SUGGESTED MODE OF ACTION OF CORTICOTROPHIN IN RHEUMATOID ARTHRITIS AND THE ALLERGIC STATE

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One of the many side-issues early brought to mind by the study of shock as the general reaction to tissue injury was the relationship of the shock reaction to all the various types of tissue insult which had been reported to ameliorate the symptoms of rheumatoid arthritis. With the finding that adenosine triphosphate (A.T.P.) was a shock-inducing agent (Green, 1943 ; Bielschowsky and Green, 1943) therapeutic trials were early considered but deferred pending fuller knowledge of the tolerated dosage in man and animals (Stoner and Green, 1945, 1950).

Preliminary trials in cases of rheumatoid arthritis (unpublished) were made in 1945, and one apparently dramatic response, though inconclusive, suggested further exploration. Meanwhile Lövgren (1945), from a different approach, reported favourable results after intramuscular and, in some instances, intravenous injections in a large series of cases. Studying the cardiovascular changes in arthritis cases, Wayne, Goodwin, and Stoner (1949) were not satisfied that there was any objective improvement in the joint condition of their patients after repeated intravenous doses of A.T.P. Recently Stoner and Green (1950) have shown that under defined conditions A.T.P. injection causes an almost complete discharge of cortical steroids.

A rather unexpected link-up has now appeared following apparently unrelated studies on the shock reaction. In view of the hyperglycaemic state in the early stages of shock and Bullough's (1949) observation that the injection of starch or glucose strongly accelerates the rate of skin mitosis, the effect of shock on skin mitosis was studied, and has been briefly reported (Green and Bullough, 1949) and followed by a detailed paper (Green and Bullough, 1950). At the very beginning of the general bodily reaction, induced by the release of limb tourniquets or the injection of A.T.P. into the mouse, mitosis in the skin ceases entirely, or is much depressed, for at least 7 hours. The injection of glucose, which strongly reinforces the existing hyperglycaemia, does not influence this inhibition in the slightest. Some facts were given in support of the hypothesis that a metabolite or metabolites from the post-ischaemic limb, and also injected A.T.P., interfere with carbohydrate utilization, possibly indirectly through a hormonal mechanism, and thus prevent mitosis. The anticipated hormonal mechanism was via the pituitary-adrenocortical route.

Effect of A.C.T.H. on Skin Mitosis

This has now been put to the test indirectly by observing the effect of A.C.T.H.* on skin mitosis in the mouse under precisely similar conditions to those used in the shock experiments. Following the subcutaneous injection of 1 mg. of A.C.T.H., skin mitosis† was depressed for several hours in a similar way to that observed in post-ischaemic shock. A full account of this work will appear later : here it is desired only to consider its bearing on the mechanism of A.C.T.H. in the allergic state.

*Using a sample kindly presented by Dr. W. J. Tindall, of Organon Laboratories, Ltd.

†I am indebted to Mrs. Savigear, of the Cancer Research Laboratories, Sheffield, for making the counts.

The rate of skin mitosis is probably only a reflection of mitotic activity in many other tissues (see Bullough, 1948), though not necessarily in all, and the well-known effect of A.C.T.H. and the 11-oxysteroids in producing lymphopenia and involution of lymphoid tissue may therefore be due to direct suppression of lymphocyte production rather than to accelerated destruction. The same considerations apply to the general inhibition of body growth, the eosinopenia, the failure of granulation-tissue formation, the inhibition of chondro-osteogenesis, etc.—all well-known features of A.C.T.H. activity.

The immediate depression, or suppression, of mitosis in the formative cells from which the lymphocytes and other antibody-producing reticulo-endothelial cells are derived may in itself depress or abolish the tissue antigen–antibody reaction and the resulting allergic inflammatory reaction. This would account for (1) the suppression not only of the local but also of the general effects of this reaction because of the failure of histamine and most probably other by-products of the reaction to appear, and (2) the non-specific nature of the A.C.T.H.–adrenal-glucocorticoid mechanism, for on this basis temporary depression of all allergic-tissue reactions, however produced, should result. It would also account for the rise in uric acid and nitrogen excretion, for on this hypothesis the temporary halt in nucleoprotein synthesis should lead to the accumulating purines and amino-acids being excreted in excess by the normal paths. On this basis also the accelerated glucogenesis following A.C.T.H. treatment might in part be explained. The hypothesis would also explain the more rapid spread of an infected focus in the tissues under the influence of A.C.T.H. or cortisone.

The Role of Allergy

The suggested mode of action of A.C.T.H. in rheumatoid arthritis and the other clinical states in which it is active does not necessarily imply that any or all of these are in fact manifestations of excessive tissue allergy. Since I first studied shock experimentally, evidence for the role of allergy in rheumatoid arthritis has to me always seemed strong, because extensive tissue damage of any kind depresses metabolism generally (see Green and Stoner, 1950), and one might therefore expect a depression of antibody formation. The explanation of the therapeutic action of heavy metals as a blocking of the reticulo-endothelial system, and the occasional favourable results of splenectomy, fit in well with this conception. However, even if the allergic hypothesis is not correct, the tissue lesions still remain, from the pathologist's standpoint, inflammatory in nature, and without cellular proliferation they could not appear. Even the proliferation of malignant cells is in some instances depressed by A.C.T.H., for there are now reports that this treatment induces temporary remissions in acute leukaemia (Burchenal *et al.*, 1950 ; Pearson *et al.*, 1950). However, Long and Miles (1950) have recently given convincing evidence that A.C.T.H. and cortisone decrease tuberculin hypersensitivity in the guinea-pig. It would therefore not be surprising if a striking general as well as local improvement following this treatment proves to be an indication that a hypersensitive state exists.

