STIMULATION OF THE SUPRARENAL GLANDS IN THE TREATMENT OF RHEUMATOID ARTHRITIS

PRELIMINARY REPORT

BY

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Since the publication of the report of the Mayo Clinic workers (Hench and others, 1949) on the spectacular improvement of rheumatoid arthritis under the influence of cortisone (17-hydroxy-11-dehydro-corticosterone) or of adrenocorticotrophic hormone (ACTH) of the anterior pituitary gland, attention has been concentrated on the problem of the production of these hormones. The present output of cortisone and ACTH by the manufacturers is very limited, and the cost of the treatment by these compounds prohibits the possibility of prolonged medication, especially as this treatment may be used in the future much oftener than, for example, insulin in the treatment of diabetes mellitus, rheumatoid affections being much commoner.

The physiopathology of the adrenal glands fascinated physiologists and clinicians in the past as much as it now intrigues general physicians. Cannon and others (1924) first proved in experiments on dogs that adrenaline is abundantly dissipated from the adrenals as a result of hypoglycaemic action of insulin, which they described as an emergency measure for an emergency state. Since this publication many papers on this subject have appeared confirming Cannon and his co-workers' findings in a great variety of experiments. It has been found that repeated insulin injections causing hypoglycaemia are able to precipitate hypertrophy and hyperfunction of the adrenal cortex in rabbits (Langecker, 1928 ; Radall, 1940 ; Godlowski, 1947 ; and many others), in mice (Goormaghtigh, 1931 ; and many others), and in pigeons (Miller and Riddle, 1941). In rabbits (Godlowski, 1947) the adrenal cortex responded to repeated insulin hypoglycaemias with hypertrophy more or less to the same degree as the medulla. It was also shown that this hypertrophy of the whole gland ran parallel to the hyperfunction of the medulla, which was characterized by increased content of the adrenaline in the whole suprarenal

gland. This functional hypertrophy of the total gland persisted throughout the whole observation period, that is, for thirty days after the last hypoglycaemia (Figs. 1, 2, 3, 4, pp. 290-1).

Apart from these experimental observations it was also found (Godlowski, 1946 ; 1948a) that intravenous adrenaline infusion or insulin hypoglycaemia in normal individuals or in allergic patients caused a substantial drop in the absolute amount of eosinophilic cells in the peripheral blood. Similar changes were noticed when ACTH or cortisone was applied (Thorn and others, 1948). In 1944 Vogt found that "intravenous infusion of adrenaline causes a strong, immediate and long lasting stimulation of suprarenal activity in the eviscerated dog and cat. The effect was obtained with doses of adrenaline which occur in the body under physiological conditions. The increased yield was of the order of several times the basal output. This action is independent of blood pressure or blood flow, and is not mediated by a hormone from pituitary".

These somewhat scattered observations can be closely correlated in the following way : adrenaline intravenously infused into human patients (Godlowski, 1948a) acts similarly to the adrenaline used by Vogt (1944) in the perfusion experiments causing increased output of cortical hormone which in turn causes eosinopenia (Thorn and others, 1948). On the other hand large doses of insulin administered to allergic patients (Godlowski, 1946 ; 1948a) precipitates the regulating mechanism of adrenaline liberation, which again in turn stimulates the output of cortical hormones ; in other words, by using intravenous adrenaline infusion or insulin hypoglycaemia one can directly or indirectly stimulate adrenocortical function applying a transitory, mild emergency state, which one can call a sub-physiological stimulation to the adrenal cortex in contrast to the physiological one caused by ACTH.

The Present Experiments

With these experimental observations in mind, one case of rheumatoid arthritis has been treated with intravenous adrenaline infusions and with insulin hypoglycaemia according to the technique described elsewhere (Godlowski, 1947; 1948a), and finally by subcutaneous injections of adrenaline suspended in oil. One case of acute muscular rheumatism and one case of acute fibrositis treated with adrenaline in oil suspension is also presented.

