

NEURAL MECHANISMS INVOLVED IN ITCH, "ITCHY SKIN," AND TICKLE SENSATIONS

By DAVID T. GRAHAM, HELEN GOODELL, AND HAROLD G. WOLFF

(From the New York Hospital and the Departments of Medicine [Neurology] and Psychiatry,
Cornell University Medical College, New York City)

(Submitted for publication August 4, 1950; accepted, October 10, 1950)

Available evidence suggests that the sensation of itching is closely related to that of pain (1). Titchener (2) observed that when the skin was explored with a fine hair, well-defined points were found which gave rise to itching when the intensity of stimulation was low, and to pain on stronger stimulation. Bishop (3) found that itching resulted from repetitive low intensity electrical stimulation of pain spots in the skin. Lewis, Grant and Marvin (4) pointed out that noxious stimuli, if their intensity be decreased, can be made to produce itching instead of pain. Förster (5) and Bickford (6) reported that in patients who had undergone section of the lateral spinothalamic tracts, thus abolishing perception of cutaneous pain but not of touch, itch was also abolished. Bickford also observed this combination of sensory changes in two patients with syringomyelia. Ehrenwald and Königstein (7), however, stated that they had found two cases of syringomyelia with loss of pain but preservation of touch and itch, and one in which pain was intact but touch and itch absent. McMurray (8) and Kunkle and Chapman (9) found that individuals who were constitutionally insensitive to pain were likewise insensitive to itching, but they experienced touch sensation. Bickford observed that itching and pain disappeared at the same time when a cutaneous nerve was anesthetized. Hardy, Wolff and Goodell (10) observed that in addition to feelings of warmth, occasional itching resulted from sustained thermal irradiation at an intensity not quite strong enough to induce pain. Thöle (11) found during spinal anaesthesia, as the sensitivity of the skin to painful stimuli decreased, that stimuli which initially induced pain later induced itching and finally no sensation at all.

In the present investigation many of the experiments described by Goldscheider (12), Bickford, and Lewis and associates have been repeated. Additional experiments were designed to illumi-

nate further the neural mechanisms involved in itch, "itchy skin" and tickle sensation.

ITCH

Subjects and methods

The subjects were healthy adults, chiefly the authors, although other individuals participated from time to time. Itching was elicited by the application of cowhage to an area of skin approximately 1 cm. in diameter. Cowhage is the familiar "itch powder," consisting of the fine fibers or spicules of the plant *Mucuna pruriens*. It was found by trial that the itch so produced was indistinguishable from that following the bites of mosquitoes, or the intracutaneous injection of histamine. When an area of skin on the arm, hand, leg or back was used for experimental procedures the corresponding areas on the opposite side of the body served as control.

Description of sensation induced following application of cowhage to the skin

Cowhage applied to an area of skin approximately 1 cm. in diameter induced, usually within 10-20 seconds, an intense itching sensation which had both burning and pricking qualities. It was localized but seemed to spread for a few millimeters beyond the borders of the stimulated area. These itch sensations sometimes merged into pain of a burning and pricking quality. The skin under the cowhage rapidly became red, and a flare sometimes spread into adjacent areas of skin. When the area involved was the volar surface of the forearm, the flare spread as far as 2 cm. proximally and distally and approximately $\frac{1}{2}$ to 1 cm. laterally. Within a few minutes after application of the cowhage, the skin several centimeters proximally and distally around the itching area became hypoalgesic to pin prick, and around the edge of this zone was a narrow band of hyperalgesia to pin prick, approximately $\frac{1}{2}$ cm. wide. The itching from cowhage spontaneously diminished after a few minutes and did not return until the cowhage was mechanically agitated; or until it was re-

vived by stroking the surrounding skin with the finger tip or a blunt object.

When the cowhage applied to the skin produced an intense itching, the sensation sometimes eventually became indistinguishable from pain. Furthermore, occasionally cowhage on normal skin and in areas of primary or secondary hyperalgesia induced pain alone. Also, as mentioned above, a heat stimulus at an intensity just below that sufficient to elicit pain, elicited itching.

Peripheral Fiber Pathways Involved in Itch Sensation

It has been demonstrated that stimulation of the human skin with a pin may give rise to two kinds of painful sensation. The first pain to be perceived after the application of the pin is described as "pricking" and is punctate, superficial and well localized. This has been referred to as "first" or "fast" pain. There is also a second, different type of pain, described as "burning," which is perceived as more diffuse and less superficial than the "pricking" pain. Since this "burning" pain is perceived after a slightly but definitely longer latent period than the "pricking" pain, it has been referred to as "second" or "slow" pain (13, 14). Although Lewis denied that these experiences constituted different qualities of cutaneous pain, others have recognized the qualitative difference. Most individuals can readily distinguish between the "pricking" and "burning" in cutaneous pain (15), especially if they are separately presented by the experimental methods described below.

The work of both Lewis and co-workers and Gasser and co-workers suggests that the "fast" pain is a function of myelinated fibers, the "slow" pain of unmyelinated ones (14).

Experiment 1. Demonstration of an itching sensation with pricking quality

In three subjects procaine hydrochloride 1% was infiltrated about a cutaneous nerve on the ventral aspect of the forearm. Within a few minutes there developed distal to the site of infiltration an area in which pin prick elicited only a sharp, superficial, well-localized pain of short latency—the "first" pain. The slower, diffuse and burning "second" pain was not felt.

Within this area of altered sensibility cowhage elicited itching which was sharp, pricking, superficial, and readily localized. There was no burning component. In areas where there was complete absence of pain sensitivity, but where light touch was still present, itching was not felt.

Experiment 2. Demonstration of itching sensation with a burning quality

a) In a series of six experiments on four subjects ischemia of the forearm was obtained by a pressure of 200 mm. Hg maintained around the upper arm by means of a sphygmomanometer cuff. After about 20 minutes of ischemia in the arm, a pin prick applied to the fingers and the hand elicited pain of long latency which was poorly localized, and burning in character. The "first" pain was absent, as was light touch.

Within these areas of altered sensibility the application of cowhage on a site approximately 1 cm. in diameter on the back of the hand resulted in itching which was different from that obtained in Experiment 1, in that it was diffuse and poorly localized, seemed to be a little distance beneath the surface of the skin, and was "burning" in quality.

