degeneration. On the other hand, the distribution of inflammation often fails to coincide with that of microfilariae, for the inflammatory reaction may be widespread in cases where microfilariae are scanty or impossible to find, or, conversely, microfilariae can be seen histologically in connective tissue free from leucocytes; and living apparently normal microfilariae may emerge from samples of skin when examined in the fresh condition. The skin slips were taken within a few centimetres of nodules containing adult worms, and some of these microfilariae might have recently migrated out of the nodules.

The action of hetrazan on onchocerca may be compared with its action on the experimental infection of *Litomosoides* in cotton-rats and on *Wuchereria bancrofti* in man. In all cases it acts most promptly on the microfilariae, while its effect on the adult worms is much less marked. In previous papers (Hawking, Sewell, and Thurston, 1950; Hawking, 1950) the hypothesis has been put forward that the action of hetrazan upon microfilariae is due to an opsonin-like effect, so that the microfilariae become attractive to the macrophages of the reticulo-endothelium system, which accordingly fix them and then destroy them. The present observations would agree with this hypothesis if one makes the additional assumption that hetrazan acts more readily on some microfilariae than on others.

Thus the first effect of hetrazan would be to "opsonize" some of the microfilariae, so that the previously indifferent phagocytes of the skin become attracted to them and begin to destroy them. The first liberation of microfilarial products would excite the acute allergic inflammation described above, which would be more widespread than the microfilariae themselves. Meanwhile some microfilariae are postulated as being less readily affected by hetrazan (because they are newly emerged from adult worms, or for some other unknown reason), and these are the microfilariae which migrate from the skin slip in the fresh condition or which are found free from inflammatory reaction in the stained section. If the treatment with hetrazan is prolonged all microfilariae in the skin are eventually suppressed by it, for the skin slips no longer liberate microfilariae in the fresh state. But the adult female worms still remain alive, and when the administration of hetrazan is discontinued they gradually replenish the skin with fresh microfilariae. Unless means of destroying the adult worms can be found, treatment of onchocerciasis with hetrazan will give only temporary relief.

The allergic reaction provoked by hetrazan in patients with onchocerciasis may be used as an additional means of diagnosis. If the skin slips of a patient suspected of this infection reveal no microfilariae and he has no allergic reaction after taking hetrazan, it is unlikely that he contains onchocerca.

Summary

Patients infected with *Onchocerca volvulus* were treated with hetrazan, and subcutaneous nodules containing adult worms and samples of skin containing microfilariae were removed for histological examination.

There was no significant difference between nodules from five untreated patients and those from nine patients treated with hetrazan, and there was no evidence that hetrazan had produced any adverse effect upon the adult worms.

In skin samples from untreated patients, microfilariae in the corium usually did not excite any reaction; if reaction was caused it was mild in degree and chronic in nature.

In skin samples after treatment with hetrazan there were numerous foci of intense acute inflammation. Microfilariae were often present in these foci, and showed evidence of degeneration and destruction; but sometimes they were also present in normal connective tissue without exciting a reaction.

It is probable that the main action of hetrazan is to destroy microfilariae (probably by an opsonin-like effect), and that their destruction liberates some microfilarial product which excites an allergic reaction in the previously sensitized patient. Some microfilariae, however, are apparently less susceptible to the opsonin-like effect of hetrazan, and so they persist in the skin for long periods without doing visible harm.

The allergic reaction provoked by hetrazan in patients with onchocerciasis can be used as an additional means of diagnosis.

Grateful acknowledgments are due to the Director of Medical Services in Uganda and his colleagues for clinical facilities; to Mr. F. Higginson for histological preparations; and to Mr. M. R. Young, A.R.M.S., for the photography.

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FURTHER OBSERVATIONS ON CAPILLARY RESISTANCE AND ADRENOCORTICAL ACTIVITY

BY

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Earlier observations on changes in capillary resistance as measured by a negative-pressure method have already been reported (Robson and Duthie, 1950). It had been shown by Scarborough (1944) that the resistance of the capillaries in the skin rose sharply after a variety of surgical operations. This was confirmed by Robson (1949). As described previously, it was then shown that similar changes in resistance were caused by other types of non-specific stress such as x-ray irradiation, intravenous nitrogen mustard, hyperpyrexia, and the intravenous injection of T.A.B. vaccine. In view of the variety of "alarming" stimuli which gave rise to similar changes, it was felt that the common factor might be the activation of the pituitary-adrenal axis. This idea was supported by the observation that insulin-induced hypoglycaemia and the injection of adrenaline both caused a rise in resistance, since both these procedures stimulate the adrenal cortex, as evidenced by a fall in the number of circulating eosinophils.