Case 1.—A man aged 41, a Regular Army N.C.O., married, had his first attack of rheumatoid arthritis in 1941; the left knee and right wrist joints were affected. During the past eight years he had several recurrences of rheumatoid episodes in various joints. He was treated with sodium salicylate, aspirin, penicillin, T.A.B. vaccine, milk injections, and physiotherapy in various forms and on many occasions, with variable results; but pain and stiffness in joints and muscles were permanently present. In September 1948, he was admitted to Ballochmyle Hospital with gross deformity of both wrists, of the metacarpo-phalangeal joints of both hands, and in the right elbow and both knee joints. The muscles of hands, forearms, and calves were grossly wasted, and there was moderately severe periarticular oedema around the affected joints. Passive and active movements in the affected joints caused excruciating pain. The muscular power of the affected limbs was very poor. The patient had no temperature and a poor appetite. The blood sedimentation rate was: first hour 59 mm., second 85 mm. White blood cells numbered 7,600 per c.cm. of blood, and red cells 4,000,000. Hb was 14 g. There was no gross abnormality in the differential cell count, nor in the urine. Radiographs of the affected joints were typical of rheumatoid arthritis. A total dose of 1 g. of meochrysine was given. Physiotherapy in the form of heat and light massage resulted in some improvement. In May 1949, while the patient was in hospital, he suffered a severe exacerbation in the left knee joint with effusion, pain, and stiffness in the other affected joints. There was no fever. The blood sedimentation rate was 37, 65. The leucocyte and differential counts were within normal limits, red cell count and Hb remaining as before. The gold therapy had to be discontinued on account of toxic dermatitis, which was alleviated by BAL injections.

On July 21, 1949, treatment with adrenaline infusions and insulin hypoglycaemia was begun.

Intravenous Adrenaline Drip.—Adrenaline, 10 mg. in 600 ml. of normal saline, was infused at the rate of from 12 to 5 drops per minute for nine hours. The blood pressure, at first 120/80 mm. Hg, rose in thirty minutes to 180/100, and when the rate of infusion was slowed down it returned in twenty minutes to its previous level. Light palpitation and tremor accompanied the rise in blood pressure. In the next adrenaline infusions only 5 mg. was used, and this caused no subjective or objective disturbances of any significance. The slight tachycardia observed in the first infusion did not occur on other

occasions. Owing to phlebitis of the infused veins adrenaline infusions had to be discontinued.

Insulin Hypoglycaemia was produced by subcutaneous injections of soluble insulin, starting with 25 units and gradually increasing to 80. A mistake was made in the last four treatments, and the patient received only 50 units of insulin, which did not produce any hypoglycaemic symptoms. On Aug. 7 the blood sedimentation rate was 19, 40, the oedema had practically disappeared, there was no pain, and passive and active movements were restricted only by the osseous deformities, which remained unchanged (Figs. 5, 6, p. 292). The red cell count was 5,000,000 per c.mm. of blood, and Hb was 15 g. The adrenaline drip having been discontinued and a mistake having been made with the insulin dosage, the patient remained for six days practically without treatment. On the seventh day of this therapeutic gap the sedimentation rate rose to 28, 54, but pain and oedema did not reappear.

The patient's weight before treatment was 10 st. 4 lb.; after fourteen days of treatment it was 10 st. 12 lb.

On Aug. 15, 0.1 per cent. adrenaline solution, 1 ml. five times daily, was injected subcutaneously. After seven days of this treatment the sedimentation rate rose to 36, 80, and pain and stiffness in joints and muscles reappeared. Palpitation, tachycardia, and light precordial pain began to trouble the patient. From Aug. 23 for seven days the patient received subcutaneous injections three times daily of 0.5 ml. adrenaline suspended in oil (Parke, Davis and Co.; 1 ml. contains 2 mg. of adrenaline). After this the sedimentation rate dropped to 17, 35, and pain and stiffness of muscles and joints once more disappeared. The patient remained in this condition for four weeks, that is, up to the time of the preparation of this paper.

Case 2.—A man aged 42, an electrician, for two years complained of recurrent attacks of muscular rheumatism and was treated with salicylates, gold injections, penicillin, and various types of physiotherapy. When the patient was seen he had had five days of pain and stiffness in the left lumbar region and thigh, which had immobilized him completely. The temperature was 100° F., and the pulse rate 110 per minute. He sweated profusely. Analgesics brought only temporary relief. Examination discovered severe pain and stiffness in the affected regions with grossly restricted passive and active movements. The sedimentation rate was 19, 49. Leucocytes numbered 10,000 per c.mm. of blood, and the differential count was within normal limits. At the end of seven days' treatment with adrenaline in oil suspension, 0.5 ml. injected subcutaneously three times a day, pain and stiffness disappeared completely, the sedimentation rate dropped to 9, 16, and the leucocyte count to 6,700 per c.mm. of blood. Insomnia occurring during treatment was relieved by light hypnotics.

Case 3.—A charwoman, aged 41, had complained for six years of recurrent attacks of acute fibrositis with pain and stiffness of the affected groups of muscles. When examined she had had for ten days an attack of severe pain in both shoulders and arms. There was pain on

pressure of the affected muscles and on movement of shoulder and elbow joints. The temperature, sedimentation rate, leucocyte, and differential counts were normal. A seven-day course of adrenaline in oil suspension, 0.5 m. injected subcutaneously three times a day, completely removed the pain and stiffness.

