailed follow-up studies of patients given cortisone over long periods.

Some observers had noted the fact that prolonged remission tended to occur most often in those patients who had received high doses. On this basis the effect of 500 mg. of cortisone daily has been tried on a number of cases for periods of 14-30 days. The results in terms of duration of remission following treatment have been encouraging, but all patients have eventually relapsed, and it is very doubtful if such high doses are justifiable unless clear evidence is obtained that there has been induced a fundamental alteration in the course of the disease.

The answers to many of the problems discussed will come from the continuation of the carefully controlled studies which have been going on in America during the past two years, and for a shorter period and on a smaller scale in Britain.

Short-term Use of Cortisone

Cortisone can be given in effective doses over short periods without undue risk, and in certain circumstances such a use of the hormone may serve a valuable purpose in rheumatoid arthritis. In severely ill bedridden patients running a progressively downhill course, and where the disease cannot be controlled by other means, cortisone may be used to reduce pain and spasm sufficiently to allow other forms of treatment to be applied more effectively. Deformities due to muscle spasm may be corrected and the position maintained by splints after cortisone is stopped.

Where deformities have developed owing to soft-tissue contractures, cortisone may render their correction by manipulation easier and damp down the flare which sometimes follows this procedure. Cortisone may be similarly useful when orthopaedic surgery is indicated in more advanced cases. Synovial inflammation and congestion can be lessened. Post-operative complications are reduced by the fact that physical methods of treatment can be applied early. Wound-healing is not significantly delayed by the doses required to secure these effects. Antibiotics are used routinely in these cases, and wounds are carefully watched for signs of infection.

Short courses of cortisone may thus prove a useful aid in the rehabilitation of crippled patients.

Intra-articular Injection.—That cortisone can act when applied locally has been clearly demonstrated in inflammatory conditions of the eye. Suppression of pain and swelling has followed its injection into the affected joints in rheumatoid arthritis: 25-50 mg. of cortisone acetate suspension has been used. The beneficial effect lasts four to five days on an average, but may be maintained in isolated cases for two to three weeks. Unfortunately, repeated injections appear to cause irritation and the joint tends to deteriorate. Compound F has proved much more satisfactory for this purpose. Mention will be made of this later.

Compound F.—In recent months increasing amounts of compound F have become available in the States for clinical trial. Up to date, it appears that there is no fundamental difference in the clinical effects of E and F. Occasionally it has been found that more F is required than E to produce the same effect, but this is by no means always the case. Side-effects are the same. Enough experience has not yet been gained to reach more than tentative conclusions regarding the value of compound F as compared with E when given by injection or by mouth, but for local injection into joints compound F seems much more satisfactory. Repeated injections can apparently be given without ill effect, with satisfactory suppression of local symptoms, and with no effects due to absorption from the joint. This method of

treatment may prove of real value, especially in cases crippled by pain and swelling in the weight-bearing joints. A weekly injection of 25-50 mg. is adequate in most cases. Much more experience is required before the real value of this mode of treatment can be assessed, but the preliminary results are encouraging.

A.C.T.H. in Rheumatoid Arthritis

From the therapeutic point of view, the action of A.C.T.H. in rheumatoid arthritis is similar to that of cortisone. The cortex of the adrenal gland is stimulated to produce large amounts of steroid hormone, probably compound F. A.C.T.H. is quickly destroyed, and to maintain its effect injections, subcutaneous or intramuscular, must be given every four to six hours. Attempts to produce the hormone in a vehicle which would prolong the time of absorption have not yet been completely successful. In several American clinics patients or their relatives are taught to give the injections at home, but abscesses often develop, and may remain unsuspected because of inhibition of the normal inflammatory reaction. These abscesses may be very slow to heal. More recently A.C.T.H. has been given by slow intravenous drip over a period of 8-12 hours (20-50 mg. in a pint (570 ml.) of saline). This method of administration, possible only in hospital, is more economical of material and is said to produce maximal adrenal stimulation. It was hoped that more prolonged remission of symptoms might follow, but experience to date has not been very promising in arthritis. Patients have relapsed within a few days of the cessation of daily intravenous A.C.T.H. given for two to three weeks.

