EFFECTS OF ACTH ON THE PERIPHERAL BLOOD FLOW IN RHEUMATOID ARTHRITIS

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In the course of the development in this Unit of a technique for the intravenous administration of adrenocorticotrophic hormone (ACTH), it was noticed that most of the patients experienced a feeling of warmth, flushing, and even sweating during and immediately after the actual infusions. Such phenomena, indicative of peripheral vasodilatation, induced us to investigate this suggested release of tone of the smaller vessels.

Following intramuscular injections of ACTH, changes in blood flow around the knee joint and an increase of skin temperature of the finger tips were reported by Janus (1950). Horwitz, Sayen, Naide, and Hollander (1951) also found an increase of skin temperature of the fingers in seven out of eleven patients after a course of intramuscular ACTH but no vasodilatation in the toes of nine out of eleven.

The simplest method of ascertaining changes in the state of the peripheral circulation is by measuring skin temperatures at appropriate points. As pointed out by Abramson (1944), if environmental factors are maintained at a constant level, the surface temperature will then depend upon the temperature of the blood and the rate of flow through the skin. By imposing a thermal response test, additional information can be gathered concerning the efficiency of the thermo-regulatory mechanism of the body. This mechanism is often impaired in rheumatoid arthritis and it is much more important if an improvement can be shown here than in simple vasodilatation.

Method

Our scheme was to measure first the preliminary skin temperatures and then the thermal response in exposed limbs following the immersion of one leg in hot water (44° C.) before and after intravenous infusion of ACTH. The tests were generally performed on Mondays and Thursdays at the same time, starting about 2½ hours after breakfast. The infusions were started on Wednesday

mornings and lasted 12-24 hours normally. They usually contained 20 mg. ACTH in 1 litre glucose-saline mixture, but doses of 10 and 5 mg. were used in some cases. The investigations were carried out in a room the temperature of which was maintained at 18.3° to 19.0° C. The form of the test has already been described by one of us (Woodmansey, 1951). The patient sat comfortably for at least 30 min. with legs exposed to the knees, feet resting on a support, and hands resting on the lap. Skin temperatures were taken periodically using an apparatus based on the Wheatstone bridge principle. One resistance arm consists of a probe containing, in a capsule, a compound with a high temperature-resistance coefficient ("thermistor"), which is placed in contact with the skin at the selected position. The current is produced by a valve oscillator, and a three-valve amplifier ensures the accurate differentiation of the null point. A variable resistance—adjusted to a minimum in the actual temperature estimation—is calibrated in degrees centigrade. The positions chosen for temperature readings were the forehead, both thumbs, and one great toe. The forehead was regarded as giving a suitable correlation with body temperature, which usually rose a degree or so during the test. The terminal phalanges were tested on the volar or plantar aspects. Lewis (1931) and Lewis and Pickering (1931) have demonstrated the superiority of the pulp of the fingertips in comparison with other digital sites for observation of the earliest and greatest temperature changes, due to the presence of dense arteriolo-venular anastomotic zones—as described by Grant and Bland (1931). Following the attainment of stability in the readings—after about 30 min.—one foot was immersed to a depth of 15 in. in a bath of hot water at 44° C. The water was controlled at this temperature. Readings were continued at the selected positions as before. The induction of vasodilatation in one foot through immersion of the other has been considered the most suitable for our purpose, the degree of vasomotor relaxation in the lower limbs being much less than in the upper limbs (Gibbon and Landis, 1932; Pickering and Hess, 1933).

If a thermal response test is repeated on other days, before therapy, the resultant graphs are almost identical in character.

Figs 1 and 2.—The lack of response before treatment is transformed by ACTH into the type of response which would be expected from a normal healthy person.

Fig. 3.—The pre-immersion portion of the curve shows a more active state of vasodilatation after treatment, although the subsequent gradient of the curve is not so steep.

The graphs show temperatures of left great toe before and during immersion of right foot in hot water; Dotted line—before ACTH; Black line—after ACTH.

Results

The patients concerned (29 cases) were all females between the ages of 25 and 55, undergoing treatment at the Rheumatism Unit. They were mainly suffering from rheumatoid arthritis, but some cases of osteoarthritis were included.

The test revealed:

(a) the state of vascular tone during the resting period, whether it increased, decreased, or remained unchanged. Finger skin temperature below 25° C. after 15 min. in a basal state in a room at a temperature of 20° C. were considered by Naide and Sayen (1945) as indicative of high peripheral vascular tone;

(b) the promptness or otherwise of the response in the exposed limbs to the thermal stimulus (reflex or indirect vasodilatation) which indicates the degree of integrity of the neurovascular mechanism involved: it is usually shown as a more or less rapid rise of skin temperature after a time-lag of 10 to 40 min.;

(c) the steepness and extent of the induced rise of temperature.

