Response of Cutaneous Sensory Units with Unmyelinated Fibers to Noxious Stimuli

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There is considerable evidence in favor of the concept that sense organs of the skin with unmyelinated (C) fibers have widely varying functional characteristics. In the mammal, a large proportion of such sensory units are excited by gentle mechanical stimuli (8, 16, 34) and by transient cooling (9). Others are described as responding best to small temperature changes (13, 18) and some are reported to have elevated thresholds for various or all stimuli (14, 15, 18, 32). Studies proposing large and important differences between various afferent units with C fibers have drawn conclusions from a small or highly selected population and no view has been provided of the way in which these differences fit into the spectrum presented by the sensory structures from a given skin region. Such information seems essential for the understanding of somatic sensation inasmuch as unmyelinated fibers far outnumber myelinated fibers in the afferent nerves from the skin. In particular, unmyelinated afferent fibers are generally agreed to have some causal relation to pain and its associated reactions (3, 6, 7, 25). A crucial issue in hypotheses correlating afferent activity to pain is whether the underlying mechanisms are set off by impulses from sensory structures responding only to noxious stimuli (i.e., intense enough to threaten or cause tissue damage) or whether they are triggered by special patterns of discharge from nonspecific afferent units (25).

In an attempt to learn more about the range of behavior associated with the terminals of cutaneous C fibers, we surveyed a number of randomly selected units for responses to a variety of graded stimuli. The results point out that a large proportion of C fiber afferent elements have elevated thresholds and that only these give signals useful for differentiating noxious from innocuous stimuli. Furthermore, observations are presented suggesting that one type among the "high threshold" group tends to increase in sensitivity after a supraliminal stimulation. Preliminary reports of the experiments have appeared previously (2, 27).

METHODS

Data were collected from 37 experiments on adult cats maintained in an areflexic state by sodium pentobarbital. End-tidal CO₂ was continuously sampled from a cannula in the trachea (typically found to vary between 4.5 and 5.5%) and blood pressure was measured from a cannula in the carotid artery (the mean typically ranged from 110 to 130 mm Hg). The environmental temperature was kept at approximately 30°C and rectal temperature was automatically maintained at 37.5°C by external heat. The nerve (the middle branch of the posterior femoral cutaneous nerve except for one experiment on the medial branch of the superficial plantar nerve) was exposed for 34 cm with care taken to preserve its blood supply and was protected from drying in a pool of warm mineral oil formed from skin flaps. Recordings were made with fine platinum-iridium electrodes from thin filaments of the nerve prepared by dissection under microscopic control. The nerve retained its connection to the skin while being suspended by a pair of stimulating electrodes between the recording site and the margin of the pool. During search for unitary activity, the nerve was stimulated once every 2 sec by a shock supramaximal for the "C" component of the compound action potential. Filaments from the nerve were progressively divided until the discharge of a single element conducting at C velocity (under 2.2 m/sec (10)), was uniquely prominent in the record and could be distinguished from all other activity on the basis of amplitude and configuration. Variation of the

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recording system's bandwidth was of substantial aid in augmenting the distinction between action potentials originating from different fibers. During the course of the experiment the neural activity was displayed on an oscilloscope and simultaneously made audible through a loudspeaker. Conduction velocity was calculated from the latency of the unitary discharge to a shock twice threshold and a postmortem measurement of conduction distance. In 31 experiments, in which all but 15 of the units were studied, no deliberate selection was made in the fiber studied; this followed solely from success in defining a unitary action potential.

In most instances, more than one fiber in a filament remained functionally active; however, the unmyelinated fiber under consideration usually had the largest amplitude of discharge and always could be distinguished on the basis of action potential configuration. The ease in preparation of unitary recordings from unmyelinated fibers varied from animal to animal; in some, only one unmyelinated element was studied, whereas in others it was possible to examine the responses of 10 fibers in detail.

Each receptive unit was studied for at least 30 min and most were under observation for 1-4 hr. Sometimes changes in amplitude of the unitary activity recorded from a filament took place, probably due to changes in the moisture content of the very fine strands. When they occurred, the changes in the leading conditions also altered the activity of elements other than the one under study. However, even with amplitude alterations the configuration of the C unitary potentials usually remained stable, a point which was repeatedly checked during the observation period by observing the response to electrical stimulation of the nerve. Since quantitative examination of the discharge characteristics was critical to the purposes of the survey, every impulse in a response sequence had to be examined to make sure that it conformed to the unit under consideration. Details of impulse configuration demanded an expanded time base, however, the time course of the stimulus sequences was long. To solve these problems, an impulse-sorting procedure was developed utilizing a large-screen oscilloscope connected to a digital computer (see Appendix).

The hair of the skin innervated by the nerve was clipped to a length of 1-2 mm. A unit's receptive characteristics were determined by stimulating the skin in a variety of ways. Receptive fields were usually outlined by exploration with the mechanical stimulators described in previous publications (4, 26). Skin cooling was accomplished by the evaporation of ether dropped on the skin, by ice placed on the skin, by small metallic probes touched to the skin, and, in one experiment, by a controlled temperature thermode of 1 x 3 mm. An infrared source was sometimes used to heat the skin. During skin cooling or infrared heating, a small thermistor probe (0.5 mm diam) was used to measure the surface or the immediately subcutaneous temperature. Most quantitative studies on the responses of receptors to elevated skin temperatures were done utilizing a heat thermode (31) with which step or gradual changes in skin temperature could be accomplished by electrically heating a smooth aluminum tip (2.5 mm diam) to predetermined levels using a thermistor buried in the probe near the contact surface for regulation. The heat probe on the skin was capable of increasing the temperature 5 C in 5 sec or less within the range of 20-60 C. Care was always taken to ensure that the thermode made good mechanical contact with the skin, and for all quantitative studies it was rigidly mounted so that no change in position or mechanical contact took place for a given series of observations.

