STUDIES IN DENERVATION

C.—INFLAMMATION AND TROPHIC ULCERS IN DENERVATED AREAS

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(RECEIVED 14TH OCTOBER, 1943)

THE clear demonstration of Bruce (1913) that the inflammatory response of the conjunctiva to mustard oil is dependent on the presence of intact afferent neurones and is mediated by axone reflexes has been accorded general agreement, though Stevenson and Reid (1915) and Hirschfelder (1924) have expressed dissidence. The work of Lewis *et al.* (1927-9), however, leaves no doubt that injury to the skin causes a flare response dependent on the mechanism described by Bruce. This local vascular dilatation would appear to be a highly appropriate response to infection and would supply a simple explanation of the caloric element of the inflammatory tetrad. Experimental evidence for this is lacking. Grant (1935) found that nerve degeneration did not affect the healing of injuries of rabbits ears and Menkin (1940) has summarized the literature and concluded that the absence of nerves does not materially alter the inflammatory reaction. Moreover, in the human, Smithwick and White (1935) have been successful in securing the healing of chronic ulcers in subjects with occlusive vascular disease by crushing peripheral nerves. Despite this there is a lingering clinical suspicion that the obstinacy in healing shown by burns of denervated digits and the pressure ulcers of denervated feet is related in some way to the nerve lesion. Thus Lewis and Pickering (1936) have ascribed the intractability to a diminished blood supply. However, it was concluded in paper B that the blood supply of denervated digits was adequate to the needs of the tissues. It appeared therefore that this matter merited further investigation.

Observations

In order to decide if the local hyperæmia found in conjunction with inflammation was lacking in denervated digits two subjects were examined by the methods described in paper A.

Subject J.M. had a right ulnar nerve lesion and the results in Fig. 1, Exp. 1, were obtained two weeks before he burned the medial aspect of the distal phalanx of R.F.5. This figure shows that the vascular reactions of this digit were typical of those of denervated digits. Fig. 1, Exp. 2 shows the con-

dition present eight days after the burn, at which time a small clean ulcer was present. The temperature of R.F.5 was now raised and, when the body was warmed, it attained a temperature much higher than in the previous experiment. It will be noted that the initial response to immersion of the feet in hot water was a vasoconstriction which relaxed when the feet were removed. This water felt burning hot and the effect on the finger temperature is ascribed to a release of adrenaline. The following day the patient sat for two hours with the hands exposed in a room at 20° C. The temperature of 25 points on the

FIG. 1.—Temperature charts of subject J. M. before and 8 days after a burn of R.F.5. The lines representing the temperature of different digits are identified on the charts. The lower line of blocks if filled indicates indifferent limbs in water at 18° C.; if empty in water at 44° C. The upper line of blocks if filled indicates the extremities under observation in water at 18° C.; if empty in water at 38° C.

palmar surface of each hand were then taken and the isotherms plotted from the data are shown in Fig. 2. These indicate that the whole of R.F.5 was abnormally warm. Isotherms obtained from cases with ulnar nerve lesions having no inflammation were found similar to those obtained from normal subjects when the hands were cold.

Subject A.H. with a sciatic nerve lesion and moderate oedema of the foot had a small ulcer at the base of the distal phalanx of the great toe. This healed when the patient was in bed with the leg horizontal or elevated, but recurred when the foot was used despite elastic bandaging and cloth boots. Eventually amputation of the leg was

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FIG. 2.—Distribution of isothermic lines in subject J.M. 9 days after a burn of the tip of the right little finger.

required. Fig. 3 illustrates the persistent high temperature of L.T.1 and a less marked elevation of that of L.T.3. Local cooling by immersion of the feet in water at 18°C. for 10 minutes did not

FIG. 3.—Temperature chart of subject A.H. with a chronic ulcer of L.T.1, conventions as in Fig. 1.

induce vasoconstriction, as it invariably did in subjects with uncomplicated nerve lesions (paper B). In Fig. 4 are plotted the isotherms as determined under conditions similar to those described above. It is evident that these lines centre around the great toe and that the whole foot is warmer than the normal one. A control subject (C.B.) with a sciatic nerve lesion showed the same pattern as the normal

FIG. 4.—Distribution of isothermic lines in subject A.H.

foot. Fig. 9 of paper E is a reproduction of a plethysmographic record of subject A.H. The marked discrepancies between the size of the pulse waves indicates the high blood flow in L.T.1. No definite response to a deep breath or to a sudden noise was present in this toe, but two sums in mental arithmetic appeared to produce a slight vasoconstriction commencing 10–15 seconds after the sum was given. A definite response to 0.2 ug adrenaline was obtained.

Discussion

These two cases represent the two causes of the majority of so-called trophic ulcers, namely, burning and pressure. It has been demonstrated that in both the cause of the delayed healing resides elsewhere than in a defective blood supply.

In the cases of ulcers following burns we lack any definite evidence of the extent of the original trauma and the usual criteria depending to a certain extent on pain and the flare are lacking. Therefore, it is unwarranted to describe the healing as slow and in fact no unduly chronic ulcers of the hands have been observed.