While temporary failure of local lesions to appear could be accounted for purely on the antimitotic hypothesis, in those diseases where a striking general clinical improvement also occurs it would be difficult to explain without supposing that the general manifestations, including the raised blood sedimentation rate, are not induced by by-products (including gamma globulins) of the hypersensitive reaction in strongly predisposed tissues. In non-allergic bacterial

inflammation, in spite of suppression of the local tissue reaction, general improvement should not occur, except perhaps very fleetingly, but rather the reverse, since spread of the local infection would be facilitated.

An inquiry into the mechanism of mitosis suppression by A.C.T.H. forms one part of current investigations into the mechanism of shock by the Sheffield team. Observations on mitosis in cancer cells under similar conditions are also in progress. The changes in carbohydrate metabolism in shock and their bearing on aspects of A.C.T.H. activity, including that reported here, are being made by Stoner, Green, and Threlfall, and will, it is hoped, be published in the near future.

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DIET IN THE TREATMENT OF ACUTE HEPATITIS

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It has long been thought that the diet for acute hepatitis should be rich in carbohydrates and deficient in fat. However, a number of experiments on animals (Schifrin, 1932; Goldschmidt *et al.*, 1939; Miller and Whipple, 1940; and others) showed that protein protected the liver against certain poisons such as arsphenamine and chloroform. It was further shown that the effect is principally connected with amino-acids of certain CH_3 and SH groups. Clinical investigations have been made by, among others, Darmady (1945), who treated 32 hepatitis cases with 150 g. protein and 100 g. fats, while a group of 31 cases received 70–90 g. protein and 60 g. fats. He found no difference between the two groups as regards duration of treatment, time up to normal van den Bergh reaction, or accumulation of hippuric acid. Beattie (1944) claimed that with a diet rich in protein he reduced the time of treatment by one-third. Hardwick (1945) gave 180 g. and 50 g. protein respectively, but found no difference in the results. Addition of amino-acids has also been tried (see article by J. Ström at p. 1168 of this issue).

The low-fat diet began to be abandoned a few years ago. Hoagland *et al.* (1946) treated 37 cases with 150 g. fats and 150 g. protein, while a control group of 33 cases received 50 g. fats and 150 g. protein. The only difference was that in the test series the increase in weight started earlier and was somewhat greater than in the controls. Wilson *et al.* (1946) gave 51 cases 200 g. fats and 52 control cases 70 g. fats, both groups receiving 100 g. protein. He found no difference as regards duration of treatment, bilirubinaemia, or bilirubinuria. Reich *et al.* (1947) observed no disadvantages when they included 200 g. of fats in the diet. On the other hand, a diet rich in fats has a high calorie value and is more appetizing. Fats may be given in the form of butter, milk, and cream, which contain unsaturated fatty acids: this is thought to have a certain significance, as the latter cannot be synthesized from other substances.

There are thus few clinical results available concerning diets for the treatment of acute hepatitis, and the objections to such results as have been obtained, apart from the fact that the series is a small one, are, first, that isocaloric diet has not been given, and, secondly, that there has often been a variation of more than one factor—for example, both fat and protein content.

Present Investigation

Since January 1, 1949, three departments of 30–35 beds each at the Hospital for Communicable Diseases in Stockholm have been constantly filled with hepatitis cases. Since that date tests have been made with a fat diet in one department, a carbohydrate diet in another, and a protein diet in the third. Special diet personnel were employed in the kitchen purely for these tests. Diets were composed in such a way that all the departments received a basic diet consisting of 80 g. fats, 80 g. protein, and 320 g. carbohydrates. Those on a fat diet were given an extra 65 g. butter, partly in sauces, etc., with the food and partly on bread. The carbohydrate diet consisted of an extra 100 g. of ordinary sugar and 100 g. of sweet fruit juice. The sugar was usually given in lemon juice.

To obtain a diet rich in protein proved very difficult, as an increase to 200 g. protein in the form of meat, skimmed milk, etc., would have considerably altered the basic diet. In fact, a greater variation than 10% in the carbohydrate, fat, and protein in the basic diet was not permitted. An increase to 150 g. has, however, proved possible, and the remaining 50 g. has been given in the form of casein—25 g. cooked into the food, in porridge, rissoles, etc., and 25 g. taken as granulated casein orally. The calorie content in the different diets is thus about 3,000. Added vitamins were given equally in the three series—vitamin A and D pills, vitamin B complex as tablets, and vitamin K in relation to the prothrombin index.

Obviously, not all patients ate exactly 3,000 calories; some ate more, others less. So far as possible, however, an attempt was made to maintain the right proportions. In spite of the extreme nature of the diets the patients fared well on them, and in only two cases on the fat diet did light bowel disorders occur for a few days.

Once all the cases of uncertain diagnosis had been eliminated and all those excluded that had been discharged after July 1, when the differences in diet ceased, there remained in the protein series results of 128 cases, in the carbohydrate series 97, and in the fat series 86. (Cases discharged after July 1, but which had been on diet at least one month previously, were, however, included.) As we were overbooked, the next patient on the waiting-list was admitted as soon as a bed became free, and, as the fat and carbohydrate departments are more modern and have a larger number of small rooms, it was unavoidable that a certain number of elderly people were put in these, which made it impossible to arrange a non-selective test series. This occurred to an even greater degree when the material was divided into cases of epidemic and post-inoculation hepatitis, which was done by means of a special questionary. All cases in which inoculation (by blood tests, injections,