The description of the temperature of a nonhomogeneous structure such as the skin is a difficult task and its actual determination would require simultaneous multiple sampling radially from the point of heating as well as transversely across the tissue. Such procedures during the course of testing receptors would be too destructive. In the quantitative descriptions that follow, when the thermode was used, the value reported is from the thermistor used for its feedback loop. This value typically was lower than the temperature indicated by a thermistor bead interposed between the thermode and the skin (by 2.5° at 35 C, 1° at 50 C, 3° at 60 C) because of the thermal gradient across the probe face, the bead itself, and the skin. During slow changes of temperature from 40 to 55 C, a subcutaneously placed thermistor directly under the thermode in the posterior thigh skin read from 1° to 7° C below the thermode temperature; a greater difference existed at higher thermode temperatures with actual values dependent on skin surface and body core temperatures. On repeated heating trials, the difference between the thermode temperature and the subcutaneous sensor remained close to the same at any given thermode temperature. Thus, the temperatures described in this study are accurate relative to one another during any given placement of the thermode and were little influenced by conditions within the skin produced by stimulation procedures. Our measurements suggest that they
indicate a temperature existing somewhere between the cutaneous surface and the subcutaneous fat.

The action potentials and voltages referable to the stimuli were recorded on an analog magnetic tape system utilizing a frequency modulation system. Preliminary analyses of the results were made by replaying the magnetic tape records onto an oscilloscope and a multichannel ultraviolet recorder. Quantitative descriptions were based on plots of "instantaneous" frequency \((1/\text{interval between successive impulses})\) using the interactive system described in the Appendix.

RESULTS

The majority of the unmyelinated fibers whose unitary action potentials were isolated using electrical shocks to the nerve also responded to cutaneous stimulation. Conduction block accounted for some that could not be excited by "natural" skin stimuli, but about 10% of the units did not respond to skin stimulation when the nerve was conducting normally and the skin was undamaged. This proportion of inexcitable fibers is substantially higher than that encountered in experiments on myelinated afferent fibers in cutaneous nerves (5, 26).

Background activity prior to noxious stimulation of the skin was rare. In the absence of skin damage it was present only in elements that exhibited marked sensitivity to thermal changes. Great variation in the sensitivity to different stimuli existed among the various units studied, confirming previous investigations (13-16, 18, 32). By considering the entire ensemble of responses to graded stimuli of different types, it was clear that there were groups of receptors with common characteristics. A single criterion was inadequate for a consistent classification, although most unmyelinated afferent units could be placed into one or another group on the basis of unique responses to a particular kind of stimulus. There were quantitative differences between receptors grouped together, but common features of the reactivity to different kinds of stimulation and the lack of overlap with other types suggested that these were continuous variations of one population.

Table 1 summarizes some general features of the sensory units encountered and their frequency of occurrence in the survey experiments.

Stimulus levels. Some perspective on the stimulus intensities used in subsequent descriptions can be gained from threshold

| TABLE 1. Classification of receptors in a survey of 131 unmyelinated fibers of cutaneous nerves* |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| No. (% | Mechanical\(^{†}\) | Noxious | Chemical |
| Threshold | | Heat | Irritants |
| Low-threshold | | | |
| mechanoreceptor | 47 (26 | 0.01 to 0.045 g | - | + | - |
| Thermal | 8 (6 | 0.2 to unresponsive | Variable | - | ? |
| Warm | 1 | | Variable | + | ? |
| Cool | 7 | | | | |
| Polymodal nociceptors | 39 (30 | 0.2 to 45 g | + | - | - |
| High-threshold mechanoreceptor | 18 (14 | 0.6 to > 45 g | - (or delayed) | - (>10 C) | - |
| High-threshold subcutaneous | 3 (2 | High with (intact skin) | - | - | - (intact skin) |
| Unclassified* | 16 (12 | | | | |

*Data from 31 experiments considering every unit whose discharge was successfully isolated. †For punctate stimulators of the von Frey type. ‡None down to 10 C prior to activation by heat or irritant chemicals. §Inadequate data collected for classification—see text.
values for previously described afferent elements and from the effects of various stimuli on human beings. The most sensitive mechanoreceptors with myelinated fibers of cat’s hairy skin respond to transient contact by a punctate object (von Frey hair) pressed against the receptive field with .008- to .02-g force (5). Provided that the rate of change is rapid enough, all known types of myelinated mechanoreceptive units from hairy skin of cat, except the high-threshold group, can be driven to maximal discharge by punctate stimulation with forces under 1.0 g (5). Small stimulators (under 0.5 mm diam) at 1.0-g force cause readily visible dimpling of cat’s hairy skin. With stimulators under 0.25 mm diameter, forces in excess of 5 g lead to penetration of the epithelial surface. Punctate mechanical stimulation with forces of 1–2 g causes unpleasant pricking sensations from certain spots of hairy skin in man and still stronger stimuli usually elicit pain from the same areas. Radiant or contact heat that raises the surface temperature of cat’s hairy skin above 48 C results in erythema after some seconds and above 53 C evokes swelling and blisterlike reactions. The contact thermode used in the present investigation causes an uncomfortable sensation interpreted as “beginning pain” at 46 C when applied to hairy skin of a man’s forearm and consistent reports of pain in naive observers at 48–49 C. In keeping with the definition of “noxious” as implying the threat to tissue damage (23, 30), mechanical stimuli defined as noxious herein consisted of contact by punctate stimulators (0.25 mm or less) with forces in excess of 2 g or its equivalent of 40 g/mm² at any velocity. Similarly, skin or thermode surface temperatures in excess of 45 C were labeled noxious.

Low-threshold unmyelinated sensory units

Approximately one-half of the units studied responded vigorously to innocuous stimuli. The majority of these were excited by the gentlest of mechanical stimuli. The remainder of the low-threshold class responded briskly to small (under 2°C) skin temperature changes in the physiological range but were relatively insensitive to mechanical stimuli.

