

Update 2011: This writing sample is from long ago. Now—after almost a year of continuous assignments in biomedical writing and editing for journals and NIH grant proposals—my approach has been greatly refined. I have adopted the standards of Mimi Zieger's *Essentials of Writing Biomedical Research Papers*, Angelica Hofmann's *Scientific Writing and Communication*, and William Gerin's *Writing the NIH Grant Proposal*. I have also been on the leading edge of writing NIH R01 proposals according to their new short form, introduced in 2010.

The neurobiology of itch

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The neurobiology of the itch sensation remains controversial and confusing. In the last ten years there have been only four attempts to experimentally resolve the issues (Torebjork and Ochoa, 1981; Tuckett, 1982; Tuckett and Wei, 1987; LaMotte, 1988). Since the observations of the 1950s remain definitive, they will be discussed along with the recent experimental and clinical evidence.

The nature of the sensation

Relationship to pain

A variety of observations imply that pain and itch are intimately related but nevertheless separable (reviewed by Graham et al., 1950; Shelly and Arthur, 1957; Denman, 1986). Clinical sectioning of the spinothalamic tract abolishes itching along with pain (Bickford, 1937). Individuals genetically insensitive to pain are also insensitive to itch (Kunkle, 1943). During stages of spinal anesthesia, stimuli that initially elicit pain will later elicit itch, followed by loss of itch but with touch and temperature intact (Thole et al., 1912, as reviewed by Graham et al., 1950). At itch spots (see later) stimuli of increasing intensities will grade from itch into pain (Shelly and Arthur, 1957). Application of cowage ("itch powder") lowers the pain threshold, suggesting that pain receptors have been activated at an intensity below the pain threshold (Graham et al., 1950). Despite this intimate relationship between itch and pain, cases of syringomyelia have been reported where pain was lost but touch and itch were preserved, and vice versa (Ehrenwald and Konigstein, 1929, as reviewed by Graham et al., 1950).

Two modalities

Two modalities of pain are recognized: sharp, fast pain carried peripherally by A-delta fibres and associated centrally with the neospinothalamic tract; and burning, slow pain carried by C fibres and associated with the paleothalamic/spinoreticular tracts (Poggio and Mountcastle, 1960; Hassler, 1970; for review see Kandel and Schwartz, 1985).

Graham et al. (1950) showed a similar distinction for itch perception with cowage: a superficial, localizable, sharp, short-latency component, and a diffuse, "burning", long-latency component. These fast and slow components of both itch and pain can be dissociated from one another. Anesthetic applied to a cutaneous nerve can produce a site where both fast pain and fast itch are felt, but not the slow components. Likewise ischemia caused by pressure, or anesthesia by cold, can produce an area where slow itch and pain can be elicited, but not fast. Both itch components can occur in the absence of touch sensation. These observations suggest that there are two separate modalities of itch, and that these may parallel anatomically the two modalities of pain.

Questions on physiology and anatomy

What are the receptors?

Experiments by Shelly and Arthur (1957) suggested that proteinases are the final common mediator for itch receptors (cowage contains a proteinase). The most recent review of itching disorders (*pruritus*) by Denman (1986) states that the final mediator is still not known, that histamine (via H1 receptors) may be a second common mediator (for bradykinins and substance P, for example), and that proteinases may act through histamine release. Histamine cannot be the final mediator in all itch, however, since itching may be induced in histamine-depleted skin (Davies and Greaves, 1981).

Itch is transduced by free nerve endings (Shelly and Arthur, 1957; Cauna, 1976) and is maximally elicited at points roughly one mm apart where endings converge (Shelly and Arthur, 1957). Each penicillate ending is a multiaxon bundle (Cauna, 1976). Cauna notes that due to the wrapping of endings in collagen and to their plexiform distribution, these endings would not be effective for making two-point discriminations. This is consistent with Shelly and Arthur's observation that proteinases produce only slow itch, slow pain, and warmth, and not prick pain or touch. But we are left without a candidate for the receptor for the fast, sharp component of itch (and pain) described by Graham et al. (1950).