Discussion

The cases of rheumatoid arthritis and acute muscular rheumatism above described, which were treated with adrenaline infusions and insulin hypoglycaemias, and in the later stages with subcutaneously injected adrenaline suspended in oil, did not show the dramatic improvement in the course of the disease that American authors have described as taking place on treatment with cortisone and ACTH. It seems obvious that the application of the active hormone itself, or the use of physiological stimuli for the natural production of cortical hormone, should, on theoretical grounds, be more effective than the subphysiological stimulation described above. However, the obvious improvement in subjective and objective findings resulting from twenty-eight days' treatment of a case of advanced rheumatoid arthritis of a few years' duration, and from a short course of treatment in two cases of acute muscular rheumatism, justifies the hope that it may serve as a temporary therapeutic measure until the active hormone itself can be available for general use. The relief in pain, the increased passive and active movements in the affected joints and muscles, the striking improvement in muscular tonus and strength, the improvement in appetite and increase in body weight, the significant decrease in periarticular oedema, and the parallel improvement in laboratory findings, such as significant diminution of the sedimentation rate and the return to normal in red cell counts and Hb values, justify a further and more extensive trial, which should be undertaken before any conclusive assessment of this method can be passed.

The treatment with intravenous adrenaline infusions and insulin hypoglycaemias has, however, certain drawbacks. Both must be carried out in medical units where nurses have been adequately trained in handling hypoglycaemic patients. The hypoglycaemia need not be carried to the level of complete unconsciousness, as is done in the treatment in psychiatric cases. A level at which there is evident clinical hypoglycaemia in the form of profuse sweating, tremor, palpitation, general profound weakness and drowsiness, with voluntary muscular movements, superficial and deep reflexes, and contact with surroundings maintained, is sufficient for the production of the mild emergency

state necessary for the development of counter-measures in the form of adrenaline liberation. The patient should himself be able to drink the glucose solution for the discontinuation of the hypoglycaemia. Return of hypoglycaemia may in rare cases occur, either in a mild form which the patient himself should be instructed how to deal with, or in a more dramatic form in which intravenous injection of glucose is necessary.

A serious disadvantage of repeated intravenous adrenaline infusions is the irritation of the walls of the infused veins which leads eventually to their occlusion. Further details of the technique of adrenaline infusion have been given elsewhere (Godlowski, 1948a). The contra-indications for this type of treatments are generalized or localized arteriosclerosis, hypertension, and cardiovascular involvement.

To avoid these difficulties an aqueous solution, 0.1 per cent. of adrenaline, has been injected subcutaneously five times daily as a substitute form for the intravenous infusion. The effect of such adrenaline administration was entirely unsatisfactory from the point of view of the therapeutic effect. The explanation of this failure may lie in rapid destruction of the adrenaline, and lack of permanent level of adrenalinaemia, which appears to be essential for the cortical stimulation. The suspension of adrenaline with delayed resorption can fulfil this demand and replace the intravenous infusions. Such form of application has another advantage, that it may be made by the patient himself at home after the preliminary treatment in hospital.

The explanation of the mechanism of the therapeutic action of ACTH and cortisone in rheumatic diseases is not yet clear. There are, however, few points indicating that the suprarenal cortex itself is not primarily involved in the aetiology of the rheumatic affections, since agents stimulating cortical functions act equally as well as the cortisone itself. This means that the suprarenal cortex has not lost its ability to produce hormones in response to the physiological stimulation of ACTH or adrenaline; positive results, however, are guaranteed if both cortisone or ACTH dosage is very high.

Another fact of great importance, which must not be overlooked in elucidating the mechanism of the curative activity of the ACTH and cortisone, is the appearance of symptoms pathognomonic of hyper-adrenalism when the dosage of these hormones is high enough to alleviate the symptomatology of the rheumatic affections; such signs as obesity, hirsutism, etc., observed in the course of successful

treatment with cortisone or ACTH are characteristic of adrenocortical hyperfunction. In other words, to achieve the desired therapeutic effects in rheumatically affected organs the cortisone concentration must reach a pathological level which leads to pathology of the adrenocortical hyperactivity type in non-affected organs. This result may be interpreted as the lowering of the sensitivity of the tissues rheumatically affected to the physiological concentration of the cortical hormone, whereas the non-affected tissues retained their normal susceptibility to the cortical hormone. The rapid recurrence of the inflammatory symptoms when cortisone or ACTH is withdrawn allows one to postulate that the high doses of these hormones necessary to produce cure have to overpower the hypo- or insensitivity of the affected tissues to the cortisone itself in order to cause a rapid regression of the inflammatory process, but that they do not affect the aetiological agent which precipitated this inflammation. If this theory is correct, the curative activity of the ACTH and cortisone exerts beneficial activity solely on the inflammation which is an integral sign of the rheumatism. The noxious agent lowering the susceptibility of the altered tissues to the physiological concentration of cortical hormones persists in the organism during the time of clinical improvement, since soon after withdrawal of hormonal treatment the full picture of previous intensity of the rheumatic disease rapidly reappears. Thus the instrument of pathogenic activity of the rheumatic noxa, that is, inflammation, is temporarily eliminated.

