INTRA-EPIDERMAL NERVE ENDINGS

By H. H. WOOLLARD

St Bartholomew's Medical College

IT has been generally accepted that the epidermis is the seat of the sensation of pain and the dermis the seat of the sensation of touch.

This belief, of some duration, was made stronger when v. Frey⁽³⁾ placed the notion of the punctate distribution of the elementary cutaneous sensations on a firm basis. The localization of pain depended much on the statement that the cornea in its central part experiences pain only, and that it is here that naked nerve terminals of the corneal nerve plexus, having become first hypo-epithelial, continue on amongst the epithelial cells of the conjunctiva. The two conclusions—that pain depends on the fine naked nerve terminals and that its seat is in the epidermis, continued henceforth to be acceptable.

Quite recently they have been challenged by Waterston⁽⁹⁾, and he has emphasized two observations in particular as supporting the contrary opinion that the epidermis is not the seat of pain, but is really the seat of touch. He has stressed the fact that the threshold value for touch is so small that it is not conceivable that the sensory apparatus for touch can lie buried below the many layers of the epidermis. In fact he asserts that organs like Meissner's corpuscles are not organs of touch but really organs of pain. It is obviously a matter for investigation what the threshold for touch is and whether the stimulus is too small to reach the dermis. Since the evidence is good that touch is only aroused by a deformation of the skin, the argument derived from the threshold value of touch as to its anatomical place in the skin does not seem a very strong one.

The second observation of Waterston depends on the fact that it is possible to shave off at least the greater part of the stratum mucosum of the epidermis without causing any pain at all, but only the sensation of touch. This second argument seems to us a much more important one.

It is to be remarked that no matter whether one accepts the epidermis as the seat of pain or as the seat of touch, in either case one would expect an overwhelming abundance of nerve fibres in the epidermis. For if one marks out on any part of the surface of the body the points sensitive to touch by means of v. Frey hairs and of pain by means of the prick of a pin, one is overwhelmed by the multitude of responding points. Indeed if the theory of the punctate distribution of the cutaneous sensations had to depend only on such observations as these, its hold upon us would be much less firm. It is therefore most pertinent to enquire if such rich epidermal innervation exists.

Before turning to our own observations a brief survey of the findings of others is of importance, since many investigations have been made on the intra-epidermal nerve endings.

The distinction of Retzius as an investigator and the wide extent of his observations seem to be the reasons why it is generally assumed that the epidermis is beset with an abundance of naked nerve terminals. In the skin of the cyclostomes, salamander and other non-mammalian forms, he has published figures of a rich plexus of naked terminal in the epidermis. In mammals, though a similar state has been assumed, nothing of the sort has ever been found. The cornea and mucous surfaces we may leave on one side for the moment, as being not comparable with ordinary epidermis, since their surfaces are always moist. In lower mammals such as the rabbit, it is possible to find more easily than in higher forms a number of epidermal nerves, but in general it can be asserted that in mammals and especially in man in the ordinary epidermis it is very difficult to find intra-epidermal nerves, and no one has figured any extensive and abundant epidermal plexuses. The Spanish school (Tello) have remarked that in man they are more common in the epidermis of the foetus and that they disappear later. Agabow⁽²⁾ has even denied their presence. Others comment on the difficulty of finding them.

ENDINGS FOUND IN EPIDERMIS

The form and situation of those epidermal nerves which have been found by many investigators have been described in a remarkably uniform manner. They are found in the snout and muzzle of animals like the pig; in Eimer's organ—a relatively huge and specially designed epicritic organ in the deer; in the hand and soles of the feet in man; in the outer root sheath coverings of the hair follicle. It is to these regions most descriptions have applied. It is from the observations in these regions that by inference and assumption the same is regarded as applying to all epidermis. This restriction, not of course absolute, is, as a critical survey of the literature discloses, a most prominent one.

It is customary for most authors to allude to naked terminals in the epidermis. These we have seen but they are uncommon. Very few descriptions of them have been made from human skin. Most observations have been made on facial and snout skin in the ungulates. Kadanoff^(4, 5, 6), who has given the best description of them in recent times, based his observations on the snout of the deer.