However, in more proximal areas of the ischemic forearm, closer to the occluding cuff, where normal pain and touch sensation were retained, cowhage produced itching no different from that in skin of the opposite arm with blood and nerve supply intact.

b) The course of a branch of a superficial cutaneous nerve in the forearm was mapped through a distance of 4–6 cm. by means of faradic stimulation in two subjects. A soft lead tubing was applied over the nerve and held in place by tapes. Brine at a temperature of -2° to -4° C was circulated through it for 30 minutes, resulting in the progressive anesthetization of the area supplied by the nerve (16).

After 30 minutes, within this area of altered sensation "second" pain could be elicited by a pin point but "first" pain and light touch were absent. In these areas "burning" itch could be elicited by cowhage but not "pricking" itch.

Comment

It was thus possible to separate the usual itch sensation, as it occurs after insect bites or the application of cowhage, into two components. These corresponded in quality to the two types of cutaneous pain, and the results of differential blocking of cutaneous nerves indicate that they are mediated by different fibers. It is suggested that "pricking" itch is carried by the myelinated fibers responsible for "first" pain, and that "burning" itch is carried by unmyelinated fibers responsible for the "second" pain. Since either kind of itch could occur in skin in which touch perception was absent, it seems probable that touch receptors and nerves are not involved in the perception of itching.

It might be objected that the sensory changes following obstruction of the circulation are due to interference of fluid movement which might modify the function of sensory end organs, rather than to any functional change in the nerves themselves.

Against this assumption is the evidence that normal sensation was retained in skin close to the occluding cuff, but still distal to the obstruction, where fluid movement was as much interfered with as in the more distal areas where sensory changes did occur.

It is not difficult, once the two sensory components of itching have been separately perceived, to identify them in spontaneously occurring itches or in itch induced by a heat stimulus, by intracutaneous puncture of histamine or by exposing the arm to multiple mosquito bites.

Since the sensations of itching and pain are apparently mediated by the same fiber pathways an attempt was made to ascertain in what way a stimulus which produces itching differs from one which produces pain. Hence, experiments to test the thesis that the stimuli are of the same kind but of lower intensity were designed.

Experiment 3. Demonstration of lowered pain threshold in itching areas

Several areas of skin of the volar surface of the forearm were blackened with India ink, as shown in Figure 1. Pain thresholds in all areas were measured by the thermal radiation method of Hardy, Wolff and Goodell (17). Cowhage was applied to the central area in the usual way. Pain thresholds were then measured repeatedly both when itching was present and in the intervals when it had spontaneously but temporarily ceased.

It was found that the pain threshold in all five areas was the same before cowhage was applied (190 ± 5 millicalories/sec./cm.²). After itching started in the cen-

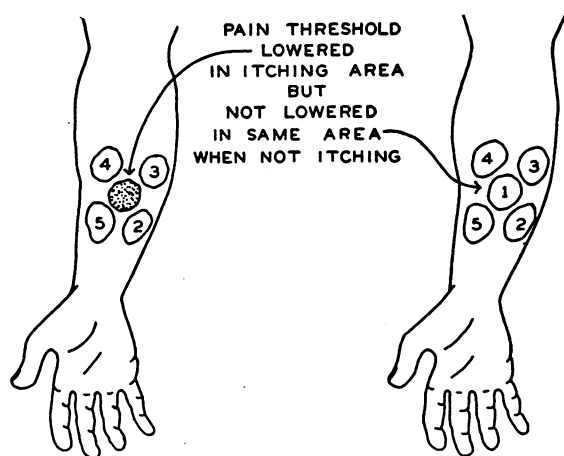


FIG. 1. LOWERING OF THE PAIN THRESHOLD IN AN AREA OF ITCHING SKIN

Cowhage was applied only to area 1. When itching occurred pain threshold was lowered in area 1, but not in adjacent areas 2, 3, 4, and 5.

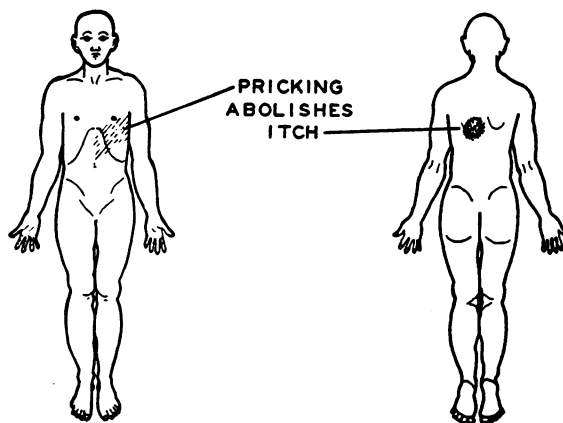


FIG. 2

Itching induced on the back by cowhage was abolished by painful pin pricks in the same dermatome on the anterior chest wall.

tral area, however, the threshold in this zone was lowered (120 to 160 mc./sec./cm.²), the lowest thresholds being found at the times of highest itch intensity. When itching temporarily ceased, the threshold returned to its initial level, and was lowered again on the resumption of itching. In the other areas the threshold remained constant or was slightly elevated to 210 ± 10 mc./sec./cm.² when the central area was itching. These observations were made in three series of experiments in each of two subjects. The application of the heat stimulus to the central area in itch free intervals was usually followed by recrudescence of the itching.

Comment

These observations are consistent with the view that stimuli which give rise to itching activate pain endings in the skin at a stimulation intensity below the pain threshold. Less additional thermal energy is therefore required to produce definite pain sensation if itching is already occurring. Hence the pain threshold as measured is lowered.

Alterations in Central Excitatory Processes Relevant to Itching

Experiment 4. Demonstration that itch can be abolished by painful pin pricks in adjacent skin

It was found in 20 subjects that when itching occurred spontaneously or when it was induced by cowhage, a pin pricked lightly several times in the zone of itching on the surrounding skin abolished the itching sometimes for long intervals. It usually returned after periods up to several minutes in duration, although the slight pain from the prick had completely faded within 10 to 15 seconds. This has been observed not only with itching due to cowhage, but also in the itching resulting from

ZONES IN WHICH PRICKING ABOLISHES ITCH

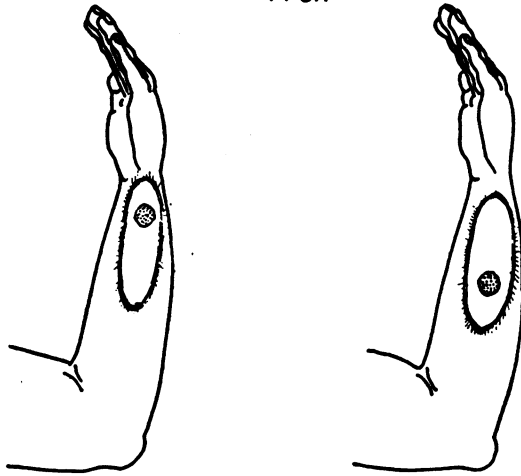


FIG. 3. ZONES IN WHICH PAINFUL PIN PRICKS ABOLISHED ITCHING INDUCED BY COWHAGE ON THE MEDIAL ASPECT OF THE FOREARM

Sites of cowhage application are indicated by stippling. The zones were surrounded by a narrow band, as indicated, of hyperalgesia.

insect bites, intracutaneous histamine puncture and intracutaneous foreign protein.

