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THE HISTAMINE TEST AS AN AID IN THE DIAGNOSIS OF EARLY LEPROSY*

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It is generally agreed that one of the greatest needs in leprosy work to-day is a reliable serological test that can be depended upon to detect the disease in its earliest stages. Unfortunately, in spite of claims of some to the contrary, such a test does not yet exist. Until one has been elaborated and since in the "incipient stage" the presence of *Mycobacterium leprae* cannot usually be demonstrated by ordinary methods of making the bacteriological examination, we have to depend almost entirely on clinical methods such as the detection of the anæsthesia, palpation of thickened nerves and superficial glands, careful history-taking, and examination of the external lesions as to appearance, location, etc., in order to arrive at a diagnosis in this stage. Naturally the accuracy of the diagnosis must depend to a great extent on the experience of the physician making the diagnosis. The introduction, therefore, of any clinical test that will tend to minimize the influence of the personal equation should prove of value.

We believe that we have found such a test in the so-called "histamine test." When a dilute solution of histamine is pricked into the normal skin, a reaction takes place in about twenty seconds, starting with the appearance of a circular, sharply defined, local reddening surrounding the prick, and measuring when fully developed from 3 to 4 millimeters in diameter. This is followed in another fifteen to thirty seconds by a flush or "flare" that appears on the sur-

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rounding skin. It is of the utmost importance to distinguish this flare from the local red reaction. The flare is dark red or scarlet contrasting with the brighter shade of the latter; it has diffused and often crenated borders that may extend from 2 to 3 centimeters from the center of the reaction. Soon after the appearance of the flare, a discreet wheal forms at the site of the prick; this is generally at its maximum development in from three to five minutes, at which time it measures from 3 to 4 millimeters in diameter and about 1 to 2 millimeters in height. The wheal usually occupies the area originally covered by the local red reaction, although in many cases the two do not coincide, the wheal being usually smaller than the localized red area.

The full reaction of the normal skin to histamine, consisting of the local redness or vasodilation, the flare, and the œdema or wheal has been called by Lewis¹ the "triple response."

Lewis has demonstrated that the triple response is a characteristic reaction of the normal skin following injury inflicted by such agents as heavy stroking, pricking, scratching, freezing, heating, electrical shocks, as well as by the introduction of irritant substances such as acids, alkalies, mustard oil, cantharidis, nettle sting, morphine, etc. Ultraviolet rays, ordinary sunlight, X-ray and radium emanations, bacterial poisons, certain chemicals such as dichloroæthylsulphide, etc., give rise to more slowly developing reactions. He has also proven that the local redness and the wheal or œdema are due to direct action of the injury or irritant on the capillaries, while the flare is produced by the dilatation of the arched arterioles and is reflex in nature, being dependent upon the integrity of the cutaneous nerves. The arteriolar dilatation is mediated through a purely local nervous reflex and does not depend upon a spinal reflex arc.

This test has been tried by Lewis and his colleagues² on anæsthetic skin to which the sensory nerves have been cut surgically or interrupted by injection of anæsthetics. When the interruption produced surgically or by anæsthesia is recent, the reaction to the histamine test is complete in all its details, although the skin has already been rendered anæsthetic; but if sufficient time (six to fifteen

¹ The Blood Vessels of the Human Skin and their Responses. Shaw & Sons, Ltd., London (1927) 47.

² The Blood Vessels of the Human Skin and their Responses. Shaw & Sons, Ltd., London (1927) 69-70.

days) is allowed for the nerve to degenerate after surgical section or if the skin is anæsthetized locally, the flare is lost. Under these circumstances, the local red reaction and the œdema appear as in the normal reaction of the skin.

Thus, the loss of the flare following a histamine test is a sign of degeneration of the sensory nerves supplying the skin tested, and possibly also of direct involvement of the nerve endings as in local anæsthesia.

Histamine, or B-iminazolyethylamine, is described by Lewis as "the amine produced when carbon dioxide is split from histidine, a substance occurring naturally in the body and a protein derivative." It was extracted by Barger and Dale³ from the intestinal mucosa, and was later thoroughly studied by Dale and Laidlaw.⁴ The histamine test as applied on the skin was first reported by Eppinger⁵ and later elaborated by Sollman and Pilcher⁶ and by Lewis and Grant.⁷

THE TEST

In most of our tests, we have used a 1 to 1,000 dilution of the phosphate in normal salt solution. With stronger solutions a larger flare is occasionally obtained, but the reactions are not as constant as with the 1 to 1,000 solution.