Low-threshold mechanoreceptors. In most experiments the element most frequently isolated was highly responsive to gentle mechanical stimuli. When tested by punctate stimulators (calibrated hairs of the von Frey type), thresholds ranged between .010 and .045 g. The response from one such fiber evoked by 0.04 g is shown in Fig. 1A. The receptive field of the typical low-threshold C mechanoreceptors was a small area 2–6 mm² when tested by liminal stimuli. With stimuli 5 to 10 times threshold the receptive area enlarged, presumably due to mechanical transmission of an effective distortion. In general, the sensitive C mechanoreceptors were peculiarly responsive to slowly moving stimuli, although their adaptation to maintained stimuli was fairly rapid (1). The majority responded well to sudden, relatively marked (10°C) cooling of the skin such as that produced by dropping ether on the skin (Fig. 1B), although the discharge frequencies to cooling (10–20/sec) never equaled those initiated by moderate mechanical stimuli. Maximal discharge frequencies to moderate mechanical stimuli such as a gentle stroke by a smooth glass rod ranged from 50 to 100 impulses/sec. Infrequently repeated strokes usually resulted in a noticeable afterdischarge. In contrast, a jab with a needle to the center of the receptive field with force sufficient to penetrate the skin evoked fewer impulses and a lower peak frequency.

FIG. 1. Responses recorded from afferent fiber of a low-threshold mechanoreceptor. Conduction velocity, 1 m/sec. A: mechanical contact with a punctate stimulator exerting 0.04-g force during upward deflection of the lower trace. B: cooling of receptive field by evaporation of diethyl ether; lower trace is the output of a thermistor on the receptive-field surface. (C6, 2.)
than that resulting from an appropriate innocuous stimuli. In general, intense mechanical stimuli "inactivated" (depressed or blocked) the terminal for some time. Furthermore, any response to noxious stimuli could be duplicated by quite weak stimuli. Heating the receptive area, either slowly or rapidly, from 25 to 60 C rarely initiated an impulse. Acid and other irritant chemicals applied to the skin surface were similarly ineffectual.

LOW-THRESHOLD THERMORECEPTORS. Ten units were highly responsive to thermal changes. Most of these had some background discharge at the usual ambient skin surface temperature (30-34 C). The general characteristics of the thermal receptors followed descriptions of earlier investigators (13, 17, 18). Changes in the skin temperature (under 2 C) provoked increases in discharge frequency in fibers with background activity or the initiation of discharge in a quiescent fiber at some skin temperature between 25 and 40 C. Eight of the ten sensitive thermoreceptors responded to skin cooling and all of these had the greatest tonic discharge at particular skin temperatures between 23 and 32 C. The two fibers that were excited by skin warming gave maximal tonic activity in the range between 35 and 40 C with transient bursts of activity as the skin temperature was raised to noxious levels (over 43 C) but showed little or no background activity at skin temperatures above 45 C. Several of the "cooling" receptors gave "paradoxical" responses to sudden elevation of skin surface temperatures to noxious levels; they were depressed or blocked when the skin temperature was maintained near 50 C for long periods. The thermal receptors generally showed poor responses to mechanical stimulation. The two "warm" receptors had thresholds for von Frey stimulators between 0.2 and 0.8 g, over 10 times that of the sensitive C mechanoreceptors. Several of the cooling receptors were essentially inexcitable by mechanical stimuli whereas others required noxious mechanical stimulation for activation. By use of a very small thermode, one cooling unit was shown to have a receptive field consisting of at least three sensitive spots separated by areas of skin which did not provoke responses for equivalent stimuli (21). On occasion, although not uniformly, marked thermal changes altered discharge pattern from a relatively regular frequency at low recurrence rate (under 5/sec) to bursts of two or three impulses (equivalent to 50/sec or over) separated by longer intervals (17).

High-threshold unmyelinated sensory units

Elements with elevated thresholds to any form of skin stimulation were divisible into at least three groups based on the environmental change that was most effective for their activation.

POLYMODAL NOCICEPTORS. The most frequently encountered high-threshold units were activated by moderately intense mechanical stimuli, noxious heat and irritant chemicals. They were also weakly excited by very low skin temperatures. The common denominator seemed to be noxious stimulation of any type, hence, the designation "polymodal nociceptors."

Provided that the area innervated by the nerve had not been subject to intense stimulation, polymodal nociceptors neither showed background discharge nor responded to thermal changes in the range between 20 and 40 C. On the other hand, elevation of the skin surface temperatures above 40 C consistently initiated discharges, the threshold level for different units varying between 42 and 56 C. Subcutaneous temperatures at threshold were 1-7 C below that of the surface thermode. In some units the rate of change of temperature was related to the threshold for the first discharges in an unusual fashion; slow increases in temperature evoked the first impulses at somewhat lower temperatures than more rapid changes. On the other hand, a rapid increase in skin temperature inevitably resulted in higher discharge frequencies than were evident with slow heating to the same level. This apparent paradox was resolved once it was recognized that polymodal units typically became more sensitive as a consequence of exposure of the skin to increased temperatures. Figure 2 illustrates a typical response to contact heating. When the thermode temperature was increased to
about 45°C for the first time (Fig. 2A), one impulse was recorded; 10 sec later (Fig. 2B), the temperature was raised an additional 5°C, initiating a burst of impulses during the increase and a low-frequency, irregular discharge during the subsequent steady temperature. Later, as the skin was allowed to cool, an occasional impulse was apparent. In the second heating test (Fig. 2 C and D), multiple impulses were evoked at about 45°C, a level which previously was just liminal.