Pin prick applied not only locally but at considerable distance from the zone of itching abolished itching. With three subjects it was found that, if the cowhage was applied to the back, pin prick near the sternum in the same dermatome as the cowhage (Figure 2) was fully effective in eliminating itch.

In two subjects an attempt to delimit exactly the area within which pin prick abolished itching on the forearm was undertaken. Cowhage was applied at approximately the mid portion of the medial aspect of the forearm. After application of the cowhage the size of the area within which this effect could be demonstrated gradually increased and reached the eventual limit in about one hour following the beginning of itch. At this time the area measured approximately 5×15 cm. Figure 3 illustrates the area as mapped on the forearm of one subject on whom cowhage was applied as shown. It was essentially the same for the second subject.

After the mapping had been completed, cowhage was applied at the distal end of the area. The effect of pin prick was again tested, and it was found that the area within which it abolished itching was approximately the same as in the first instance, extending only 1-2 cm. further distally. Around this zone was a band of hyperalgesia to pin prick about 4 mm. wide.

A similar experiment was carried out on the legs of three subjects (Figure 4). The cowhage was applied just below the knee on the outer aspect of the left leg. Again there was an area within which the pin prick was

effective in abolishing itch. After 60 minutes the area extended 7 cm. proximally and 24 cm. distally to the itching spot. On the leg, also, there was only slight difference in the area of effectiveness of the pin prick if the cowhage was shifted to another point within this area. A narrow band of hyperalgesia also surrounded this zone on the leg.

Comment

Scratching is known to relieve itch. It has been held (1) that the relief so obtained resulted from replacement of the itch with frank pain. In the above observations the painful stimulus of the pin prick was not only brief but also far removed, as much as 24 cm. on the leg or back from the itching area, yet the itching sensation could thus be obliterated. Furthermore, the itch did not return until some time after the pain from the prick had subsided.

These observations seem most readily explicable mainly in terms of central rather than peripheral processes, as will be discussed below. The areas mapped on the forearm fall within the limit of the first thoracic dermatome; those on the leg correspond closely to L-4 or L-5 as determined by Förster (5).

Experiment 5. Demonstration that a zone of secondary hyperalgesia is "anti-pruritic"

A superficial branch of a cutaneous nerve on the volar surface of the forearm was located by means of

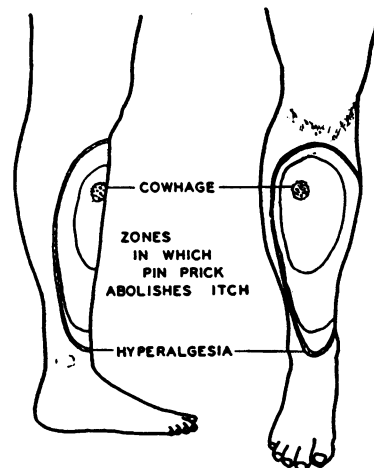


FIG. 4. ZONE ON THE LEG IN WHICH PAINFUL PIN PRICK ABOLISHED ITCHING INDUCED BY COWHAGE

The inner line indicates the extent of the zone after 15 minutes of itching; the outer border is its extent at the end of an hour. Sites of cowhage application are indicated by stippling. The zone was surrounded by a narrow band of hyperalgesia.

faradic current, and then was painfully stimulated for two minutes. Following this procedure there was established within 20 minutes in the surrounding skin a zone of "secondary hyperalgesia." In this zone of hyperalgesic skin the pain threshold as ascertained by the thermal radiation method was not lowered (10) but stimuli at threshold or above were perceived as more painful and longer lasting than stimuli of equal intensity in the surrounding skin.

Cowhage was applied in such an area of secondary hyperalgesia in four subjects in 11 observations. It evoked either occasional bursts of pain or no sensation at all, but not itching.

The secondary hyperalgesia was abolished in two subjects by infiltrating procaine at the site of injury by faradization and by vigorous pin pricks in a zone within 1-2 cm. around the point of faradization. Cowhage was again applied and itching now occurred as it did in control areas on the other arm.

In 12 other experiments on two subjects, areas of secondary hyperalgesia were induced by painfully pinching with forceps a small fold of skin on the volar surface of the forearm. Approximately 10 minutes after the pinch, when the secondary hyperalgesia was well developed, cowhage when applied failed to elicit itching. When the cowhage was pressed into the skin, a maneuver which intensifies itching in control non-hyperalgesic skin, pricking pain was experienced, but itch did not ensue.

Comment

Lewis, Grant and Marvin (4) observed that faradic stimulation of a cutaneous nerve was followed by a state in adjacent skin in which itching did not occur after intracutaneous histamine puncture. Bickford (6) called this state "anti-pruritic" and found that it also occurred after other forms of noxious stimulation, such as a sharp blow, a gnat bite, burn or freeze. These authors, however, did not investigate the relation of hyperalgesia to the anti-pruritic state.

The observations on the effect of pin prick in abolishing itch, and on the failure of itching to occur in areas of secondary hyperalgesia, seem to indicate the existence of events of a special sort in the central nervous system. Similarity of the size and shape of the affected areas to the dermatome suggests that the spinal cord is the site of such processes. Bickford also concluded that the "anti-pruritic" state must depend on some spinal cord mechanism.

Discussion

It has been held (1) that itching is a "protopathic," as opposed to an "epicritic" sensation. In these terms, the "first" itch might be considered

epicritic, since it is readily localized, the second as protopathic since it is more diffuse. It is not clear, however, that any useful purpose is served by retaining this terminology.

The use of cowhage as a stimulus has been criticized on the grounds that the itching which results is impure (6). Histamine has therefore often been employed, but it was found that the itching which resulted was not nearly so intense as that produced by cowhage, and seemed to be chiefly of the "second" type. The "impurity" of the cowhage-provoked itching may well be simply the result of the simultaneous presence of both types of itch.