A small drop of the solution is carefully placed within the suspicious macule to be tested and another is dropped on normal skin at least 2.5 centimeters from the border of the lesion for control. With a sharp pin, a prick is made through the drop into the skin underneath, taking care to exert just sufficient pressure to drive the point through the epidermis without causing any bleeding. The histamine solution is wiped off immediately, and the pricks are closely observed under good natural light.

The test is said to be negative when the complete response is elicited and positive when the flare is absent.

³ Journ. of Physiol. 41 (1910-11) 499-503.

⁴ Journ. of Physiol. 41 (1910-11) 318-344; 43 (1911-1912) 182-195.

⁵ Wein. med. Wochenschr. 43 (1913) 1414.

⁶ Journ. of Pharmacol. and Eper. Therap. 9 (1917) 309-340.

⁷ Vascular Reactions of the Skin to Injury. Part II, Heart 11 (1924) 209-265.

There are some individuals on whom the normal reaction is diminished; in a few, the flare is so faint as to be practically absent. When the response is weak and the skin tested is on an extremity, the flare may be brought out to its maximum extent and intensity by previously congesting the extremity with the help of a broad rubber band or the pneumatic cuff of a blood-pressure apparatus.

Finally, it must be recognized that the reaction is harder to elicit on the dark skin of a Filipino than on white skin.

RESULT OF THE HISTAMINE TEST IN LEPROSY

In the pale macule.—The flush is always absent in the depigmented macule of leprosy. When the histamine prick is made just outside the border, a flare develops on the normal skin but stops sharply at the border and does not extend into the macule. When the prick is made just inside the border, the flare is prevented from appearing even on the bordering normal skin.

A word of caution must be given at this point. The flare generally masks the local redness following the histamine test on the normal skin. When the flare is abolished as in a leprotic macule, the local redness becomes prominent and may be mistaken for the flare by the beginner. The area of local redness is sharply localized, circular in shape, bright red or pink in color, extending at the most 2 or 3 millimeters beyond the wheal, and tends to become cyanotic before fading. On the other hand, the flare is not definitely localized, the size is usually about 3 to 4 centimeters in diameter, irregular in shape, although it tends to be oblong with its long axis along the length of the member, and the color is dark red. On fading, the flare becomes speckled, but the color remains the same from beginning to end.

The wheal in the macule is usually of the same size as that on the normal skin. Sometimes the œdema may be less; at other times the wheal develops faster in the macule, reaching its full development in two minutes, while the wheal on the control skin is at its height in three to five minutes. The ultimate size, however, is almost the same.

The test has been applied on the macules of *Tinea flava* and other types of pale-looking pityriases, on leucoderma, old scars, fading psoriasis lesions, etc., which may be mistaken for the pale macule of leprosy. In every case, the flare is present provided the individual is not unsusceptible to histamine, in which case, the flare is also diminished or absent on the normal skin.

In the reddish macule.—When the redness of the lesion is marked, only the wheal may be elicited; but when the color is not so striking, the local redness may be seen.

When hyperæsthesia is present, as is usually the case when the lesion is bacteriologically positive, the flare is not constant. In a few macules the flare is present; in the majority of the cases it is absent. If there is accompanying infiltration or œdema so marked

that the skin looks tense, glistening, and bright red in color, the wheal is apt to be slight or absent.

The histamine test was tried in cases of dermatitis from various causes, active psoriasis lesions, tinea circinata and other ringworm infections, fresh scars, and other lesions that may simulate the red macule. When the inflammation in such lesions is active and there is considerable redness, the wheal is generally diminished or even absent while the flare is present, manifested by increased redness of the skin. It must be stated that when the redness of the original lesion is at all bright, it is next to impossible to distinguish the flare. When this is the case, the best way to perform the test is to prick the histamine solution just inside the border. In the nonleprotic lesion, the flare appears on the adjacent portion of the skin outside the border, whereas there is no such flare extending from the macule in early leprosy.

SUMMARY

1. The histamine test has been found to be a fairly reliable clinical test in differentiating the patches characteristic of the early stages of leprosy from nonleprotic macules.

2. This test is "positive" (the flare is absent) in the large majority of the bacteriologically negative leprotic macules tested.

3. The method of performing the test is described and its limitations mentioned.

¹ *The Blood Vessels of the Human Skin and their Responses.* Shaw & Sons, Ltd., London (1927) 47.

² *Op. cit.* 69-70.