Side-effects are similar to those which occur during the administration of cortisone, but there is a greater tendency for salt retention and potassium loss to occur. Clinicians have noted considerable differences in potency between batches, although there has been little variation in the results of the ascorbic-acid-depletion test of Sayers and Sayers. It may be that this test is not a reliable guide to the effectiveness of A.C.T.H. in the clinical field. These variations and the necessity for several injections daily have limited the use of A.C.T.H. in long-term treatment of rheumatoid arthritis. Suppression of symptoms is attained more quickly by A.C.T.H., and where the rapid effect is required A.C.T.H. may be preferred to cortisone. These circumstances will rarely arise in rheumatoid arthritis, but may be important in more acute diseases such as rheumatic fever. Astwood, in Boston, has evolved methods for obtaining a much purer form of A.C.T.H., and he states that some patients can be maintained in remission by a total daily amount of about 1 mg. given in three doses. Possible future developments in the use of A.C.T.H. may depend upon the availability of purer forms, prepared as long-acting substances which will reduce the number of injections required. In general the factors limiting the long-continued use of cortisone are also applicable to A.C.T.H. For short-term administration, where a rapid suppression of symptoms is the main object, A.C.T.H. is the more suitable of the two.

Research

To a person from Britain visiting centres of research in the United States the first impression is one of awe at the scale on which modern techniques are being applied to the study of basic problems in health and disease. In many university centres large laboratory buildings have been built since the war, or are in process of erection. All the basic sciences are represented in these research institutes. Equipment is on the most lavish scale, and personnel are of the highest calibre. The policy in regard to clinical research varies. In some centres the laboratories are primarily devoted to research on clinical material. In others fundamental research is given the first priority. In the latter it is felt that if the individual worker is left entirely free to pursue his basic studies there is a sufficiently strong possibility that discoveries will be made which will illuminate problems in the clinical field.

The direction of research may be in the hands of the pure scientist with an interest in medical problems, or in those of a doctor with additional scientific training. This dual approach will be fruitful in bridging the gap so commonly present between clinical and basic research. On the other hand, modern scientific techniques have become so exacting, and equipment so costly, that there is a real danger of the young scientist, whether he be a doctor of medicine or not, becoming tied to a narrow and possibly unproductive line of investigation which leaves him little time or opportunity for original thought. As someone has said, learning the technique of electron microscopy is like catching a bull by the tail. The danger that the necessity for acquiring difficult techniques may exact too great a toll on young research workers is more real in America than in Britain, where finance places distinct limits on the amount of apparatus available.

This problem has been met to a certain extent in the States by training technicians to a high degree of competence and paying salaries of an order appropriate to their skill; but this solution is only a partial one, and tends to produce an undue reliance on laboratory results reported by technicians who have no knowledge of their significance and who are not always fully aware of the limitations of the methods they have been trained to use. This point is well illustrated in connexion with the published results of work on urinary steroid excretion. The methods used in different laboratories differ fundamentally, and in actual fact no reliable techniques have as yet become available in this field, although a perusal of literature gives rise to the impression that estimations of 11-oxysteroids, 17-ketosteroids, etc., are now a matter of routine in many centres. These criticisms are of a very general nature and are not intended to detract in any way from the value of the vast amount of useful work going on in American laboratories and research institutes.

It is not intended to review in detail the work of individual groups, but merely to survey the general trend of research in the field of the rheumatic and allied diseases in America, within the limits of what can be learnt from a short visit.