The objection might be raised that one of the two kinds of itch described above was not really itch, but was, instead, pain. The ultimate appeal in such a case must be to the introspection of the person experiencing the sensation, and the subjects in this investigation agreed that there were two kindred but distinguishable sensations which were both felt as "itch." They had in common their association with an urge to scratch the involved skin. Brack (18) also referred to two qualitatively different itch experiences.

It seems likely, in view of all the available data, that stimuli which produce itching initiate impulses which, after traversing the peripheral pain nerves, pass up the spinothalamic tracts of the cord. Since painful stimuli in general can be made to produce itching by lowering their intensity, it is reasonable to suppose that the difference between a painful and an itch-producing stimulus is one of intensity. The reduction in the pain threshold at times when itching is being experienced is further evidence in support of this view. The probable reason for the lowered threshold is that the peripheral pain endings are already partially activated by the cowhage, so that the radiant energy which must be applied to give pain is less than that necessary if they have not been stimulated at all.

Potelunas, Meixner and Hardy (19) reported that there was no consistent difference in the cutaneous pain thresholds of patients with itching dermatoses as opposed to healthy individuals. As they pointed out, however, structural changes such as thickening had often occurred in the diseased skin, with consequent alterations in pain sensitivity. All of the observations in the present investigations have been made on skin of subjects

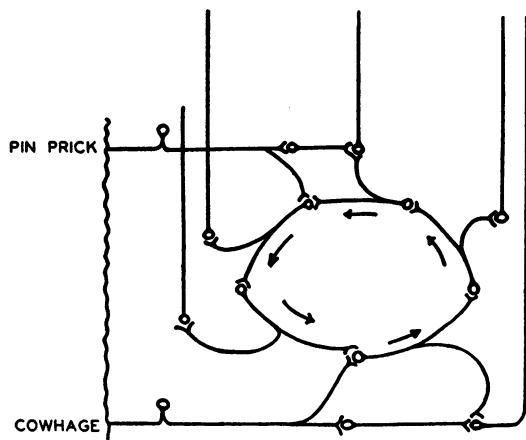


FIG. 5. SUGGESTED ARRANGEMENT OF CIRCUITS IN INTERNUNCIAL NEURONS RESPONSIBLE FOR ITCHING
Painful pin prick presumably breaks up the circuits.

without skin disorders, and without alteration of any sort except by the test procedures themselves. It must be emphasized that the threshold was found to be lowered only when the skin was itching.

One thesis which will explain all the findings is that the perception of itching depends on the presence in the cord of a circuit of internuncial neurons, analogous to those described by Lorente de No (20), around which impulses are constantly traveling. According to the hypothesis the establishment of such a circuit is the result of the low discharge frequency in a peripheral nerve which is weakly stimulated. As the circuit is traversed, discharge to spinothalamic neurons occurs, and hence impulses in the spinothalamic tract are sent upward to the brain in an orderly pattern (Figure 5). We suppose that the presence of this pattern of discharge in the brain is a necessary condition for the perception of itching. It is of interest that recently one subject following frontal lobotomy had an unaltered appreciation of itch, tickle and "itchy skin."

Such a circuit of excitation in an internuncial system of neurons would, of course, require a rather delicate adjustment of impulse frequencies and refractory periods. A pin prick in the dermatome in which itch is arising would, it is assumed, bring about a diffuse discharge in the corresponding cord segment, ramifying along many of the internuncial neurons involved in the itch circuit. The orderly pattern would therefore be temporarily destroyed, and itching halted. It would

presumably require an appreciable time for it to be re-established, a time represented by the interval after pin pricking before itching is again perceived.

Hardy, Wolff and Goodell (10) have concluded that secondary hyperalgesia in the skin adjacent to a source of noxious impulses, results from the presence of an augmented central excitatory state in internuncial neurons. Such a state is indicated by the stipplings in Figure 6. It presumably acts to facilitate the passage of impulses at synapses. When cowhage is applied to skin in which such hyperalgesia is present, it may be supposed that the resulting impulses cannot set up the usual orderly circuits in the cord which result in itch sensation. The occasional burst of impulses elicited by the cowhage which is intense enough to cross the pain threshold of the pathway involved brings about a widespread discharge of the excitatory state and pain alone is experienced.

Such an explanation may outrun the data currently available about events in the human spinal cord, but on the other hand it does not do violence to any of the known facts of neural activity. The "all-or-none" law of impulse size in single nerve fibers does not come into question in this connection since differences in stimulus intensity, experienced as graded intensities and qualities of sensation, are generally considered to be reflected in differences in impulse frequencies in peripheral nerve fibers.

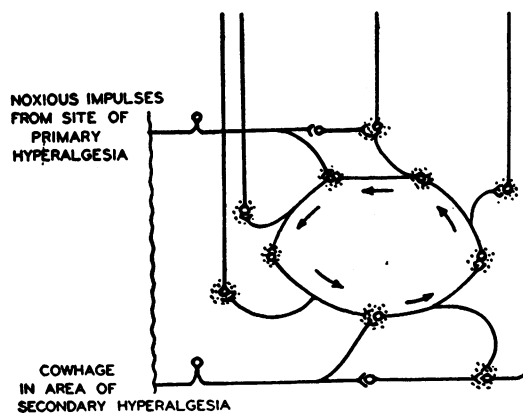


FIG. 6. INHIBITION OF ITCHING IN AREA OF SECONDARY HYPERALGESIA

The stippling represents the excitatory state of internuncial synapses which is responsible for the hyperalgesia and which prevents the formation of circuits necessary for itching.

ITCHY SKIN

Lewis, Grant and Marvin (4) noted that spontaneous itching is an accompaniment of nearly all forms of skin damage, provided that the damage is relatively slight in amount. Bickford (6) further noted that itchy skin surrounds such skin damage. He described "itchy" skin as that which gives rise to an itching sensation when the skin is stroked with the finger, or a blunt object. He extensively investigated and described the phenomenon of "itchy skin" associated with the itch induced by intracutaneous histamine puncture and noted its close relationship to tickle. Goldscheider (12) described the occurrence of itching and "itchy skin" in the palm of the hand accompanying pinching of the web between two fingers. In the following investigations various modifications of both Goldscheider's and Bickford's experiments have been made in an attempt to illuminate further the mechanism of this phenomenon.