The other commoner forms upon which all can agree are at least two. One is the general occurrence of Merkel's discs. These have been found in the deeper layers of the stratum mucosum generally in all parts of the body, but most abundantly in parts like the hand, lips, etc., which are already distinguished for their high degree of tactile acuity. These endings are the offspring of well-medullated fibres, but the best reason for accepting their tactile office is the fact that they are frequently borne on the continuation of the neurofibrillae of Meissner's corpuscles.

These continuations pass on into the epidermis, and there form these Merkel's discs. It is still at any rate a credible idea that a nerve fibre subserves

one kind of sensation and one only, and if Meissner's corpuscles are for touch then these discs are of necessity also for touch. The abundance of Meissner's corpuscles in the hands and feet in man and the anthropoids make it difficult to accept any other functional allocation for them; to say nothing of all our notions about the primitive simplicity of pain suggesting a similar unpretentiousness in its anatomy.

Medullated fibres form some sort of spiral ending in many of the papillae of the dermis. These are thought to be a very simple form of a Meissner's corpuscle. It is a common observation that from such fibres terminals are continued to the stratum Malpighii. They do not pass much beyond this in the epidermis. Usually they end about the epidermal cells in some sort of an expansion resembling a Merkel's disc. These again suggest a tactile function. No one has ever suggested for hairs any other function in cutaneous sensation than that of increasing tactile acuity. It is an observation that helps our suggestion that the intra-epidermal endings are associated with touch for Merkel's discs, and even more elaborate endings are found in the outer root sheath of hairs.

Thus we want to stress the fact that no one has claimed in man to have found abundant intra-epidermal innervation either of the naked terminal kind which would suggest pain or of a more organized kind that would suggest touch. The naked terminals of pain we would not exclude absolutely, but we believe it to be uncommon. In those parts of the body especially where tactile acuity is high, and in other parts, much less abundantly, epidermal endings are to be found often in themselves well organized, often traceable to medullated nerves, and finally perhaps the continuations of especially intricate structures like Meissner's corpuscles.

We thus come to the conclusions that the epidermis is not in any way the special site of pain. We agree with Waterston that it is an organ of touch. Waterston, however, goes too far in emphasizing it as the exclusive organ of touch. We see it rather as an accessory organ of touch.

Obviously such an opinion would be more secure if we could find a sufficiently abundant terminal nervous apparatus conforming to our ideas of what ought to be the anatomy of a pain plexus, and situated in a place that satisfies the requirements of experimental observations.

EXPERIMENTAL OBSERVATIONS

It is a fact that much of the epidermis can be shaved away without exciting at any rate a severe sensation of pain. Mr McIndoe with a razor used for cutting grafts made three slices along the outer side of the thigh in a particular subject before it was necessary to resort to local anaesthesia. Before the cuts were made a map had been constructed of the points from which touch, cold and pain could be elicited with the least stimulus. This map could be superimposed on the skin after each cut.

When the knife was traversing the epidermis an attempt was made to correlate the situation of these spots, where a light prick elicited the most severe pain with the exclamations made by the subject on his sensations of pain. Though such an experiment is fraught with many difficulties it was claimed that this was done with considerable success, and it was agreed that the exclamations coincided with the cutting through of the marked pain spots. These points of severe pain were found further to coincide with the cutting through of the papillae of the dermis. The oozing from the capillary loop in the dermis indicated that this was what had happened. The later cuts which severed many capillary loops, and this was passing through more and more of the subepidermal tissues, were so violently painful that cutting without an anaesthetic was out of the question.

These experiments which agree with the observations of Waterston⁽⁹⁾ suggest that an abundant pain plexus should be found above all in the subepidermal region.

Pain is a sensation that relatively is poorly localized, that irradiates widely and lacks discriminating value. In those situations where it is the only elicitable sensation, it has the form of fine varicose fibres without ensheathment and forming no complex kind of ending. The results of experiments such as those of Ranson⁽⁷⁾ that pain is conveyed by non-medullated or finely medullated fibres have on the whole been accepted. The study of the action potentials of single nerve fibres, thresholds, rates of conduction, etc., all point in the same way to the pain nerves being subserved by a much finer and simpler anatomical structure than that of the other sensations. It is only fair to point out that the physiological and anatomical results are not altogether in harmony on this matter, nor can the restriction of pain conduction to the finest nerve fibres be regarded as proven.