Alterations of the responsiveness of polymodal elements in successive heating trials are emphasized by the graphic displays of instantaneous discharge frequencies in Figs. 3-5. The solid line of the lower half of Fig. 3A marks the course of skin heating in the first test on one unit, and the dots indicate the equivalent firing frequency. In this test, discharges appeared as the temperature was raised in a 5°C step to just above 50°C. The relation between temperature and discharge frequency for these data is given in Fig. 3B by a plot of discharge frequency (vertical axis) against the thermode temperature at the time of discharge (horizontal axis). Except for one impulse, all activity occurred at slightly over 50°C and comparison of Fig. 3A and 3B shows that the exception took place during the cooling phase. After the thermode temperature had passively dropped to about 30°C in 90 sec, the stepwise heating shown in Fig. 3A was repeated. The plot of Fig. 3C indicates that while most of the impulses again appeared at slightly over 50°C, a number occurred at lower temperatures. Some of the latter impulses represented the background discharge commonly seen with polymodal units after their activation by heat, but others were associated with the step increase of temperature to 46°C. The receptive field of the fiber was heated a third time in the manner of Fig. 3A with the highest step (46-51°C) omitted. Activity equivalent to that noted at over 50°C in the first test was now manifest at about 46°C.

Figure 4 describes the response of a polymodal unit with a very elevated thermal threshold. In the first test of heat sensitivity, the thermode temperature was elevated in 5°C steps from about 30 to 60°C (Fig. 4A); as shown by Fig. 4B, discharges appeared only during the temperature step from 55 to 60°C. Figure 4C is a continuation of Fig. 4A, illustrating a slow passive decrease of temperature and the several discharges associated with a rapid cooling of the probe. Prior to testing with heat, this receptor had been unresponsive to larger decreases of temperature between 40 and 20°C. Figure 4C depicts a second stepwise increase of thermode temperatures and, as the plot of Fig. 4D shows, significant activity appeared at levels that were below threshold for the first heating.

The relation between discharge and more gradual temperature increase for still another polymodal element are shown in Fig. 5 to emphasize a common feature of the discharge pattern. Figure 5, A and B, was derived from the first heating of the receptive field and point out that a low impulse frequency, under 5/sec, was inter-
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temperatures were under 55°C, the change was often slight, representing a drop of 1–3°C in threshold with no obvious enhancement of discharge at a particular temperature. In other cases, threshold temperatures dropped by 10°C (e.g., from 55 to 45°C) and were associated with a severalfold increase in the number of discharges at temperatures above threshold. Larger decreases in heat threshold ordinarily followed prolonged or repeated exposure of the receptive field to temperatures at least 5°C supraliminal. A 5°C drop in threshold occurred for the majority of polymodal units subjected to at least two brief or one prolonged (50–60 sec) exposures to thermode temperature 5°C above the original liminal level; however, precise identification of threshold was often hampered by the development of background discharge after initial activation. For this reason the graphic methods of Figs. 3–5 proved particularly useful. Sensitization brought the temperature at which a number of impulses were evoked down to levels that were not considered noxious (thermode or surface temperatures of 39–41°C) in numerous instances. Skin temperatures above 45°C eventually result in visible changes of the epidermis so that initial activation and sensitization by heat was presumed to be associated with incipient tissue damage. Prolonged heating by temperatures in excess of 60°C or transient contacts with very hot objects (+75°C) led to partial “inactivation” of polymodal nociceptors or a reversal of enhanced responsiveness and may have reflected damage to the nerve terminals.

The mechanical threshold of polymodal units varied greatly. The most sensitive had thresholds for punctate stimulators 5–10 times that of low-threshold mechanoreceptors of the same nerve. With punctate stimulation (von Frey) the median threshold value was deformation produced by 0.6-g force, although four units responded with a single impulse to 0.2 g and six had thresholds in excess of 20 g. There was a rough tendency
for mechanical threshold to correlate with thermal threshold; polymodal receptors with lower mechanical thresholds on the average had lower thermal thresholds, but there were several exceptions. In every case, polymodal nociceptors progressively augmented their discharge as mechanical stimuli were graded from threshold to frankly damaging levels. Typical examples are shown in Fig. 6 for the unit whose responses to contact heating are illustrated by Fig. 2 and make clear the greater responses as the stimulus increased from innocuous to damaging. The most effective mechanical stimuli appeared to be scratching, firm rubbing of the skin, or a slow prodding with a sharp object. Even with such stimuli, the peak discharge frequency often did not reach the same level as in the bursts of activity as associated with noxious heating. Figure 7 plots the discharge frequency of the Fig. 6 receptor as a function of time for two mechanical stimuli (A, 1.1 g von Frey; B, needle). The discharge evoked by needle prick in Fig. 7B (the first response shown in Fig. 6C) was comparable to that recorded from other units (Figs. 3–5) with heat stimuli. As Figs. 2, 6, and 7 indicate, adaptation to mechanical stimuli was more rapid.

**FIG. 5.** Discharge of a polymodal nociceptor during skin heating. *A* and *C*: instantaneous discharge frequency versus time with a parallel record of skin temperature for sequential 150-sec periods. *B* and *D*: plot of discharge frequency as a function of thermode temperature for period covered by graph directly above each. Other details as in Fig. 3. (CM, 4.)

**FIG. 6.** Responses of a polymodal receptor to punctate mechanical stimuli. Same receptor as Fig. 2. Bars under each trace mark approximate time of skin contact, all at one spot of receptive field. *A*: 0.8 g von Frey stimulator. *B*: 4.4 g von Frey stimulator. *C*: pressure with needle sufficient to penetrate skin.
FIG. 7. Discharge of polymodal nociceptor to punctate mechanical stimuli. A: 1.1 g von Frey stimulator. B: pressure with needle sufficient to penetrate skin (note that burst at 7 sec occurs as needle was withdrawn). Plots formed as in Fig. 3. Same receptor as Figs. 2 and 6.

than to suprathreshold heat for this particular unit. As far as was tested, mechanical excitation of polymodal "nociceptors" did not produce sensitization to subsequent mechanical stimuli. Occasionally highly noxious mechanical stimuli such as repeated penetrations of the receptive field with a needle resulted in an "afterdischarge" of a few impulses. Such procedures were not carried out often enough to determine whether background discharge of this type was related to any measurable change in mechanical sensitivity. On the other hand, activation by heat sometimes enhanced sensitivity to mechanical stimuli. This was tested by carefully establishing a threshold for a polymodal element with punctate stimulators prior to heating of the receptive field. After one or two cycles of heating, the mechanical threshold dropped 50% or more for approximately one-third of the group. As with thermal activation, an effective stimulus sometimes changed from the noxious to innocuous (i.e., 4.1–0.8 g). Several receptors that exhibited enhanced responsiveness to mechanical stimuli after noxious heating showed a gradual return of the mechanical threshold toward the preheat level in 15–30 min.