Experiment 6. Demonstration of "itchy skin" and hypoalgesia adjacent to a focus of itching

Cowhage was applied to a small (1 cm. in diameter) area of skin on the volar surface of the forearm in various locations. It was found by trial that when it was placed on the wrist near the hand, or somewhat toward the medial aspect of the arm, the phenomenon of "itchy skin" could best be elicited. When the itch had become intense, usually within 30 to 60 seconds after application of the cowhage, stroking of the adjacent skin with the tip of a finger frequently induced an itchy sensation and more frequently intensified the primary itch. This zone extended approximately 2-3 cm. proximally, 1-3 cm. distally and 1-2 cm. laterally. Indeed, when the primary itch had entirely subsided, stroking the surrounding skin often revived it. Pin pricks in this surrounding "itchy skin" zone were dulled, but there was a narrow zone of hyperalgesia entirely surrounding it, where pin prick was experienced as sharper than in control skin. With the passage of time (30 to 60 minutes) after a long-lasting and intense itch, hyperalgesia was noted to have displaced the hypoalgesia and to extend 5 to 10 cm. proximally and 3 to 6 cm. distally. Such hyperalgesia after an intense itch sometimes persisted for several hours.

Experiment 7. Demonstration that the skin about a site of noxious stimulation is "itchy" until the development of secondary hyperalgesia

In 12 experiments on three subjects a small fold of skin on the volar surface of the forearm was painfully pinched by forceps for two to eight minutes. The following description of the observations in an experiment in one subject is characteristic of all of this series (Figure 7). Pin pricks in a 1 cm. wide zone surrounding the

pinch during the first 15 seconds intensified the pain of the pinch and there was *hyperalgesia* immediately surrounding the pinch. Within the first minute a wider zone of *hypoalgesia* to pin prick had developed and extended for 3 cm. proximal and distal to the pinch. In this zone stroking with the finger induced an itchy sensation which was indistinguishable from intense tickle, and itch was readily induced by cowhage. Surrounding this zone there was a narrow band of secondary hyperalgesia in which itch could not be induced either by stroking or by cowhage. In four minutes the hypoalgesic zone extended 3 cm. distally and 5 cm. proximally from the pinch.

It was repeatedly noted that pin pricks within the hypoalgesic zone, although they felt less sharp, accentuated the pain from the pinch. Furthermore, the pain elicited by the forceps gradually diminished. In the fifth, sixth, and seventh minutes when pain was no longer ex-

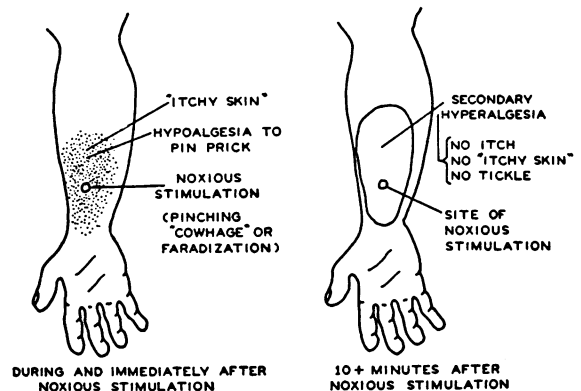


FIG. 7. SENSORY PHENOMENA IN THE SKIN ASSOCIATED WITH NOXIOUS STIMULATION

perienced, even rubbing the adjacent area with a finger or a blunt tongue depressor evoked a sensation of itching in the skin as well as at the point of the pinch.

The pinch was maintained for seven minutes, when the "itchy" area was found to extend 4 cm. distally and 10 cm. proximally from the injury, still surrounded by a narrow band of hyperalgesia. Immediately after removal of the forceps, the hypoalgesic area diminished, its outer borders receding. The hypoalgesia was thus gradually replaced by hyperalgesia. In five to 10 minutes after removal of the forceps, the *hyperalgesia* completely filled the zone which had been *hypoalgesic* and "itchy." Cowhage applied to this hyperalgesic skin induced no itch, nor was it "itchy" in response to stroking.

The observations in Experiments 6 and 7 of hypoalgesia to pin prick in skin surrounding sites stimulated either by cowhage or by pinching prompted further study of this phenomenon. The experiments of Lewis, and of Hardy, Wolff and Goodell, in which they evoked secondary hyperalgesia by faradic stimulation, were repeated as follows:

Experiment 8. Demonstration of hypoalgesia in skin adjacent to a focus of faradic stimulation

In three subjects a branch of a cutaneous sensory nerve on the volar surface on the forearm was painfully stimulated with faradic current for four minutes. The adjacent skin was tested at the end of one minute and pin prick was found to be dulled. In the fourth minute just before the stimulation ended the pin was appreciated more as pressure than as pain. However, each prick markedly increased the pain from the faradic stimulation. Immediately after the end of the stimulation the hypoalgesic zone extended 4 cm. proximally, 6 cm. distally and 1 cm. laterally from the site of injury. Within 10 minutes no hypoalgesia could be detected. There was now a zone of marked hyperalgesia which extended 8 cm. proximally from the site of faradic stimulation, and 6 cm. distally. No itch or tickle could be elicited by drawing a thread across this area.

Comment

It has been observed when an individual is experiencing one pain that the threshold for pain elsewhere is raised (17). Thus, one possible explanation of the hypoalgesia which was noted in the vicinity of the injured skin in Experiments 7 and 8 might be such an elevation of pain threshold. However, this cannot be the only explanation, because the hypoalgesia was limited in extent and persisted despite decreasing pain intensity as adaptation to the forceps pinch occurred, and for a few minutes after the removal of the forceps. This phenomenon might easily escape attention unless the adjacent skin area were tested during the period of noxious stimulation.

The observations of the last three experiments correspond to those of Experiment 5, in that skin in which secondary hyperalgesia existed was not "itchy" to stroking nor could itching be induced in it by cowhage. Also tickle was not elicited in the zone of secondary hyperalgesia. In short, although itchiness and secondary hyperalgesia may both be associated with skin damage, they do not occur in the same area at the same time.

Experiment 9. Demonstration of the occurrence of both "itchy skin" and itching associated with skin injury

Goldscheider's experiment was repeated in a series of 20 experiments on three subjects. The web between two fingers was tightly pinched with fine forceps. Within half a minute not only could "itchy skin" be demonstrated on stroking of the palm and the back of the hand, but also itch occurred in the palm of the hand spontaneously. Again the "itchy skin" was hypoalgesic to pin prick and was surrounded by a band of hyperalgesia which was not

"itchy." There was also a small area of hyperalgesia a few millimeters in diameter at the site of the pinch, presumably primary hyperalgesia.