ANATOMICAL OBSERVATIONS

Pl. III, fig. 1, which is an actual photomicrograph of a nerve plexus discovered in a subepidermal position, is regarded as affording the anatomical basis for pain. This nerve apparatus is composed of the finest fibres. As they come up from the deeper layers of the dermis they are about 3μ in diameter. Soon on becoming more superficial they become finer still and assume the dotted irregular varicose form. The filaments so formed have a marked tendency to run in the form of a closed loop. These loops have been most carefully examined, and at times actual fusion of neurofibrillae occurs and so a closed loop is formed. Frequently, however, single fibres come to an end. This mode of termination is regarded as the actual ending of the nerve fibril. The endings achieve no complexity and for a considerable distance they are naked neurofibrillae without ensheathment of any kind.

This plexus occupies a subepidermal position immediately below the stratum Malpighii, and can be found presumably all over the body in this position. Our

own observations have found it in many places in the upper and lower extremities.

Occasionally some fibrils can be traced into the epidermis but this is rare. One drawing (Text-fig. 1) is included to exhibit this uncommon impingement

Text-fig. 1. A drawing of the plexus of fine beaded fibres ramifying at the subepidermal level. There are points at which the plexus appears to be reinforced from below. Discs indicate capillaries and red blood corpuscles. Methylene blue. Human skin from amputated leg. $\times 284$.

on the epidermis. Similar terminal fibres to these are found throughout the dermis, and they are also present as an additional or accessory fibre to more highly organized endings. Many have described these, and we have observed them in relation to Meissner's corpuscles, in relation to hairs, and Pacinian corpuscles, Krause end bulbs and the like. Some have jumped to the con-

clusion that these fine accessory fibres belong to the sympathetic nervous system. It is more probable that they belong to the pain system and act as protective nerves to these more complex endings.

Experimentally we have felt that the evidence suggested that the anatomical situation of pain begins at the subepidermal level. The discovery in that situation of a plexus and endings in sufficient abundance and of the appropriate character reinforces the experimental conclusion.

Thus we come to regard the epidermis as being accessory to touch, this being more especially the case in regions where tactile acuity is high. Intra-epithelial neurofibrils and endings are figured as occurring abundantly in such places as the conjunctiva and the mucous membranes of the mouth, pharynx and larynx. Even if this be so we regard the innervation of these surfaces as distinct from that of the epidermis and offering no grounds for the belief that this also would enjoy a similar richness of nerves.

SUMMARY

1. Experimental and anatomical evidence suggesting that the epidermis in man is only occasionally accessory to pain is discussed.
2. Evidence for the appearance of touch endings, especially in places of high tactile acuity, is mentioned.
3. The discovery of a terminal nerve apparatus in which both free ends and continuity of neurofibrils occur agrees with the anatomical and experimental evidence that pain is immediately subepidermal.

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EXPLANATION OF PLATES I-III

PLATE I

- Fig. 1. Fine varicose naked terminals in the epidermis. Methylene blue. Counter-stained carmine. Human thigh. 10 μ section. $\times 2000$.
- Fig. 2. Merkel's discs formed from medullated fibres in the dermal papillae. Cajal's silver method. Human thigh. 10 μ section. $\times 1200$.
- Fig. 3. Intra-epidermal nerve fibre extending to the stratum granulosum of the epidermis. Note immediately below the stratum Malpighii the thick transversely running nerve fibre from which the intra-epidermal fibre starts. Cajal's silver method. Human skin. 10 μ section. $\times 212$.
- Fig. 4. Intra-epidermal nerve fibre extending to the stratum granulosum of the epidermis. Cajal's silver method. Human thumb. 10 μ section. $\times 212$.

PLATE II

- Fig. 1. A photomicrograph of heavily medullated thick fibre. Its termination and the dense flocculated and spiral endings are seen. From the termination of ordinary Meissner's corpuscles further extensions into the epidermis occur where they end as Merkel's discs. Methylene blue. Human skin. Amputated leg. $\times 300$.

PLATE III

- Fig. 1. A photomicrograph of the subepidermal plexus. The tendency to form a neurofibrillar net and occasional free endings is seen. It is composed of the finest beaded fibres. The cells seen between the fibres are red blood corpuscles. Methylene blue. Human skin. $\times 315$.

Fig. 1.

Fig. 2. ×1200.

Fig. 3. ×212.

Fig. 4. ×212.

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