Receptive fields of polymodal nociceptors to greatly supraliminal mechanical stimuli, usually consisted of one small area or "spot" of less than 2 mm². In the case of units with very elevated mechanical thresholds, the sensitive region was quite limited, under 1 mm², but occasionally two or three spots of sensitivity were located.

Cooling, even to -10°C for several seconds, was never as potent a stimulus as noxious heat. After sensitization by heat, sudden cooling between 40 and 20°C regularly initiated a limited number of impulses (Fig. 4C). In the absence of sensitization, cooling in this range was routinely ineffectual. In a few instances, ice or a special cold thermode was located on a favorably situated receptive field and some impulses appeared after the surface temperatures had dropped to near 0°C, but their number and maximal frequency were a fraction (10%) of those produced by intense mechanical or heat stimulation. In contrast, irritant chemicals such as dilute hydrochloric, sulphuric, or acetic acid consistently evoked activity from polymodal nociceptors whether or not they had been previously subjected to noxious heat. Typically, the discharge of a polymodal unit to dilute acid was low in frequency and was maintained for the time that the solution remained in contact with the receptive field, ceasing shortly after it was washed off. A particularly vigorous response to acid is shown in Fig. 8. The receptive field of this fiber had been heated prior to the application of acid and an occasional background impulse was evident. A drop of 0.1 N HCl was placed on the skin at the time indicated by the arrow in Fig. 8 and periods of discharge and silence followed until the acid was washed off (downward arrow). Extensive testing of the sensitivity of polymodal nociceptors to different chemical agents was not attempted, although it was noted that a histamine liberator (48/80, 160-
Burroughs Wellcome) placed on scratches in the receptive field elicited responses that were weak in comparison to those evoked by dilute acid.

In one experiment an attempt was made to determine characteristics of unmyelinated fibers stemming from the glabrous and hairy skin of the foot. The discharges of three fibers were isolated which had the general characteristics exhibited by the polymodal nociceptors of the posterior thigh and leg. Two had terminals in hairy skin between the pads and one had a receptive field limited to a spot on the central pad. Mechanical thresholds for these three elements were among the highest encountered in the polymodal group, although suprathreshold stimuli evoked many impulses at relatively high frequencies (up to 80/sec). Thermal thresholds and sensitization by heat were similar to those described for the posterior femoral cutaneous units.

SUPERFICILY LOCATED MECHANO RECEPTORS WITH HIGH THRESHOLDS.

Approximately 15% of the fibers studied were excited by strong mechanical stimuli and either could not be activated by, or were inconsistently responsive to, any of the other stimuli tried. Certain of this group were shown to have superficially located terminals since they responded to mechanical distortion limited to the epidermis. Their characteristics varied sufficiently to make it likely that more than one receptor type was represented. In particular, at the time of most of these experiments, adequate means were not on hand for maintaining low temperatures, i.e., under 10°C. This fact was of particular importance since several units especially responsive to very low cutaneous temperatures have been described (14). None of the high-threshold receptors studied in our experiments were shown to be more responsive to cold than to mechanical stimuli; however, the testing procedure may have been inadequate.

The responses of a high-threshold mechanoreceptor are shown in Fig. 9. Increased force from the threshold of 2.2 g gave rise to increased responses, and punctate stimuli with a needle or other sharp objects evoked short bursts with intervals between impulses equivalent to frequencies of 20–30/sec (Fig. 9C). Adaptation to a maintained mechanical stimulus was relatively rapid (Fig. 9). Repeated forceful stimuli such as probing or squeezing portions of the superficial epidermis with a forceps tended to “inactivate” this group. All units classified as high-threshold mechanoreceptors were tested with heat stimuli sufficient to excite any of the polymodal nociceptors and they invariably failed to give a prompt response (Fig. 9D). In a few instances maintaining the temperature of the skin at 55°C or above for many seconds was associated with delayed activity at a very low frequency (under 1/sec). Transient cooling of the skin to between 10 and 20°C did not initiate activity from such elements. In some instances ice was placed on the receptive field and held there for 5
sec or longer; two units responded weakly, raising the possibility that a means had been on hand for maintaining skin temperature at a low level for prolonged periods, others of the group would have shown activity and/or some fibers would have given more impressive responses. Certain units gave only two to three discharges when the points of a serrated forceps penetrated the skin and then were inactivated for a prolonged period. The relatively few discharges initiated by strong mechanical stimuli and the prolonged subsequent unresponsiveness is characteristic of afferent units specifically activated by mild cooling (17, 26) and was taken as a further suggestion that the responsiveness of the high-threshold mechanoreceptors may not have been fully determined.

The receptive field of elements classified as high-threshold mechanoreceptors had two forms. One type bore a relationship to receptive fields for the other C fiber sensory units in that the skin area was small, typically measuring 1 x 2 mm. On the other hand, several of the group had distinctly larger receptive fields, in some cases extending well over a centimeter in length and several millimeters in width. The long axis of such receptive fields was oriented in the proximal-distal direction and in more than one case paralleled a superficial vein visible through the skin. Units whose receptive sites were distributed along the course of a superficial blood vessel had the highest thresholds to mechanical stimuli, raising the possibility that they, in fact, were not associated with afferent terminals but were motor fibers to blood vessels or other cutaneous structures. On the other hand, units with equally high mechanical thresholds and large receptive fields have been found in recordings made in dorsal root ganglia, suggesting that they at least have the traditional pathway for afferent elements (P. R. Burgess, unpublished).