Similarly, pinching a web between the toes for less than two minutes gave rise to spontaneous itching and "itchy skin" in the sole of the foot, especially on the underside of the great toe and the ball of the foot. In one of the subjects, the itching induced by such slight injury between the toes continued for more than an hour.

In one subject itching in and around an insect bite on the medial aspect of the left thigh, about eight inches above the knee, persisted for three days. On the third day a zone of "itchy skin" was found to extend for 5 to 6 cm. around the reddened bite, which was itself spontaneously itching, and hyperalgesic to pin prick. In the zone of "itchy skin" pin prick was dulled, but the area was surrounded by a clearly perceptible narrow band of hyperalgesia. A few pin pricks within this area abolished the itching from the bite for 30 to 60 seconds.

Similar observations were made in a second subject who had "itchy skin" on the top of the left foot associated with a slight abrasion of the skin.

Experiment 10. Demonstration of the spread of itching from a primary focus of itching

In a series of four experiments on two subjects cowhage was placed on an area of skin approximately 1 cm. in diameter on the volar surface of the wrist at the junction between the hand and the arm. Accompanying the intense itch elicited on this site not only was the itchiness in response to stroking of adjacent skin marked, but spontaneous itching which spread into the thenar and hypothenar eminences and into the palm of the hand occurred. Here, again, the area of itchy skin was surrounded by a narrow zone of hyperalgesia which was not "itchy."

Comment

Goldscheider reported that painfully pinching the skin led to the development of hyperalgesia in the surrounding area. He apparently did not notice that the more remote border of hyperalgesia was only a narrow zone and in fact surrounded an area of *hypoalgesia* to pin prick. It is only after the passage of several minutes following a pinch of four to seven minutes duration that the hyperalgesia completely displaces the hypoalgesia. Goldscheider inferred that the "itchy skin" was related to hyperalgesia, but from the experiments reported here, it appears that only the skin which is *hypoalgesic* to pin prick is "itchy" in response to stroking. These findings are in agreement with the observations that itch is not induced by cowhage in a zone of secondary *hyperalgesia*. This is evidence of fundamental similarities between

"spontaneous itching" which follows the application of cowhage or histamine, and that which can be elicited by stroking in skin adjacent to a source of noxious impulses.

Experiment 11. Demonstration of the relation of "itchy skin" and pain, and of the occurrence of "itchy skin" in the absence of touch sensation

In three subjects a blood pressure cuff was wrapped around the upper arm, inflated to 200 mm. Hg, and kept at this pressure for the duration of the experiment. At the end of eight to 15 minutes when pin prick was slightly dulled in the palm of the hand, drawing the end of a tongue depressor across the palmar skin elicited an intense burning itch, and stroking with a finger also elicited tickle or itch. At the end of 20 minutes in all three subjects the sensation of touch in response to laying the flat side of the tongue depressor on the wrist was gone. Itch powder (cowhage) was then applied and within two minutes elicited a burning itch. Stroking the skin both proximal and distal to the cowhage, was felt as "itchy" and also intensified the itch from the cowhage. The zone in which "itchy" skin could be detected was well demarcated for a distance of 8-10 cm. proximal to the itch spot, and throughout the palm to the tips of the fingers. In the distal zone of "itchy skin" no touch sensation could be detected.

Comment

Bickford reported that the perception of "itchy skin" failed at a stage of asphyxia at which both touch and pain sensibility were still present, and was therefore forced to postulate that special peripheral nerves transmitted the sensation. The observations described above, however, are evidence that "itchy skin" can occur in the absence of touch as long as pain is preserved.

They indicated that both itch and "itchy skin" occur independently of touch sensation, and as long as some fibers are still conducting pain impulses. Perhaps Bickford failed to make this observation because he used intracutaneous histamine puncture to produce spontaneous itching and "itchy skin" and in our experience the latter was less intense and more difficult to detect when histamine was used to evoke itch.

Discussion

The "itchy skin" phenomenon is indistinguishable subjectively from tickle (see next section). The sensation evoked by light stroking of otherwise unstimulated skin is called "tickle," that evoked by light stroking of skin in the neighbor-

hood of a source of itching has been called "itchy," but they are otherwise alike, and both provoke a desire to scratch. "Itchy skin" is like itch and tickle in that it could not be elicited in skin manifesting secondary hyperalgesia. Bickford observed that if it was impossible to elicit "itchy skin" as a result of nervous system disease or of experimental procedures, it was also impossible to elicit tickle. He concluded that the development of "itchy skin" depended on axon-reflexes similar to those responsible for the development of the flare around sites of skin injury. Whether or not this is correct, the "itchy" sensation elicited in the area presumably results from a kind of activity in internuncial neurons similar to that which is responsible for the primary itching at the site of cowhage application.

TICKLE

When a stiff nylon thread is drawn across the skin a peculiar esthetic experience usually ensues, which long outlasts the period of stimulation. This is best demonstrated on the margin of the upper lip. The sensation has two distinct components. The first of these resembles itch and has in common with it an associated urge to rub or scratch the skin. The second consists of an awareness of movement of a light object touching the skin. In some parts of the body, *e.g.*, the finger pads and the extensor surface of the elbow, only the second component is prominent, whereas at the lip margin the itching component is conspicuous. It is for the itching component of the sensation evolved by a moving stimulus that the term "tickle" has been reserved in this paper.

In the following experiments the relation of tickle, itch, "itchy skin" and pain were further investigated.

Experiment 12. Demonstration that tickle and itch differ only in that tickle has the additional element of movement

A fine nylon thread was touched to the skin of the forehead in one spot. Ten subjects so tested reported that the sensation elicited was itch, and was accompanied by the urge to rub or scratch. When the thread was lightly drawn across the skin, some of the subjects changed their report of the sensation to tickle, but stated that the only change in the quality of the experience was the additional perception of movement of the thread, although the desire to rub or scratch was intensified.

In six subjects, the difference between touch and tickle or itch was clearly demonstrated by touching first the pad of one finger and then the forehead. A light touch by the finger of the experimenter on the finger pad of the subject elicited only touch, but on the forehead, itch or tickle were elicited, with an invariable accompaniment of a desire to rub or scratch the stimulated skin.

Comment

These observations make clear that the conception of tickle in everyday experience conforms exactly to the definition given above, *i.e.*, tickle is the itching component of the sensation evoked by a light moving stimulus on the skin.

Experiment 13. Demonstration that tickle is obliterated by stimulation of pain endings

The forehead was rubbed briskly so that a slight after-pain was experienced, and again tested by lightly drawing the nylon thread across the skin. Now the sensation elicited was purely that of touch without the unpleasant component arousing the urge to rub or scratch. Similarly, immediately after the forehead was pricked vigorously with a pin, for at least as long as the faint after-pain of the pricking persisted the sensation elicited by the thread was again only touch.