Mode of Action of the Adrenal Steroids in Rheumatic Diseases

It is an undoubted fact that experience in the use of A.C.T.H. and cortisone in the clinical field has far outrun the advance in knowledge of their mode of action in the rheumatic diseases. It is a reflection of the difficulty of the problem that two years' intensive research in many centres all over the world has shed very little light on the fundamental mechanism whereby adequate amounts of the steroid hormones, whether exogenous in the form of compounds E and F, or endogenously produced by stimulation of the adrenal cortex, can largely suppress the manifestations of the disease process. The hope that a study of the action of these hormones would lead to an unravelling of the aetiological problems of the rheumatic diseases has not as yet been fulfilled. It has become clear that their action in rheumatic diseases is in no way specific. It seems to depend upon a suppression of the inflammatory process, and it has been shown that inflammation arising from many diverse agents can be similarly reduced. In other words, the action of the adrenal steroids in this respect seems to depend on a reduction of tissue reaction to injury, and bears no apparent relationship to the nature or origin of the agent responsible.

This anti-inflammatory effect can apparently be dissociated from most of the other known effects on the physiological processes of the body. It does not depend on the changes induced in electrolyte pattern, carbohydrate, protein, or fat metabolism. There is no evidence that the rheumatic diseases are associated with any deficiency in adrenal hormones. In fact, evidence of hormonal excess usually becomes evident before symptoms are adequately controlled. The action of the cortical hormones that appear to be important in relation to their therapeutic effect is their apparent ability to inhibit or damp down the reactivity of

mesenchymal tissue, which is the site of the primary injury in the rheumatic group of diseases. The fact that they are also effective in allergic or hyperimmune states suggests that one possible mode of action may be through their effect on antibody-antigen reactions. No clear evidence that such reactions are involved in the pathogenesis of rheumatic disease has yet become available.

In summing up, it can be said that, although a vast amount of knowledge of the action of the adrenal steroids on the physiology of the body has been gained since A.C.T.H. and cortisone became available, we are as yet completely ignorant of how they act in disease. Certain lines of investigation may prove productive, and some of these are discussed below in a little more detail.

Action on Immune Response

A good deal of the evidence regarding the action of the adrenal steroids on immune response is conflicting. Early work suggested that circulating antibody was increased by cortisone, by release from lymphoid tissue undergoing involution. More recent work has failed to confirm these earlier results. It seems that antibody production may be diminished under certain circumstances, but the union of antibody and antigen is not prevented. A further possibility is that the action of some product of the union of antigen and antibody is inhibited. A possibility that is in the minds of some workers is that proteolytic enzyme systems may be activated by antibody-antigen union, and that the action of the steroid hormones is to inhibit this activation. The whole subject is under intensive study in a number of laboratories and, although some interesting results have been the subject of preliminary reports, no definite proof of any of the theories outlined has as yet been obtained.

Action on Mesenchymal Tissue

It is well known that in pathological states of hyperadrenalism striae appear and wound-healing is delayed. As some degree of hyperadrenalism appears to be necessary to induce remission in the collagen group of diseases, investigation of the effect of A.C.T.H. and cortisone on connective tissue has been undertaken by a number of workers. Satisfactory evidence that fibroblastic activity is markedly depressed has been obtained in experimental animals. This so-called depression of reactivity to injury might be related to the suppression of symptoms of inflammation. On the other hand, wounds have healed satisfactorily in patients receiving doses of cortisone adequate to maintain them in good clinical remission. Cortisone has been used to facilitate orthopaedic surgery in rheumatoid arthritis without causing undue delay in wound-healing.

Little change in the histology of nodules excised before and during cortisone administration has been noted beyond a reduction in cellular infiltration. It is not yet clear, therefore, whether the action of steroids in depressing the reactivity of connective tissue to injury is in fact the explanation of their action in diseases of the collagen group.

Research into the structure of collagen, ground substance, and basement membranes by electron microscopy and microchemical methods is now beginning to provide information about the function and relationship of these components of mesenchyme. Increased knowledge of their chemical structure and physical properties, together with detailed studies of the changes induced by the steroid hormones, may well provide information of fundamental importance to the elucidation of the mode of action of cortisone in the collagen diseases. Due credit must be given to the scientists who are at present pursuing this laborious, exacting, and relatively undramatic type of research in many centres in America.