The hypothesis was then tested more directly by studying the effects of adrenocorticotrophic hormone (A.C.T.H.). It was found that a single dose of 25 mg. of A.C.T.H. produced a significant rise in resistance in about four hours. Repeated injections, usually of the order of 25 mg. of A.C.T.H. eight-hourly, resulted in a marked elevation of capillary resistance, which was sustained during the period of administration. Such observations were made on patients suffering from a variety of conditions, including rheumatoid arthritis, ankylosing spondylitis, disseminated lupus erythematosus, and idiopathic

thrombocytopenic purpura. In all cases in which the clinical response to A.C.T.H. was satisfactory, the capillary resistance rose, to fall again when administration of the hormone was stopped.

The present report describes investigations which continued from this point, with the object of establishing the relationship between adrenocortical activity and these changes in capillary resistance. The methods used were the same as those detailed in the previous report.

Observations on Cases of Hypopituitarism

Six patients suffering from hypopituitarism have been studied. Capillary resistance was found to be abnormally low in all of these subjects, under resting conditions. Each

FIG. 1.—Effect of adrenaline, insulin, and A.C.T.H. on capillary resistance in a case of hypopituitarism.

of these patients was given a single injection of 25 mg. of A.C.T.H., and in no instance was any change in resistance observed. One of these cases is illustrated in Fig. 1, where it may be seen that, although there was no response to 25 mg. of A.C.T.H., both adrenaline and insulin caused transient but definite rises in resistance, accompanied by significant reductions of the eosinophil count. When the administration of A.C.T.H. was continued or repeated, however, a rise in resistance was obtained. This is illustrated

FIG. 2.—Effect of two courses of A.C.T.H. on capillary resistance in a case of hypopituitarism.

by the findings in another patient (Fig. 2), in whom adrenaline and insulin caused a rise in resistance but no fall in the eosinophil count. The intramuscular injection of 25 mg. of A.C.T.H. twice daily for two periods of 10 and 7 days led to dramatic clinical improvement and a definite rise in capillary resistance. After both courses clinical relapse was prompt and resistance fell abruptly.

These findings illustrate clearly the closeness of the relationship between the activity of the adrenal cortex and changes in capillary resistance.

It is of some interest to note in passing that both adrenaline and insulin are apparently capable of activating the adrenal cortex in Simmonds's disease, when a single injection of A.C.T.H. has no effect. This might suggest that the action of adrenaline and insulin does not necessarily depend on an intact pituitary-adrenal mechanism, or that, in these doses, their stimulus is more intense than that of A.C.T.H.

Effects of Cortisone

Having implicated the adrenal cortex in the production of these changes in capillary resistance, our next step in the investigation was an attempt to ascertain which of the hormones secreted by the gland was responsible. Fifteen patients to whom cortisone was administered have been studied. Nine were suffering from rheumatoid arthritis, and the others were cases of rheumatic fever, ankylosing spondylitis, periarteritis nodosa, gout, Still's disease, and haemolytic anaemia.

Eleven patients received cortisone acetate by intramuscular injection. Fig. 3 shows the effects of a single injection of 200 mg. of cortisone intramuscularly in a man aged 20 suffering from rheumatoid arthritis. A rise in resistance and a fall in the eosinophil count occurred, but these changes

FIG. 3.—Effect on capillary resistance, in one patient, of single injections of 200 mg. of cortisone and of 25 mg. of A.C.T.H.

were slower in appearing and less in extent than those induced by 25 mg. of A.C.T.H. in the same patient. However, continued administration of cortisone intramuscularly caused a significant and sustained increase in resistance in all cases tested. One example is shown in Fig. 4. The effects of continued administration of cortisone and of A.C.T.H. on capillary resistance were compared (Fig. 5) in a patient suffering from rheumatoid arthritis. Capillary resistance rose in both instances, although rather more slowly on 100 mg. of cortisone daily than on 50 mg. A.C.T.H. daily. The slowness of the response to intramuscular cortisone as compared with A.C.T.H. was considered to be due to delay in absorption, since, on continued dosage, resistance became raised to the same extent with both hormones.