Comment

Although drawing a wisp of cotton across the skin in most skin areas is used as a bedside testing procedure to indicate perception of light touch, it is also used on the upper lip, a very "ticklish" area, to test for the integrity of fiber systems conveying noxious impulses in the skin supplied by the fifth cranial nerve.

It is apparent that the drawing of a thread or wisp of cotton across the skin may under varying circumstances give rise to qualitatively distinct sensations. As stated above, it has seemed profitable to reserve the word "tickle" for that part of the sensation thus elicited which resembles itch and arouses the desire to rub or scratch. The effect of painful stimuli in abolishing or preventing tickle is apparently analogous to the phenomenon of abolishing itch by pin prick.

Experiment 14. Demonstration of the absence of tickle in a zone of secondary hyperalgesia

In two subjects zones of secondary hyperalgesia were defined on the volar surfaces of the forearms after faradic stimulation of a superficial cutaneous sensory nerve. When the hyperalgesia was fully developed a nylon thread drawn lightly across the area elicited a sensation of touch; when the thread was applied with slightly greater

force, touch commingled with pain was elicited, but the sensation was definitely not tickle. The same thread elicited tickle in control areas on the opposite arm, and in areas of skin on the same arm outside of the area of secondary hyperalgesia. In these two subjects the secondary hyperalgesia was abolished by pin prick within its borders. Immediately thereafter, tickle could again be elicited.

Comment

It appears that tickle, like itch, is inhibited by the presence of secondary hyperalgesia of the skin; that a stimulus clearly eliciting tickle in control skin, elicits in hyperalgesic skin either a sensation of touch without the special quality of tickle or itch, or of touch commingled with pain. Areas of secondary hyperalgesia have thus been demonstrated to be "anti-ticklish" as well as "anti-pruritic."

Experiment 15. Demonstration of the occurrence of tickle in the absence of touch sensation

In three subjects a blood pressure cuff was inflated about the upper arm at a pressure of 200 mm. Hg. About 20 minutes later the light touch of a flat tongue depressor could not be perceived on the back and side of the forefinger. At this time, however, a stiff nylon thread drawn across this area elicited a distinct tickle which merged into an itching sensation.

Comment

It has been previously noted that during asphyxia of an arm touch sensation disappears at a time when pain can still be elicited. This experiment demonstrates that tickle, like itch, is independent of touch, and is indeed also probably carried over the afferent fibers which mediate pain.

Discussion

No general agreement on the relation of the sensation of tickle to touch, pain and itch has previously been reached. Discussion has focussed on whether tickle was essentially different from itch, and whether the mediation of tickle sensation was to be assigned to touch or to pain receptors.

With regard to the first question, Murray (21) reported that her subjects found that itch differed from tickle only in being "more persistent, painful and intolerable." Torök (22), on the other hand, asked patients with pruritus to compare their spontaneous itching with the sensation elicited by drawing a wisp of cotton across the skin. From these comparisons he concluded that itch and tickle

were different sensations which could be distinguished by his subject. It should be noted, however, that motion adds an element to the sensation which makes it different from itching, and probably accounts for the patients' statements that they could distinguish between the two. It is also important that under certain circumstances, as discussed above, the same moving stimulus provokes a sensation which induces no desire to scratch, consists entirely of touch, and is not ordinarily called tickle by the subject experiencing it. It is conceivable that difficulties of communication with patients might lead to a report of "tickle" for this sensation also.

Thöle (11) also separated itch and tickle as regards the structures involved, concluding that tickle was related to stimulation of touch receptors. He failed to make the observation that tickle can be elicited in areas of skin in which touch is no longer present, nor did he differentiate between true tickle and a sensation of moving touch in areas where pain could not be elicited.

Bishop (23, 24) suggested that tickle sensation was a function of touch rather than pain receptors. He found that weak and rapid electrical stimulation of touch endings failed completely to elicit tickle but this he attributed to the lack of movement of the stimulus. He argued that tickle can be elicited by a contact with the skin so light that it is clear that the receptors concerned must have a very low threshold, and that therefore participation of pain receptors is out of the question. In his own observations on cutaneous sensation, however, he found that in most areas of skin, except notably on the balls of the finger, prick has a *lower* threshold than touch. Furthermore, in reviewing (25) von Frey's observations, Bishop calls attention to the fact that in using mechanical stimulators of small diameter, thresholds for touch and pain closely approximate each other. Likewise, Hardy, Wolff, and Goodell (10), testing for touch threshold with von Frey hairs in hyperalgesic and control areas of skin, found that the thresholds for touch and for pain were not grossly different. Bishop's second piece of evidence linking tickle with touch was that tickle, like touch, "adapts" to continued stimulation (24). However, continuous noxious stimulation also ceases to produce pain, as can be readily demonstrated by holding a pin point stead-

ily against the skin for several seconds, or by pinching a fold of skin with forceps.

Bickford observed that tickle, "itchy skin," itch, and pain were all absent in patients with anterolateral tract lesions, even though touch sensation remained intact.

Pritchard (26) considered that tickle, itch and pain all lay on the same continuum of sensation, and that tickle, like itch, was a variety of pain. He nevertheless concluded that tickle and pain involved different peripheral pathways. He failed to present evidence that tickle could be elicited in the complete absence of pain. On the other hand, Sarnoff and Arrowood (27) reported that tickle sensation elicited "by scratching the soles of the feet" persisted in some of their patients in the absence of pain from pin prick during spinal block with procaine. However, the intensity of their scratch stimulus was not described, and it is not clear that it elicited true tickle, especially since there was no description of the qualities of the sensation experienced. It is also possible that their observations may be related to Thöle's findings (11).

Zotterman (28) on the basis of his studies of axone potentials in cat nerves concluded that tickle and itching sensations are mediated by the fibers which are responsible for the pain elicited by pin prick. He also observed that tickle could not be elicited in patients with analgesia of the face following trigeminal tractotomy, although touch sensibility was intact.

On the basis of the observations reported here it is inferred that the sensation called "tickle" is mediated by the same neural fibers as are involved in itch and pain. This conclusion is based on the experiments involving differential anesthetization, for tickle could be elicited when touch sensitivity was absent and pain sensitivity retained, thus exactly paralleling cowhage-induced itching in like circumstances. Furthermore, tickle is inhibited in an area of secondary hyperalgesia, as is itch; and it is obliterated in skin to which a painful pricking or rubbing has been applied, just as itch is obliterated by pricking in adjacent areas of skin. It is concluded, therefore, that the pathways concerned in the perception of tickle are those for pain, and that touch mechanisms do not participate, except to add something which is essentially extraneous.