Adrenal Function in Rheumatoid Arthritis

It has already been stated that no unequivocal evidence of adrenal insufficiency has been obtained in patients suffering from rheumatoid arthritis. On the other hand, some

evidence of abnormal adrenal function has been advanced by Dobriner and his colleagues in the Sloan-Kettering Institute, New York. In comparing the steroid-excretion pattern of normals with patients suffering from rheumatoid arthritis, a striking qualitative difference has been demonstrated. Two compounds—17-hydroxy-pregnanolone and 11-hydroxy-etiocholanolone—were present in the urine of the arthritic subjects. The former abnormal metabolite has been demonstrated in cases of adrenal tumours and adrenal virilism. The latter has been found in the urine of patients with neoplastic disease. On this evidence it is tentatively concluded that abnormal function of the adrenal cortex may play a part in the pathogenesis of rheumatoid arthritis. The administration of both A.C.T.H. and cortisone causes these abnormal metabolites to disappear. This suggests the possibility that they may arise, not from an abnormal function of the adrenal cortex, but from an altered metabolism of adrenal steroids in the peripheral tissues. Much more work is necessary before a final conclusion is reached, but the results of further investigations by Dr. Dobriner and his staff will be awaited with the greatest interest.

Selye has advanced the hypothesis that an excessive output of mineralo-corticoids by the adrenal cortex may be of importance in the causation of diseases of the collagen group. He bases his theory on the demonstration in rats sensitized by the removal of one kidney, high salt intake, and D.C.A. of lesions resembling those of nephrosclerosis, periarteritis nodosa, rheumatic fever, and rheumatoid arthritis. In more recent reports he claims to have demonstrated that this suggested adrenal imbalance may be caused by an overproduction of somatotrophin or growth hormone.

No direct evidence of the existence of such a hormonal imbalance has been demonstrated in human patients. If this were correct, the administration of desoxycortone acetate (D.C.A.) to patients suffering from rheumatoid arthritis should make the disease worse. This is not the case. There is no evidence of major alteration in the electrolyte pattern in these patients, and corticosteroid levels in the urine tend to be lower than normal. D.C.A. does not oppose the anti-inflammatory action of cortisone, and stimulation of the adrenal cortex, which might be expected to cause an exacerbation of symptoms, abolishes them as effectively as cortisone. Selye suggests that A.C.T.H. may stimulate the secretion of glucocorticoids while somatotrophin may stimulate the gland to produce mineralo-corticoids, thus explaining the apparent paradox. No satisfactory evidence in support of his contention is as yet available in human subjects.

Further studies of the production and metabolism of the adrenal steroid hormones in health and disease are obviously of the greatest importance for a more complete understanding both of fundamental physiological processes and of their possible role in disease states.

Role of the Spleen

Ungar, working in the rheumatic fever research unit in Chicago, suggests that the spleen may be important as an endocrine organ. He claims that two substances, splenin A and splenin B, are produced by the spleen in certain circumstances. A small amount of splenin A is normally present in the blood, but no splenin B. He believes that splenin A is produced by the action of the adrenal hormones on the spleen and that it is important in the defence mechanism of the body. It probably acts by acceleration of the neutralization of proteolytic enzymes. He states that some of the effects of cortisone are abolished by splenectomy. Splenin B appears in the blood only in disease states, including rheumatic fever and rheumatoid arthritis. Splenin A can be synthesized by the incubation of ascorbic acid and a suspension of spleen tissue, and isolated in a crystalline form.

Ungar postulates that splenin A may be of therapeutic value in rheumatic fever, and clinical trials are being made at the present time. Preliminary results, he states, have been

encouraging, and trials on a larger scale await the preparation of a more adequate supply of splenin A, which is now being made commercially. If the anti-inflammatory effect of cortisone depends upon its action in stimulating the production of splenin A, then the undoubted fact that cortisone is effective when applied locally is difficult to explain. It is also true that A.C.T.H. and cortisone produce their effects in patients in whom the spleen has been removed, but a possible explanation might be the development of accessory spleens. Whatever the truth, the results of more extensive clinical trials of splenin A will be of great interest.