This explanation being accepted as working theory, it would be of interest to find the answer to two other questions: (1) Which part of cortisone activity may be made responsible for the protective action against inflammation of the organs affected by the rheumatic noxa?; (2) Is this anti-inflammatory activity of the adrenocortical hormone specifically directed against inflammation occurring in rheumatic diseases only?

The conclusive answers to these fundamental questions are beyond the scope of this paper. Certain suggestions, however, based on the previous observations, may be permissible.

Injections of sufficient quantities of ACTH cause in men a significant eosinopenia which is equally well produced by cortisone itself (Thorn and others, 1948). The same eosinophilic drop was observed when adrenaline was administered intravenously in prolonged infusion (Godlowski, 1948a). Another observation indicated that eosinophils possess the transportation ability of the specific antigen (Godlowski, 1948b). There is also the generally

known fact that adrenocortical hormones and adrenaline itself produce definite improvements when administered in allergic conditions. (The immediate improvement in allergic reactions caused by adrenaline may also be explained by its action on the capillaries.) Might it then be possible that cortisone, in producing eosinopenia, makes the transport agent for the antigen unavailable and thus temporarily eliminates it from the antigen-antibody reaction?

There may, however, be another answer to the first question. Cortisone has a potent regulating activity on the electrolyte metabolism of tissues (Prunty and others, 1948; and others). The quantitative alteration in the potassium and sodium equilibrium is commonly observed in the inflammatory reaction. Significant intracellular retention of sodium salts and water retention in extracellular compartment on the one hand, and substantial elimination of the potassium salts from the cytoplasm on the other, may be the biochemical mechanism of the cortisone activity on the affected tissues. This process may also take place in the eosinophils to such a degree that disturbed balance finds its expression in the physico-chemical alterations of their cytoplasm, with resulting surface-tension changes. In the course of the capillary passage eosinophils with such surface alterations adhere to the capillary walls and are thus temporarily eliminated from circulation.

The histological features of the inflammation observed in rheumatism do not differ essentially from any other inflammation of an allergic type. The answer to the second question may therefore be that the therapeutic effect of the cortisone on the rheumatic inflammation may be regarded as a *non-specific but very potent factor in regulating the essential mechanism of the inflammation itself but not affecting the aetiology of the disease*. In other words, cortisone acts specifically against inflammation but not against rheumatism.

This theory requires for its support the evidence produced by clinical trials of cortisone in various conditions characterized by inflammatory processes of allergic aetiology.

Summary

1. Stimulation of the adrenal cortex by adrenaline administered intravenously or subcutaneously and by repeated insulin hypoglycaemias has been used for the treatment of rheumatoid arthritis and for non-articular rheumatism.

2. The rationale of this treatment is put forward with tentative explanation of the mechanism of the ACTH and cortisone action in rheumatic affections.

3. A case of advanced rheumatoid arthritis and two cases of non-articular rheumatism which benefited by this treatment are presented.

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Stimulation des glandes surrénales dans le traitement de l'arthrite rhumatismale chronique

RÉSUMÉ

La stimulation de l'écorce surrénale au moyen de l'adrenaline administrée par la voie intraveineuse ou sous-cutanée et au moyen de l'hypoglycémie insulinique répétée fut employée dans le traitement de l'arthrite rhumatismale et du rhumatisme musculaire aigu. On discute la raison logique de ce traitement. On décrit un cas d'arthrite rhumatismale avancée et deux cas de rhumatisme musculaire aigu qui ont bénéficié de ce traitement.

FIG. 1.—Section of a suprarenal gland of an average normal rabbit. Staining, haematoxylin and eosin. Magnification, $\times 11$. Details : Godlowski, 1947.

FIG. 2.—Section of a suprarenal gland of a rabbit killed three days after the last attack of insulin hypoglycaemia. Other details as in Fig. 1.

FIG. 3.—Section of a suprarrenal gland of a rabbit killed fifteen days after the last attack of insulin glycaemia. Other details as in Fig. 1.

FIG. 4.—Section of a suprarrenal gland of a rabbit killed thirty days after the last attack of insulin hypoglycaemia. Other details as in Fig. 1.

FIG. 5.—Maximal flexion in both wrist joints with grossly restricted movements in the left hand. Gross impairment of finger flexion of the right hand. Condition before treatment.

FIG. 6.—Significant improvement in flexion in the left wrist and right fingers. The remaining impairment in flexion is due to permanent osseous deformity. State after twenty-eight days' treatment.