SUMMARY AND CONCLUSIONS

1. The sensation of itch has two subjectively distinguishable components, one pricking and the other burning. These correspond to the two kinds of cutaneous pain, and are mediated respectively by the two types of nerve fibers involved in the transmission of pain from the skin. Touch receptors and fibers are not involved.

2. Cutaneous tickle and the sensation elicited in "itchy skin" do not differ qualitatively from itch, except by the addition of an awareness of movement, and are mediated by the same neural structures, *i.e.*, those which transmit pain. Touch receptors, when functioning, probably add an essentially extraneous component to tickle and to the sensation elicited in "itchy skin," but both phenomena occur in the absence of touch.

3. When itching is present, the pain threshold at the site is lower than it is in the same skin during itch-free intervals.

4. Itch occurs when pain receptors are weakly stimulated.

5. Tickle, itchy skin and itch are abolished by pin pricks in adjacent skin. In the case of itch, this abolition is possible if the skin is pricked anywhere in the dermatome which contains the site of itching.

6. Tickle, "itchy skin," and itch do not occur in areas of secondary hyperalgesia. They do occur in skin surrounding sites of noxious stimulation when the area is hypoalgesic to pin prick.

7. It is suggested that the sensation of itch results from the presence in the spinal cord of impulses traveling in circuits of internuncial neurons, with a consequent patterned discharge up the spinothalamic tracts. Such circuits are presumably established when peripheral pain nerves discharge into the cord at a low frequency. When the circuits are broken up—by strong stimulation in the same dermatome, for instance—itching ceases.

REFERENCES

- Rothman, S., Physiology of itching. *Physiol. Rev.*, 1941, 21, 357.
- Titchener, E. B., *A Text-Book of Psychology*. Part I. The Macmillan Co., New York, 1909.
- Bishop, G. H., The peripheral unit for pain. *J. Neurophysiol.*, 1944, 7, 71.
- Lewis, T., Grant, R. T., and Marvin, H. M., Vascular reactions of the skin to injury. X. The intervention of a chemical stimulus illustrated especially by the flare. The response to faradism. *Heart*, 1927, 14, 139.
- Förster, O., Symptomatologie der Erkrankungen des Rückenmarks und seiner Wurzeln, in Bumke, O., and Förster, O., *Handbuch der Neurologie*. Springer, Berlin, 1936, Vol. 5, p. 1.
- Bickford, R. G., Experiments relating to the itch sensation, its peripheral mechanism and central pathways. *Clin. Sc.*, 1937-38, 3, 377.
- Ehrenwald, H., and Königstein, H., Klinische und experimentelle Untersuchungen über das Juckgefühl, vorläufige Mitteilung. *Wien. klin. Wchnschr.*, 1929, 42, 1397.
- McMurray, G. A., Experimental study of a case of insensitivity to pain. To be published.
- Kunkle, E. C., and Chapman, W. P., Insensitivity to pain in man. *A. Research Nerv. & Ment. Dis. Proc.*, 1943, 23, 100.
- Hardy, J. D., Wolff, H. G., and Goodell, H., Experimental evidence on the nature of cutaneous hyperalgesia. *J. Clin. Invest.*, 1950, 29, 115.
- Thöle, Ueber Jucken und Kitzeln in Beziehung zu Schmerzgefühl und Tastempfindung. *Neurol. Centralbl.*, 1912, 31, 610.
- Goldscheider, A., Über Irradiation und Hyperästhesie im Bereich der Hautsensibilität. *Arch. f. d. ges. Physiol.*, 1916, 165, 1.
- Lewis, T., and Pochin, E. E., The double pain response of the human skin to a single stimulus. *Clin. Sc.*, 1937-38, 3, 67.
- Gasser, H. S., Pain-producing impulses in peripheral nerves. *A. Research Nerv. & Ment. Dis. Proc.*, 1943, 23, 44.
- Bigelow, N., Harrison, I., Goodell, H., and Wolff, H. G., Studies on pain; quantitative measurements of two pain sensations of the skin, with reference to the nature of the "hyperalgesia of peripheral neuritis." *J. Clin. Invest.*, 1945, 24, 503.
- Bickford, R. G., The fibre dissociation produced by cooling human nerves. *Clin. Sc.*, 1939, 4, 159.
- Hardy, J. D., Wolff, H. G., and Goodell, H., Studies on pain. A new method for measuring pain threshold. Observations on spatial summation of pain. *J. Clin. Invest.*, 1940, 19, 649.
- Brack, W., Die Bedeutung des vegetativen Systems für die Entstehung des Juckens. *Deliberationes, Ninth International Congress of Dermatology*, Budapest. 1935, 1, 129.
- Potelunas, C. B., Meixner, M. D., and Hardy, J. D., Measurement of pain threshold and superficial hyperalgesia in diseases of the skin. *J. Invest. Dermat.*, 1949, 12, 307.
- Lorente de No, R., Analysis of the activity of the chains of internuncial neurons. *J. Neurophysiol.*, 1938, 1, 207.
- Murray, E., A qualitative analysis of tickling; its relation to cutaneous and organic sensation. *Am. J. Psychol.*, 1908, 19, 289.

22. Török, L., Über das Wesen der Juckempfindung. *Ztschr. f. Psychol.*, 1907, **46**, 23.
23. Bishop, G. H., Neural mechanisms of cutaneous sense. *Physiol. Rev.*, 1946, **26**, 77.
24. Bishop, G. H., The skin as an organ of senses with special reference to the itching sensation. *J. Invest. Dermat.*, 1948, **11**, 143.
25. Bishop, G. H., Relation of pain sensory threshold to form of mechanical stimulator. *J. Neurophysiol.*, 1949, **12**, 51.
26. Pritchard, E. A. B., The clinical significance of variations in tickle sensibility. *Proc. Roy. Soc. Med.*, 1933, **26**, 697.
27. Sarnoff, S. J., and Arrowood, J. G., Differential spinal block. II. The reaction of sudomotor and vasomotor fibers. *J. Clin. Invest.*, 1947, **26**, 203.
28. Zotterman, Y., Touch, pain and tickling: an electrophysiological investigation on cutaneous sensory nerves. *J. Physiol.*, 1939, **95**, 1.