Pleuropneumonia-like Organisms in the Collagen Diseases

At the Atlantic City Conference of the American Rheumatism Association a paper was read by Wickelhausen suggesting that organisms of the pleuropneumonia group might play a part, as living antigens, in the aetiology of certain of the collagen diseases. It was claimed that these organisms could be demonstrated in the genito-urinary tract in a high percentage of cases, although they could rarely be recovered from the joints in cases of rheumatoid arthritis. On this basis, clinical trials of the newer antibiotics have been run. "Terramycin" is said to have proved the most effective. The clinical response may be of three types: (1) gradual improvement; (2) reactivation of symptoms after withdrawal of the drug; and (3) severe exacerbation after a single dose—thought to be due to destruction of the organisms, with release of antigenic material. The method of treatment adopted has been to give the antibiotic every three days and to control exacerbations in the intervals with cortisone or albumin, which reduces hypersensitivity. Careful adjustment of the dose of antibiotic is required if the best results are to be obtained.

It was felt at the conference that this report was of considerable interest, but that much further work was required before accepting the idea that the pleuropneumonia-like organisms were in fact the living antigen in collagen diseases. Newer cultural methods have shown these organisms to be present in a high proportion of healthy people, although this does not rule out the possibility that in certain circumstances they may assume a pathogenic role.

Blood Flow in Joints

Hollander and his colleagues in Philadelphia have been investigating the effect of intra-articular injections of compounds E and F on joint temperature, using copper-constantan thermocouples mounted in a needle. Compound F has been found more effective than compound E in causing a fall in temperature, which becomes evident within 24 hours and corresponds in general to a suppression of symptoms in the joint. That this effect is a local one is evidenced by the observation that the temperature in the other knee, used as a control, was unaffected. Such observations on the local changes induced by the adrenal steroids are of undoubted value in reaching an understanding of their mode of action.

Pathogenesis of Gout

Wolfson and his colleagues in Ann Arbor claim to have demonstrated an abnormally low output of 17-ketosteroids in patients suffering from gout, although this disease is most common in males in the absence of any other signs of hypogonadism. They postulate that androgenic function in these patients is maintained by an abnormal male sex hormone, originating from the adrenal cortex. The role of this hormone in the pathogenesis of gout may depend upon its ability to evoke hyperuricaemia. That the action of the hormone is opposed by the glucocorticoid hormones is suggested by the suppression of symptoms by the administration of A.C.T.H., and the precipitation of an acute attack on withdrawal, when the level of glucocorticoids temporarily falls below normal. Attacks of gout not uncommonly follow stress, and Wolfson postulates that the gouty patient

responds inadequately to these situations in terms of 11-oxysteroid output, and a relative deficiency of these hormones follows, preparing the way for the acute attack.

There are a good many theoretical objections to this theory, but such studies of the hormonal pattern in gout may well lead to a better understanding of this disease and provide important information regarding the function of the adrenal steroids.

Chemical Structure of Fibrinoid

Fibrinoid change in connective tissue has been regarded as the characteristic lesion in diseases of the collagen group, thus implying that fibrinoid was in some way derived from collagen or its precursors. Kantor and his associates in New York University have now been able to show by chemical and histological methods that this substance is in fact non-collagenous in origin. This observation may be of considerable importance, as it throws doubt upon the view that changes in the structure of collagen form the basis of the pathological lesions in this group of diseases. This is a good example of how the use of combined chemical and histological techniques may provide more accurate information than more conventional methods. This more dynamic approach to the elucidation of the nature of pathological change is likely to have an increasing application, as histochemical techniques are combined with electron microscopy.