SUBCUTANEOUS RECEPTORS. Four fibers were distinctly different in that their receptive terminals were not located in the epidermis or in subcutaneous structures that could be lifted from underlying tissue. In each instance, stimuli exerting deep pressure evoked activity. Manipulation of the skin indicated that no particular portion was consistently related to responses but that activity was regularly initiated by stimuli which distorted the fat pad in the popliteal fossa. These elements were neither excited by heating the skin to surface temperatures above 60°C nor by cooling the receptive field with ice. Acid applied to the skin was also without effect except in one case after the epidermis had been repeatedly broached by sharp objects; in this instance a delayed, low-frequency discharge (under 2/sec) appeared that was interpreted as resulting from acid penetrating to deeply located endings through holes in the surface. Firm pressure directed against deep structures by a blunt object or by extremely firm, squeezing pressure evoked a slowly adapting, relatively regular, discharge at 5–20/sec from three of the deeply located receptors. This contrasted with the highly irregular activity of the polymodal units as well as with the transient responses of the superficially located high-threshold mechanoreceptors.

Sample of receptive characteristics and conduction velocity

One hundred twenty-nine units of 147 were placed into one or another of the categories described. Ten units were not classified because inadequate information had been gathered regarding their features. In some cases the difficulty was separation of high-threshold mechanoreceptors from the polymodal nociceptors since postexperimental analyses indicated that skin temperatures had not been carried high enough to rule out the polymodal type. Another kind of problem was encountered with two units responsive to warming below 40°C which were studied after their receptive region had been heated to noxious levels in earlier tests. The latter could have been either low-threshold thermal receptors (warm) or sensitized polymodal elements. The remaining eight unclassified units were unresponsive and were observed in experiments attempting to determine the fraction of C fibers inexcitable by skin stimulation.

The number of C receptive units that are considered herein represent no more than a small fraction of those to be found in a given nerve the size of the posterior femoral cutaneous. In spite of this, the
range of receptor characteristics and their relative frequency of occurrence seemed to be a reasonable reflection of that typically present, since roughly the same percentage of major "types" appeared if blocks of 5-10 sequential experiments in the survey (15-40 units) were considered. Furthermore, recordings from dorsal root ganglion units suggest about the same frequency of occurrence of receptive characteristics from the skin of the cat's tail (P. R. Burgess, unpublished). On the other hand, it seems likely that different kinds of unmyelinated and sensory units or relative proportions will be present in other body regions, such as the distal parts of the extremities or the head.

Figure 10 summarizes the results from the 37 experiments, indicating the conduction velocity of fibers for the different types of elements. These composite data do not suggest correlation between conduction velocity of the unmyelinated afferent fiber and the responsiveness of its sensory terminal.

In individual experiments some systematic relation between conduction velocity and terminal sensitivity seemed to exist. In the usual preparation the conduction velocity of the sensitive mechanoreceptors fell into the limits marked by the first major deflection of the C compound potential whereas polymodal nociceptors usually were associated with more slowly conducting fibers. Experiments in which 5-10 units were studied, suggested that deeply located types and those highly sensitive to cooling tend to have the most rapidly conducting C fibers of a particular nerve, equivalent to the leading edge of the first compound peak; however, such elements were relatively rare. Thus, most of the fibers contributing to the first C deflection stemmed from low-threshold mechanoreceptors. This is in keeping with Douglas and Ritchie's observation (8) that occlusion of the first component of the C compound action potential could be produced by gentle mechanical stimulation of the skin. The probable reason for the absence of differences in the conduction velocities of receptors classified in Fig. 10, even though one may be apparent in the individual animal, is that absolute conduction rate for the population varied considerably from one animal to another. Nevertheless, even in individual experiments, some overlap of conduction velocities existed between low-threshold mechanoreceptors and polymodal nociceptors; a polymodal nociceptor and a sensitive mechanoreceptor whose fibers had identical conduction velocities were seen in about one-third of the experiments.

DISCUSSION

The present survey has shown that a fraction of unmyelinated afferent units in cutaneous nerve requires strong stimulation of the skin for effective activation. Results obtained by the use of stimuli graded from innocuous to noxious emphasize that high-threshold C fiber sensory elements signal threatening and damaging stimuli in a unique fashion whereas this is not possible by the more sensitive (low-threshold) units. Specifically, low-threshold mechanoreceptors of the unbroken skin are unresponsive to noxious heat and to irritant chemicals; low-threshold thermal receptors...
are less responsive to noxious temperature changes than to those within the physiological range (this study; 13; Whitehorn and Burgess, unpublished). The converse is also true; high-threshold receptors are weakly excited, if at all, by innocuous stimuli. If one considers stimuli provided by the natural habitat, the overlap in responsiveness is small between cutaneous receptors classified as low threshold and those considered as high threshold. For instance, a maximal discharge is evoked from low-threshold C mechanoreceptors by a gentle, slow stroking of the hairy skin, a stimulus that would initiate few, if any, impulses in the most responsive polymodal nociceptors or the high-threshold mechanoreceptors. In this context it seems reasonable to consider all high-threshold receptors of the integument as nociceptors; these are the sense organs of the skin that appropriately serve to warn of impending or present tissue damage. Qualitative variations in the responsiveness of high threshold unmyelinated sensory units are apparent from the descriptions of previous investigations (14, 16, 32) and this conclusion is supported by our results. The different sensitivities of the various cutaneous nociceptors permit information on the nature of noxious stimuli to be transmitted to the central nervous system. Of the various nociceptive elements, only the polymodal type responds promptly to noxious heat and irritant substances. On the other hand, noxious mechanical stimuli specifically excite the high-threshold myelinated sensory units described by Burgess and Perl (4), high-threshold mechanoreceptors with C fibers, and the polymodal elements with unmyelinated fibers. A comparison of the activity simultaneously arriving from polymodal nociceptors and high-threshold mechanoreceptors could give a reliable indication of the existence of danger from mechanical as opposed to heat-chemical events. How the nervous system uses these data is a matter for speculation at the moment.