Shelly (1957) showed that itch can be produced by chemical, mechanical, thermal, and electrical stimulation. This leaves open the question of whether axons that are bundled in endings at an itch spot are separately transducing different physical stimuli and sending all to be interpreted centrally as itch, or whether individual *polymodal* endings are carrying their information to central itch centers—alongside other polymodal axons that carry the same information, but to centers that interpret it as a pain. The present consensus is that individual sensory axons for itch are of the same polymodal type that convey pain (Cauna, 1976; Torebjork and Ochoa, 1981; Tuckett and Wei, 1987a). Tuckett and Wei (1987a) used intracellular recordings in cat sensory afferents to show that separate mechanoreceptors, thermoreceptors, or mechanical nociceptors do not respond to cowage whereas those afferents that do respond to cowage also respond to

mechanical and heat stimuli. Most recently, however, contradictory experiments on monkey and human sensory afferents by LaMotte (1988) show that no polymodal receptors, either C or A fibres, responded to histamine and only a few responded weakly to capsaicin. LaMotte therefore postulates the existence of separate "chemonociceptors" for both pain and itch.

What are the peripheral pathways?

The two dissociatable itch modalities observed by Graham et al. (1950) with cowage suggest separate pathways mediated by A-delta and C fibers, but two studies conflict with this conclusion. Shelly and Arthur (1957) produced itch with wire and electrical square waves at mapped itch points on highly trained observers. They found a delayed itching sensation whose latency depended on distance from the head and matched the conduction speed for C fibres only. Tuckett and Wei (1987b) recorded from cat myelinated afferents and found that of those neurons that did respond to cowage their response was far less than their response to mechanical stimuli, and they concluded that cowage was not an adequate stimulus for this neuron population (A fibres).

One possible way to resolve the anatomical question of the two modalities is to suggest that both are mediated by C fibres but that the "sharp" modality is mediated by the neospinothalamic tract and is not fast. This is consistent with the fact that C fibres do contribute input to the neospinothalamic tract for localized pain perception (reviewed by Kandel and Shwartz, 1985).

Itch and pain subpopulations or differential encoding?

The doctrine of specific nerve energies remains controversial with respect to the separation of pain and itch sensation. Tuckett (1982) attempted to resolve this question in the following way. Intracellular recordings were made from cat polymodal neurons responding to electrical square waves, cowage, or heat, and these recordings were then played back as electrical stimulation to the skin of human subjects. Electrical stimulation normally produces only itch. Tuckett reasoned that if pain was encoded differently from itch by the same neurons, then the different neuronal firing patterns to pain or itch may evoke pain or itch when played back as electrical stimulation. He found consistent perception of itch, increasing linearly with stimulation frequency, and produced also by a steady stimulus rate even though polymodal neurons do not fire steadily. This is support, but not direct proof, of separate afferent populations, especially since it is not clear whether the cutaneous electrical stimulation would be transduced into an identical firing pattern by the receptor neurons.

To reconcile the issue of specific nerve energies with the early observations of itch grading into pain one should recognize that as pain fibres are recruited they may mask the perception of itch. For example, when Torebjork (1974) recorded extracellularly from C fibres he observed that burning pain was reported when stimuli induced intense afferent activity, whereas itch was reported when stimuli

induced low-frequency activity. He suggested that both sensations may be mediated by different impulse patterns from the same polymodal neurons. Later (1981), he and Ochoa reversed this position when, upon stimulating polymodal afferents *intracellularly*, they found afferents whose modality remained itch regardless of the frequency of stimulation, and no afferents that switched to pain.

What are the central mechanisms?