Conclusion

These brief notes on research in the field of rheumatism are far from complete, but may serve to illustrate the diversity of approach and the increasing application of the disciplines of the basic sciences to the solution of problems in the field of medicine. It becomes increasingly obvious that, with advancing knowledge, opportunities for individual research are becoming more limited. The team of scientists, representing many fields of knowledge, has largely replaced the lone worker in the small laboratory. Opportunities for the brilliant individualist still exist, but the co-ordinated activities of a group with the command of many techniques seem likely to contribute more to the store of knowledge in the long run. The place of the clinician in such a team must be clearly defined. There is a tendency at the moment to relegate him to the background along with the patient from whom material for study is obtained. Unless he has additional training in some scientific field, he finds it difficult to get on terms with his laboratory colleagues. It would be unfortunate if this trend were to develop further, as the clinician must ultimately relate new knowledge to the practical problem of applying it to the treatment of disease in the human patient. The clinician must exert himself to grasp at least the principles of scientific methods used in research, and the scientist must unbend enough to make his results and their implications comprehensible to his clinical colleague. Both must consider the best interests of the sick patient when research has produced some new approach to the treatment of his disease.

The Ministry of Health has asked the Liverpool Blood Transfusion Service, together with the Manchester and Cardiff Services, to collaborate with the Medical Research Council in a survey of patients who have received transfusions of irradiated plasma or small-pool plasma, in order to compare the incidence of homologous serum jaundice in the two groups. At present irradiation with ultra-violet light is the most promising method of sterilizing plasma. A control series of cases receiving only blood will also have to be surveyed. It is proposed to provide each hospital in the region with either irradiated or small-pool plasma, but not with both, and to follow up patients who have received either after a period of five months. The survey will last three years.

THE INVOLUTION OF THE CERVIX*

BY

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Are post-partum erosions normal in the involuting cervix and do they persist if untreated? The question is important, since the common treatment of erosions after delivery rests on the assumption that they are pathological and give rise to symptoms such as leucorrhoea and backache (Browne, 1946).

Clinically, the cervix often appears to have reached its nulliparous state six weeks after delivery, but a biopsy will show that the changes of pregnancy are still obvious—for example, the stroma is cellular, vascular, and oedematous, while the glands are so numerous as to appear as a honeycomb (Stieve, 1927; Fluhmann, 1948; Murphy and Herbut, 1950). In other words, from a histological point of view the cervix, six weeks after delivery, is still in a pregnant state, although involution is proceeding.

In this clinical and histological study, observations on the post-partum cervix were followed by observations on post-natal erosions which were allowed to heal without treatment. The object was to ascertain if the process of involution in cases with erosion differed materially from the normal post-partum case.

Methods of Investigation

A total of 262 patients were investigated: 121 with post-partum erosions and 141 without post-partum erosions (controls).

The following investigations were carried out approximately six weeks after delivery. First, in every case I completed a standard case-sheet with a detailed description of symptoms such as leucorrhoea and backache. Vaginal smears were then taken and a "Cusco" speculum was passed. A diagram was made outlining the portio and giving details of the amount and type of cervical mucus. The mucous plug was then removed and an endocervical specimen of mucus was taken by an ordinary throat swab for microscopy. The physical properties of the cervical mucus were observed by attempting to draw the specimen out into threads (*Spinnbarkeit*). A laryngeal punch was then used to obtain squamo-columnar biopsies, and finally the bleeding area was treated with a nasal-wire cautery.

An attempt was made to correlate simple erosions with symptoms such as backache and leucorrhoea, and therefore complications such as parametritis and fixed retroversion of the uterus were excluded by bimanual examination.

Clinical Results

1. Backache Six Weeks After Delivery

	Erosions	Controls
Total number of patients	121	141
Backache present	43 (35%)	26 (18%)
Inadequate information	14	38

Backache was present in 35% of patients with erosions and in 18% of those without erosions. It became obvious after taking a careful history from the patient and examining her back, testing its mobility, and so on, that the cervix could

*Preliminary report, read before the Birmingham and Midland Obstetrical and Gynaecological Society, Nottingham, October 13, 1950.