The facts that nociceptors make up a large proportion of the unmyelinated receptive units in a cutaneous nerve and represent a class of sense organs distinct from the several low-threshold types, argue strongly for a form of specificity in peripheral mechanisms responsible for pain. The correlation between pain, its associated reflex reactions and the conduction of impulses in C fibers is well established (3, 6, 7), yet stimuli capable of exciting only the low-threshold mechanoreceptors or thermal receptors with C fibers do not cause pain. It seems evident that the relation between pain and C fiber impulses demands impulses in the nociceptor fraction of the population as an initiating condition. Even though the trigger for pain resides in sense organs specially tuned to intense stimuli, it is probable that concurrent activity in other receptors contributes to the sensation and its related phenomena.

Altered responsiveness of sensory units with unmyelinated fibers after skin damage by elevated skin temperatures has been noted before (14, 32, 33), but its relation to the type of element and the nature of the “sensitizing” stimulus was uncertain. We found that sensitization of polymodal nociceptors can be consistently demonstrated provided that measurements are based on the threshold or the response for the first stimulus. Changes in responsive characteristics following noxious heat also can be shown for certain myelinated high-threshold mechanoreceptors but appears in these only under special conditions (Whitehorn and Burgess, unpublished). The unique feature of sensitization of polymodal nociceptors is that their enhanced responsiveness becomes manifest after a liminal level of a particularly effective form of stimulus. In many instances, sensitization of a polymodal type led to a sufficient lowering of threshold so that elements initially responsive only to damaging stimuli could be activated by innocuous manipulations. This degree of change recalls the psycho physical and clinical observations on hyperalgesia following pain-provoking stimuli (23). It is common knowledge that pain or discomfort may be elicited by quite weak stimuli applied to the erythematous skin that follows exposure to the sun or other sources of radiant energy. Furthermore, threshold alterations for heat pain in human subjects have been reported that parallel sensitivity changes described above for polymodal nociceptors (11). The existing evidence only permits conjectures on
the mechanisms underlying such sensitization. It certainly is not a uniform feature of all unmyelinated sensory units; intense mechanical stimuli especially effective in exciting high-threshold elements usually result in inactivation of the low-threshold mechanoreceptors. The fact that threshold changes are so prominent and readily produced in polymodal nociceptors suggests that their ubiquitous responsiveness and sensitization may have some factor in common. From time to time it has been proposed that cutaneous pain is associated with the release of a substance from injured tissue which in turn excites the relevant afferent terminals (12, 20, 22, 24, 29). It is not hard to conceive that a substance produced by cell damage and capable of exciting sensory units of the polymodal fibers could produce a long-lasting increase in sensitivity by its continued presence in small quantities. Regardless of underlying mechanisms, afferent fibers that may be reckoned with good cause to have a part in the initiation of certain types of pain, are sensitized by a particularly effective stimulus. Although enhanced sensitivity of certain nociceptors may not explain all of the questions posed by hyperalgesia, it does suggest that in some situations the sensory nerve terminals themselves are involved.

SUMMARY

The functional characteristics of cutaneous sensory units with unmyelinated afferent fibers was judged by recording impulses from single elements. The appendix describes a computer-based graphics system that greatly aided the analyses of data. A total of 147 unmyelinated units were isolated from a nerve supplying hairy skin of cats. The sensory units were divided approximately equally between those that were highly responsive to either gentle mechanical or innocuous thermal stimuli (low threshold) and those that required strong stimulation for effective activation (high threshold).

The most frequently encountered low-threshold sensory unit was excited by weak mechanical stimuli, and usually discharged briskly to sudden, marked cooling of the skin. Other low-threshold receptors responded to slight temperature changes of the skin between 25 and 40°C. Low-threshold mechanoreceptors and thermoreceptors did not give unique responses to noxious stimulation.

The commonest high-threshold receptor was activated by moderate to intense mechanical stimuli but usually reserved its most vigorous response for noxious heat. Irritant chemicals (acid) applied to the intact skin also evoked activity from such elements, indicating a broad or polymodal sensitivity. Polymodal elements were characterized by a lowering of threshold and enhancement of responsiveness to thermal and other stimuli following elevations of skin temperature to noxious levels.

About one-third of the high-threshold sensory units gave their sole or greatest response to intense mechanical stimuli. This group may have included elements responsive to skin temperatures below 10°C. A few high-threshold mechanoreceptors had receptive terminals located in subcutaneous fat and were unusual in their regularity of discharge and slow adaptation to deep, noxious pressure.

The intensity of the liminal stimulus and the unique ability to provide signals marking the difference between innocuous, threatening, or overtly damaging stimuli was taken as convincing evidence in favor of a nociceptive function for the high-threshold, unmyelinated sensory units. Furthermore, the sensitization of the "polymodal nociceptors" following noxious heat was argued to be consistent with certain kinds of hyperalgesia.

APPENDIX

A computer system was used to aid analysis and presentation of results in two ways: 1) Representations of all impulsive events in the records were carefully scanned to make sure that only the discharges of a particular unmyelinated unit were considered. 2) The responses could be displayed as readily constructed plots of frequency against time or frequency as a function of a stimulus parameter to permit study of discharge patterns.

1Further details on the computer system described below can be obtained from the Computer Sciences Division.