In the cases of ulcers from pressure the major predisposing and perpetuating factor is not the loss of cutaneous innervation but is the oedema caused by the paralysis of the leg muscles. This statement is supported by the fact that healing occurs when drainage of the limb is promoted and by the fact that in a series of six complete sciatic nerve injuries five showed a tendency to oedema and four developed ulcers, while in a series of four posterior tibial nerve injuries none developed oedema or ulcers. This was true though the pressure points were anaesthetic and no special precautions were observed to avoid trauma. Pressure ulcers are, therefore, determined in patients with nerve lesions not by the loss of cutaneous innervation or defective arterial circulation, but by an impaired lymph drainage.

The term trophic which has been applied to the ulcers under discussion not only lacks precision but seems to imply that some peculiar defect of tissue nutrition is present. Neither the experimental work nor the observations reported here justify this view. It is not uncommon for patients to be entirely ignorant of any cause for a blister or ulcer, but this in itself hardly warrants an adjective other than painless and there appears to be no other reason for the use of the term "trophic." Lewis and Marvin (1927–9) have doubted the traumatic origin of these lesions, but the mere fact that they always occur on the most exposed part of the digits argues strongly in favour of such a view. These unperceived injuries are explained by the insentient nature of the part and by the deficiency of vasodilator axonal reflex. In paper B it was shown that immersion in hot water caused a greater rise in the temperature of denervated digits than of normal digits, presumably because of this deficiency. One subject, S.R., with an ulnar nerve lesion was tested with this point in mind. Immersion of the gloved hand in water at 49°C. caused the temperature of

the little finger to rise to 47° C. while that of the normal index finger rose only to 43° C. Thus it would be possible for an agent to damage the denervated digit while being innocuous to a digit in which vasodilator axonal reflexes were present. Wybauw (1936) has in fact shown that if a cat's leg, the afferent fibres of which have been caused to degenerate, is immersed in water at 60° C. for five minutes there results a considerable œdema. This does not occur if the leg is normal or if only the posterior roots are cut.

Disturbances of growth which appear to have more claim to the term trophic have been attributed in paper B to the effects of temperature. Experience of the trophic disturbances associated with causalgia has been too limited to merit description, but it is desirable to record the incidence in subjects with peripheral nerve lesions of herpetic eruptions which resemble those described as occurring in causalgia.

Routine examination of cases with peripheral nerve lesions revealed not uncommonly minute vesicles on the palms and fingers. It seemed that these were especially likely to be found in patients who, because of paræsthesiæ or some other reason such as osteomyelitis of the radius, did not use the hand and in which the skin tended to be kept moist by sweat. No particular association was noticed between areas affected by the nerve lesion and those affected by the eruption though thinning of the skin made the vesicles more evident. The condition was therefore thought to be a variety cheiropompholyx to which it bore an absolute resemblance. Attempts to isolate a fungus were as unsuccessful as other attempts (Roxburgh, 1939) in this condition.

These considerations do not prove that the minute vesicles described by Mitchell *et al.* (1864a) in cases of causalgia are not due to irritation of the nerve fibres and the similarity of the vesicles to those of zoster of the extremities might suggest a similar causation. In this connection it may be noted that the view of Lewis and Marvin (1927-9) that the vesicles of zoster are due to stimulation of posterior root fibres is still a hypothesis. They were unable to show that prolonged experimental stimulation of posterior root fibres gave rise to wheals or vesicles while the presence of the virus in the fluid of the vesicles offers an alternative explanation (Wilson, 1940). The early involvement of the regional lymph glands also indicates an inflammatory reaction not limited to the posterior root ganglia. The argument that symptomatic zoster also produces vesicles (Lewis and Marvin, 1927-9) loses force with the present day conception that all cases of zoster are due to specific virus and that the symptomatic variety is the same infection localized at the site of pre-existing disease. Lewis (1942), however, still favours his original view, but it is clear that any analogy that might be drawn between the herpes of zoster and of causalgia need not necessarily indicate a neurogenic causation. There is therefore little basis for the generally accepted view that the vesicles occurring in cases of causalgia are due to the nerve lesion and it is not improbable

that they are a variety of cheiropompholyx. Even the interesting case reported by Ross (1933) in which the vesicles were singularly limited to the hyperæsthetic area might be explained if the skin of this part was rendered unduly susceptible by moisture and lack of friction.

The following quotation from Mitchell, Morehouse and Keen (1864b) is given not only to support the present thesis that the vesicles are not neurogenic in origin, but to indicate the strong prejudice of these authors in favour of the neurogenic theory. Referring to a case of typical causalgia they state "It is an admirable example of the presence of eruption associated with depraved nutrition. We mention it here only to call attention to the fact that the right hand was the injured member, and that the eczema appeared secondarily in the left palm, and was relieved by the treatment which was addressed to the right limb. Was this a case of reflex influence?" It is also worth noting that in many of their cases the description of the eczema is typical of a gross infection by a species of trichophyton. It is possible that a condition of this sort occurring in an area of dysæsthesia would give rise to severe pain and this would be an acceptable explanation for the present rarity of typical cases of causalgia.

Summary

Evidence has been presented to show that the vascular response of inflammation is present in denervated digits.

The intractability of ulcers in denervated areas has been ascribed to the fact that as the extent of the damage is not appreciated the healing only appears to be slow, while in the foot œdema rather than denervation is the responsible factor.

The use of the term trophic has been found unwarranted in this connection.

It has been suggested that the vesicular eruption present in some cases of peripheral nerve lesions is not primarily due to the affection of the nerve.

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