Four patients were given cortisone by mouth. In one case of rheumatoid arthritis, that of a woman aged 56, oral cortisone in doses of 100 mg. daily effected little change in resistance or in the clinical state, although there was later an excellent response to single injections of A.C.T.H. In three patients, two suffering from rheumatoid arthritis and one from periarteritis nodosa, cortisone by mouth produced a rapid and effective clinical response. In all three instances there was a significant rise in resistance within six hours of the ingestion of 50 mg. of cortisone acetate.

FIG. 4.—Effect of a course of intramuscular injections of cortisone on the capillary resistance.

FIG. 5.—Effect of A.C.T.H. and of cortisone on capillary resistance in a case of rheumatoid arthritis.

Effects of Other Hormones

From the above results it could be inferred that elevation of the resistance of skin capillaries following alarming stimuli and the injection of A.C.T.H. is due to increased production by the adrenal cortex of steroids similar to cortisone. (No opportunity has arisen to test the effect of compound F.) The close correlation between rises in resistance and the clinical response is also in favour of this hypothesis. As a further test of this theory, four patients suffering from rheumatoid arthritis were given 5 mg. of

deoxycortone acetate (D.C.A.) by injection. The results were indecisive, but on the whole capillary resistance showed a tendency to fall. Accordingly, the effect of much larger doses was studied in two individuals maintained on a salt-free diet (Fig. 6). It can be seen that in both cases the injection of D.C.A. in doses of 10, 20, and 30 mg. caused a distinct fall in resistance, maximal about 12 to 16 hours after injection. This is an observation of interest in view of the suggested antagonism, in some respects, between the glucocorticoid and mineralocorticoid hormones of the adrenal cortex (Pirani *et al.*, 1951; Seifter *et al.*, 1949).

Observations on capillary resistance were made following the administration of other steroid hormones. Seven patients suffering from rheumatoid arthritis were given 100 mg. of progesterone by intramuscular injection. No significant changes in capillary resistance or in eosinophil counts followed. The daily injection of 25 mg. of testo-

FIG. 6.—Effect of D.C.A. on capillary resistance.

sterone in two patients, and the administration of oestradiol benzoate, 10 mg. by mouth, in three patients, caused no rise in resistance. Pregnenolone in doses of 300 mg. daily for three days was also without effect.

In view of the claims (Lewin and Wassen, 1949; Le Vay and Loxton, 1949) that the simultaneous injections of D.C.A. and ascorbic acid were rapidly effective in the treatment of rheumatoid arthritis, six patients were given 5 mg. of D.C.A. intramuscularly, followed by 1 g. of ascorbic acid intravenously. No constant or significant changes in capillary resistance followed. None of these cases showed any clinical improvement attributable to this therapy.

Discussion

The evidence presented would seem to confirm the idea that rises in capillary resistance following non-specific stress are due to increased activity of the adrenal cortex, as similar changes follow the administration of A.C.T.H. The effect of cortisone would indicate that the specific form of adrenocortical activity responsible for these changes is the increased production of glucocorticoids. Confirmation of this view is provided by the fact that D.C.A. causes a fall in resistance, and other steroid hormones have no effect. Further evidence in favour of this theory is provided by the demonstration of abnormally low capillary resistance in cases of hypopituitarism and by the fact that a rise in resistance could be obtained in these subjects only by the continued administration of A.C.T.H., coincident with other signs of renewed adrenal activity. Finally, clinical response to both A.C.T.H. and cortisone, in a variety of diseases, has been invariably associated with significant elevation of capillary resistance.

It has thus been found that measurement of resistance by the technique described is a simple and sensitive index of

adrenocortical response, and on occasion has been found to be more sensitive than the circulating eosinophil count. The test has proved of practical value in screening substances with a possible cortisone-like action. The connexion between these observations on capillary resistance and the ability of cortisone to suppress an inflammatory reaction is not at all clear. If it may be assumed that changes in the skin capillaries represent what is happening throughout the capillary bed, and if the inflammatory response is influenced by changes in the state of the capillaries, then these observations may provide a clue to the mode of action of cortisone in a wide variety of disease states.

Summary

Investigations have been continued in an attempt to establish the relationship between adrenocortical activity and changes in the resistance of skin capillaries (negative-pressure method).