Group 1.—Nineteen out of the 29 cases (65·5 per cent.) showed after ACTH a definite improvement in the previously sluggish thermal response in the foot, which, for reasons explained elsewhere, is considered a better criterion for the test than the hand. In the absence of graphs (three specimens only of which are reproduced, Figs 1, 2, and 3) a numerical assessment of the thermal response in each case was calculated. This "index" (Woodmansey, 1951) was the gradient of the curve in (fractions of) ° C. per minute. This

was counted from 19° C., i.e. room temperature, to the peak of the rise (or if the peak was not attained, to the temperature rise at the end of 30 min. of immersion) divided by the time in minutes.

The average response was 0·23° C./min. before ACTH, and 0·43° C. after ACTH.

The toe temperatures of twelve out of these nineteen cases were considerably higher (average 2·9° C.) during the resting period after ACTH than they were before.

Group 2.—Five out of the 29 (17·2 per cent.) showed no change in the response test after ACTH, but showed a higher skin temperature of some upper or lower digits before the immersion. The average increase was 4·1° C.

Group 3.—The remaining five out of 29 showed no circulatory effect due to ACTH.

Discussion

The peripheral blood flow exhibits two main modifications following ACTH therapy. The first consists of a diminution in the peripheral vascular tone, permitting increased cutaneous blood flow with increased digital temperature. This effect was not evident in the five failures (Group 3). One of these patients showed a low vascular tone initially and little clinical effect from a 10-mg. dose given over 13 hrs; another had a lower vascular tone in the toe than in the fingers, but felt some improvement in the

joints following a dose of 20 mg. given over 5 hrs—an improvement in vascular condition in these cases perhaps could not be expected. The other three cases had initially a high degree of vascular tone in the toes, which was not overcome by the hormone.

It is of interest that the second patient indicated above has been re-admitted recently for a second course of infusions and tests for both vasodilatation and thermal response now show positive results.

Of the five patients who did not respond to the test yet showed some degree of limb vasodilatation after therapy (Group 2) a release of high vascular tone was noted in the fingers but not in the toes of two. A similar release occurred in all limbs of two others, and the fifth case showed a still further release of low initial tone.

The second and more important effect of ACTH therapy was demonstrated in the nineteen cases (Group 1) who showed an improvement in the previously sluggish thermal response.

The increase in peripheral blood flow due to ACTH therapy may be a significant factor in the pharmacological effect of the hormone. As Horwitz and others (1951) pointed out, the vasodilatation may have resulted from effects of ACTH either directly on the vessels or on their autonomic control or indirectly on disease factors that had caused excessive vascular tone. The accelerated response in the other limbs to a thermal stimulus in one, suggests that the effect is neuro-vascular *via* the thermo-regulatory mechanism. This is so frequently defective in rheumatoid arthritis that any improvement in this respect must be an important part of ACTH therapy.

Summary

Skin temperature measurements and thermal response tests were applied to a group of 29 patients with rheumatoid arthritis. Nineteen showed improved vasomotor activity after ACTH, and a further five showed an increased digital temperature. One of the five who showed no effect responded quite well to the hormone on re-admission for further infusions.

It is suggested that the effect of ACTH on the peripheral circulation takes place *via* the thermo-regulatory mechanism.

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Effet de l'hormone adrénocorticotrophique sur le sang périphérique

RÉSUMÉ

On mesura la température cutanée et fit des tests de réponse thermique chez 29 malades atteints d'arthrite rhumatoïdale. Après le traitement par l'ACTH l'activité vasomotrice augmenta chez 19 d'entre eux et la température digitale chez cinq autres. Les cinq restants ne réagirent pas, mais un d'eux répondit assez bien à l'hormone lorsqu'il fut readmis à l'hôpital pour des infusions ultérieures.

On suggère que l'action de l'ACTH sur la circulation périphérique s'exerce par l'intermédiaire du mécanisme thermo-régulateur.

Efecto de la hormona adrenocorticotrófica sobre la sangre periférica

SUMARIO

Se midió la temperatura cutánea y se hizo tests de respuesta térmica en 29 enfermos con artritis reumatoide. Después del tratamiento con la ACTH la actividad vasomotriz aumentó en 19 de ellos y la temperatura digital en otros cinco. Los demás cinco no reaccionaron, pero uno de ellos respondió bastante bien a la hormona después de su internación para infusiones ulteriores.

Se sugiere que la acción de la ACTH sobre la circulación periférica se ejerce por intermedio del mecanismo termo-regulador.