2Present address: Dept. of Computer Sciences, Montana State University, Bozeman, Montana.
As a first step in this procedure, signals recorded on analog magnetic tape during an experiment were converted to digital form using a system taking about 20,000 samples of the nerve channel (voltage) per second. Fifteen sequential conversions were stored in a buffer memory of a small computer (DEC, PDP-9). If a predetermined voltage was not reached by the 15th conversion, the first of the stored conversions was discarded and the latest one added. When the analog voltage equaled or exceeded the threshold during this process, 54 additional conversions were added to the stored 15 to make up the digital description of an action potential or other voltages that appeared in the recording. The time of occurrence of the threshold relative to the start of the recording was kept with the 69 voltage conversions. Thus, each nerve impulse, including its initial phase, was identified as a 70-word digital statement and these were sequentially ordered in the main computer storage. Since computer memory was not wasted by the storage of analog data between impulses, it was possible to work with many impulses occurring over long time periods. A channel in which stimulus information appeared as an analog voltage was converted to digital form at 100/sec with time of each conversion period. A channel in which stimulus information was represented and identify the data. The computer in conjunction with a large digitally controlled oscilloscope (CRT) with the main computer (Univac 1108). Commands to the program by the CRT viewer are entered into the main computer by means of a teletype or by an electronic stylus. The stylus position is sensed by a tablet on which there is a point-by-point representation of the large oscilloscope. Small arcs on the CRT are displayed as places from which frequently used commands may be activated by appropriately positioning the stylus on the tablet. Under control of a program in the main computer, the CRT displays a set of points, lines, numbers, and letters to represent and identify the data. The computer in turn is controlled by means of a set of words and abbreviations, entered via the teletype or activated by stylus positioning. A program, written in FORTRAN for the main computer interprets each command and carries out the indicated function. Entering "NEXP = N," for example, causes the data of experiment "N" to be transferred from random access storage unit to the computer's core memory where it can be processed using the other commands of the language. New words may be added and the meaning of existing words easily modified. As used for these data, the language consisted of 22 commands.

To characterize the potentials recorded from a single C fiber conduction velocity, the responses to a maximal electrical shock were digitized. The conduction velocity of discharges was determined from the difference in time between shock artifact and each response. Time for any detection can be obtained by typing "TIME (# of event) = ———— ." The computer then answers with the time of that event. The experimenter uses the shape of an impulse with a given conduction velocity to define a category of pulse shapes by pointing to an integer at the top of the screen and subsequently to a series of impulses that he recognizes as being generated by the same fiber; the criteria for a single fiber's potential being the familiar one of amplitude and shape. The program files the choices under the indicated category as a sample of shapes in that category. Additional frames of 12 impulses which occurred later (or before) can be examined at will and other examples of the desired impulse added to the sample. The program uses the sample to compute a composite shape which is characteristic of that category. On command, the program proceeds through the impulses sequentially, comparing the shape of each impulse with the composite shape determined from the samples, and selecting those which fit between predetermined limits. After this comparison is completed, lists of the impulses classified into each of the categories are displayed. Whenever the impulses are again pictured, the category number is placed below each pulse. Figure 12 shows a frame after the program had sorted several hundred impulses. Events 57, 58, 59 were used as the pattern for category 1; no other categories were defined. The program selected 60, 62, 63, 64, 65, and 66 as also belonging to category 1 (placing 1 below each impulse number), and rejected 56, 61 (indicated by "0"). Note that the peak amplitude of 56 is identical to those placed in category 1. The automatic shape discrimination of the program is fail-safe, and provisions were made to allow the experimenter to add or remove impulses from any category after the machine sorting is completed. For instance, the experimenter may recognize that an event was formed by the summation of potentials from two different fibers, and he could include it in both categories. In the present work, every decision of the machine was checked by the experimenter, the computer sorting being used only as a time-saver.

After sorting, the impulses produced by a given fiber are in a list in order of occurrence. Typing "GRAPH = 1" causes the program to compute a set of time intervals between pulses and the instantaneous frequency at the time of occurrence for each pulse. At this point, the program displays a set of parameters including the time of occurrence

**FIG. 11.** Outline of steps in data handling for impulse sorting and graphical analyses with digital computer.
FIG. 12. Display of sequential nerve impulses as viewed on oscilloscope (CRT) of the graphic system during sorting procedure. The numbers 0, 1, 2, 3 at top indicate categories for the sorting of impulses. The numbers 56-67 under each representation of an impulse are the sequential labels for events reaching “threshold” in the analog to digital conversion. Number under each sequential event indicates category (i.e., the receptor unit giving rise to the impulse) into which the event has been placed.

The program that interprets this set of commands makes use of the Interactive FORTRAN V Graphics System developed by Reed, Dallin, and Bennion (28) for the Univac 1108. This makes it possible to interrogate or change the value of any of the variables of the program from the teletype with a prompt response. In addition, control may be transferred to any numbered statement of the FORTRAN program, and this transfer may be effected by typing a six-letter word or abbreviation on the teletype. These two operations may be combined:

**CATLOG**
Lists experiment numbers stored in the random access storage.

**NEXP = (N)**
Brings data for an experiment (N) into core memory.

**PULSES**
Displays pulses starting at LP.

**LP = (N)**
Changes start point for display of pulses.

**L**
Brings the next 12 pulses to the screen.

**R**
Brings the previous 12 pulses to the screen.

**COMPAR = (N1), (N2)**
Displays pulses N1 and N2 side by side and overlaid.

**CAT = C, (N)**
Puts pulse N from the sample of category C.

**ERASE = C, (N)**
Removes pulse N from the sample of category C.

**CANCEL = (C)**
Deletes category C.

**LISTEM = (C)**
Displays the samples.

**SORTEM**
Uses average characteristics to sort pulses.

**REMOVE = C, (N)**
Removes N from the sorted list of category C.

**ADD = C, N**
Adds N to the sorted list of category C.

**PRSPKS**
Prints the sorted lists with time’s, DT time’s, and 1/Δ time’s.

**GRAPH1 = (C)**
Produces frequency vs. time graph for category C.

**STMPLT**
Displays the stimulus under the frequency vs. time.

**CORREL**
Displays a frequency vs. stimulus plot.

**STMVST**
Displays stimulus vs. time graph.

**PLOT**
Sends whatever is displayed on the CRT to the mechanical plotter.
REFERENCES