Cases of hypopituitarism were found to have abnormally low capillary resistance. These patients did not respond to single injections of 25 mg. of A.C.T.H., but when repeated doses of the hormone were given a rise in resistance was obtained.

Distinct rises in resistance followed the administration of cortisone, either intramuscularly or orally, in a variety of disorders.

D.C.A. caused a fall in resistance, while progesterone, testosterone, oestradiol, and pregnenolone were without effect.

It is concluded from these and previous observations that rises in capillary resistance which follow non-specific stress are due to increased adrenocortical activity and increased output of glucocorticoid hormone. The test has been found to be a simple and sensitive index of adrenocortical response to stimuli.

During the period when this work was done the Rheumatic Unit, Northern General Hospital, was in receipt of grants from the Medical Research Council and the Nuffield Foundation. Part of the cortisone used was provided from a generous gift made jointly to the Medical Research Council and the Nuffield Foundation by Merck and Co., Inc. We should like to express our appreciation for much valuable assistance given by Dr. J. L. Potter, Elizabeth MacAdam Research Fellow.

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Emergency conditions in Egypt have as yet had no serious effect on the health of the troops in spite of the departure of many Egyptian labourers in the sanitary and antimalaria services. Labour has now been obtained from other sources, and there seems no reason to anticipate serious health difficulties when the hot weather arrives. About 20% of all admissions to hospital are accounted for by diseases of the skin, of which the majority are septic infections. Infections may be due to the combined effect on the skin of dry heat, dust, and sand. Scientific investigations are taking place. Bacillary dysentery and diarrhoea occur during the summer months and are certainly associated with the presence of flies. Extensive measures are taken to control fly breeding. Tonsillitis and pharyngitis form an important group of diseases twice as prevalent as in other tropical and sub-tropical commands, and on a level with experience at home. The possibility of an outbreak of enteric fever is always a source of some anxiety in the Middle East.

RESPONSIVENESS TO A.C.T.H. AND CORTISONE IN RHEUMATOID ARTHRITIS*

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During some early investigations a few patients with rheumatoid arthritis were given courses of A.C.T.H. in a dosage of 12.5 mg. eight-hourly for periods of 10–14 days. The clinical and metabolic effects of these courses differed greatly in different patients: in one patient the symptoms and signs of rheumatoid arthritis were almost completely relieved, and this relief was accompanied by definite signs of hypercorticism such as oedema with marked sodium retention, decreased sugar tolerance, the development of "moon face" and striae, and a tenfold increase in urinary excretion of corticosteroids; while another patient presenting a somewhat similar clinical picture failed to respond in any way to the A.C.T.H. The absence of response in the second patient was at first attributed to lack of potency in the second batch of A.C.T.H., but administration of some of the batch of A.C.T.H. which had given such good results in the first patient was equally ineffective in the second patient. This marked difference in responsiveness seemed to be of some practical and theoretical interest, and we therefore proceeded to investigate the possible variation in responsiveness of patients with rheumatoid arthritis to both A.C.T.H. and cortisone.

The Investigation

During the first part of this investigation the limited material at our disposal led to the development of a technique for assessing the response to single intramuscular injections of A.C.T.H., using as indicators the depression of circulating eosinophils four and six hours after the injection and the changes in joint tenderness and power of grip occurring six hours after the injection (Janus, 1950).

Cortisone first became available at the beginning of 1951, and the effects of single injections of that substance were compared with single injections of A.C.T.H.; but this was unsatisfactory, since the effects of A.C.T.H. reach a maximum about six hours after injection, while intramuscular cortisone is only slowly absorbed, and the effects of a single injection take as long as 24 hours to reach their maximum. Fortunately this difficulty could be overcome by giving cortisone by mouth, since the time relations of the effects of a single oral dose of cortisone resemble closely those of a single injection of A.C.T.H. (Boland and Headley, 1951; Kellgren and Janus, 1951). Our studies were therefore enlarged to include the effects of single oral doses of 50 mg. of cortisone, which were compared with single intramuscular injections of 25 mg. of A.C.T.H. in the same patient. Fourteen patients with rheumatoid arthritis were studied in this way, and these preliminary studies showed a great variation in individual responsiveness to both corti-

*This work was financed by a grant from the Oliver Bird Fund of the Nuffield Foundation.