Spinal cord

Two divergent observations demonstrate spinal cord mechanisms for itch. Graham et al. (1950) showed that a sharp prick in the same dermatome as itching from cowage application abolished the itch, even if the prick was to the other side of the body. This suggests a gating of itch by pain comparable to that of pain by touch in the substantia gelatinosa (Melzack and Wall, 1965). Kryzhanovsky (1976) applied tetanus toxin, strychnine, and penicillin to the spinal cord of rats and produced itching so severe the animals literally chewed the flesh off of their leg bones. Kryzhanovsky interprets this in terms of reduction of inhibitory mechanisms in a theoretical central "determinant dispatch station," but this model has not been carried forward by other researchers.

Brain

Two different experimental observations suggest modifications of the itch sensation by the brain. Tuckett (1982) found that after his electrical stimulation to human skin was stopped, itch was still reported, even though intracellular recordings of cat responses to itch show no afterdischarge upon stopping stimulation. Chapman et al. (1960) showed that proteinases, which cause itch, can be produced in a subject's skin solely by hypnotic suggestion that the skin is itching. This latter observation is consistent with the finding by Hokfelt et al. (1975) that C fibres may modulate their own input by peripheral release of substance P.

Three clinical cases of unilateral pruritus produced by brain lesions yield clues to the anatomy of brain pathways for itch. King et al., 1982: after surgery for a basilar artery aneurysm a patient developed left-body pruritus, hypesthesia, and paroxysmal warmth, later retaining the pruritus but losing pain, touch, temperature, and proprioception in the same area. A CT scan showed an infarction of the right posterior internal capsule (carrying fibres from the ventral lateral nucleus to somatosensory cortex). The authors noted that the progression of symptoms paralleled a "central pain" or "thalamic" syndrome, and they suggested spontaneous activity of thalamic or cortical areas. This case suggests that the anatomical representation of the other affected sensations are contiguous with that for itching. If the itch pathways parallel or run with those for pain then this case indicates involvement of a neospinothalamic pathway for itch; the itch modality affected here would then presumably be of the sharp type, but this distinction was not addressed in the paper. In a second case (Sullivan and Drake, 1984) a patient presenting with continuous and paroxysmal itching along with

sensory and motor deficits was shown by CT to have a fungal brain abscess in the contralateral frontal lobe with edema spreading posteriorly. The authors suggest a cerebral representation for itch contiguous with other somatosensory modalities.

A third case of chronic contralateral pruritus following a parietal lobe stroke (Shapiro and Braun, 1987) could be interpreted as supporting the idea of a cortical representation, but the authors have offered an alternative explanation. Since the lesion produced sensation rather than blocked it, and since descending motor systems were also chronically affected (hyperreflexia), they suggest that the stroke interrupted descending corticospinal, extrapyramidal, or endorphin/5-HT tracts synapsing in the midbrain periaqueductal grey, thus pointing to a modulating pathway rather than the source of representation itself. Such a mechanism would parallel the known mechanisms of pain modulation (via the dorsolateral funiculus to the substantia gelatinosa [Basbaum & Fields, 1978]), and is not inconsistent with a cortical representation for itch.

Opiates

Administering epidural and spinal opiates can cause itching (reviewed by Ballantyne et al., 1988). The opiate blocker naloxone is used for relief of intractable pruritus (Bernstein and Swift, 1979). Ballantyne et al. (1988) develop an elaborate hypothesis to attempt to explain the opposite response of itching to opiates as compared to pain, and its evolutionary significance. Discussion of this hypothesis is beyond the scope of this paper. The point to note is that itching is a different protective response than pain and although we have seen that pain and itch pathways may be similar, nonetheless they can be modulated differently.

References

- Ballantyne, J., Loach, A., and Carr, D. 1988. Itching after epidural and spinal opiates. *Pain* 33, 149-160.
- Basbaum, A. and Fields, H. 1978. Endogenous pain control mechanisms: Review and hypothesis. *Ann. Neurol.* 4, 451-462.
- Bernstein, E. and Swift, M. 1979. Relief of intractable pruritus with naloxone. *Arch. Dermatol.* 115, 1366-67.
- Bickford, R. 1937. Experiments relating to the itch sensation, its peripheral mechanism and central pathways. *Clin. Sc.* 3, 377-341.
- Cauna, N. 1976. Morphological basis of sensation on hairy skin. *Prog. Brain Res.* 43, 35-45.
- Denman, S. 1986. A review of pruritus. *J. Amer. Acad. Dermatol.* 14, 375-391.
- Ehrenwald, H. and Konigstein. 1929. Klinische und experimentelle untersuchungen uiber das juckgenfuhr vorlaufige mitteilung. *Wein. klin. Wchnschr* 42, 1397-.
- Graham, D., Goodell, H., and Wolff, G. 1950. Neural mechanisms involved in itch, "itchy skin", and tickle sensations. *J. Clinical. Invest.* 30, 37-49.

- Hassler, R. 1970. Dichotomy of facial pain conduction in the diencephalon. In R.Hassler and A. Walker (eds) Trigeminal neuralgia: pathogenesis and pathophysiology. Philadelphia: Saunders, 123-138.
- Hokfelt, T., Kellerth, J.O., Nilsson, G., and Pernow, B. 1975. Substance P: Localization in the CNS and in some primary sensory neurons. *Science* 190, 889-890.
- Kandel, E. and Shwartz, J. 1985. Principles of Neural Science. New York: Elsevier.
- King, C., Huff, F., Jorizzo, J. 1982. Unilateral neurogenic pruritus: paroxysmal itching associated with central nervous system lesions. *Ann. Intern. Med.* 97, 222-223.
- Kryzhanovsky, G. 1976. Experimental central pain and itch syndromes: modeling and general theory. *Adv. Pain Res. Ther.* 1, 225-230.
- Kunkle, E. and Chapman, W. 1943. Insensitivity to pain in man. *A. Research Nerv. & Ment. Dis. Proc.* 23, 100-109.
- LaMotte, R. 1988. Psychophysical and neurophysiological studies of chemically induced cutaneous pain and itch: the case of the missing nociceptor. *Prog. Brain Res.* 74, 331-335.
- Melzak, R. and Wall, P. 1965. Pain mechanisms: a new theory. *Science* 150, 971-979.
- Poggio, G. and Mountcastle, V. 1960. A study of the functional contributions of the lemniscal and spinothalamic systems to somatic sensibility: central nervous mechanisms in pain. *Bull. John Hopkins Hosp.* 106, 266-316.
- Shapiro, P. and Braun, C. 1987. Unilateral pruritus after a stroke. *Arch. Dermatol.* 123, 1527-30.
- Shelly, W. and Arthur, R. 1957. The neurohistology and neurophysiology of the itch sensation in man. *Arch. Dermatol.* 76, 296-321.
- Sullivan, M. and Drake, M. 1984. Unilateral pruritus and Nocardia brain abscess. *Neurology* 34, 828-829.
- Thole. 1912. Ueber Jucken und kitseln in beziehung zu schmerzgefühl. *Neurol. Centralbl.* 31, 610-.
- Torebjork, H. 1974. Afferent C units responding to mechanical, thermal, and chemical stimuli in human non-glabrous skin. *Acta. physiol. scand.* 92, 374-390.
- Torebjork, H, and Ochoa, J. 1981. Pain and itch from C fibre stimulation. *Neurosci. Abst.* 7, 228-235.
- Tuckett, R. 1982. Itch evoked by electrical stimulation of the skin. *J. Invest. Dermatol.* 79, 368-373.
- Tuckett, R. and Wei, J. 1987a. Response to an itch-producing substance in cat. I. Cutaneous receptor populations with myelinated axons. *Brain Res.* 413, 87-94.

Tuckett, R. and Wei, J. 1987b. Response to an itch-producing substance in cat.
II. Cutaneous receptor populations with unmyelinated axons. *Brain Res.*
413, 95-103.

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