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Itch is an unpleasant sensory experience

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The International Association for the Study of Pain (IASP) defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. In a note attached to that definition (http://www.iasp-pain.org.terms-p.html#Pain), the IASP further states that "unpleasant, abnormal experiences (dysesthesias) may also be pain but are not necessarily so because, subjectively, they may not have the usual sensory qualities of pain." While everyone would agree that itch does not have the sensory qualities of pain, for those patients with intense, unrelenting itch the sensory and emotional experiences can be as unpleasant as pain. Clinical colleagues have told me anecdotal stories of patients with itch due to spinal intrathecal opioid administration who indicated a desire to stop the opioid administration because they would rather experience the pain than the itch.

It is difficult to define the number of patients whose quality of life is adversely impacted by uncontrolled itch. However, as suggested in Table 1 by a partial list of dermatologic and systemic diseases that are associated with itch, it is likely that the number is quite high. Because itch does cause unpleasant sensory and emotional experiences in a large number of humans, it seems appropriate to focus more attention on efforts to understand the physiology of itch. In addition, because most current treatments for itch are quite inadequate, it also seems appropriate to attempt to develop better treatment modalities for patients suffering with intense, unrelenting itch. This topic is also of potential interest to the anesthesiology community because of opioid-induced itch and the apparent similarities between the neurophysiology of itch and of pain [1].

In the last few years, two important advances have been made in our ability to study and understand itch. The first was the development of an animal model of itch by a group of Japanese scientists. Dr. Yasushi Kuraishi of the Department of Applied Pharmacology, Toyama Medical and Pharmaceutical University, is leading a research team that has developed and validated a mouse model that can be used to study scratching behavior associated with itch [2]. The absence of an animal model for itch was a major barrier to our ability to study and understand the sensation of itch. (For those readers more interested in pain than in itch, Dr. Kuraishi has recently reported a mouse model that replicates many aspects of postherpetic pain states [3]).

A comparison of the initial report by Kuraishi and colleagues and subsequent reports reveals an important issue for investigators interested in the study of itch: not all strains of mice are equally sensitive to itch-producing substances. In their 1995 paper, Kuraishi and colleagues reported that the ddY mouse strain did not scratch when doses of up to 300 μg of histamine were injected into the skin on their backs. However, in 1999 another Japanese research group reported that histamine, at doses as low as 2 μg, produced robust scratching in ICR mice [4]. The Kuraishi group subsequently reported that although serotonin could elicit scratching behavior in both ddY and ICR mice, histamine only caused scratching in ICR mice [5]. This strain-specific sensitivity has subsequently been consfirmed by other investigators [6]. The selective sensitivity of mouse strains to histamine is similar to the strain differences in response to various types of pain stimuli reported by Mogul [7]. Mogul and colleagues reported at the International Association for the Study of Pain Meeting in San Diego in August 2002 that there is a genetic correlation between histamine-induced scratching and aspects of

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Table 1. Examples of dermatologic and systemic conditions associated with itch

Dermatologic	Systemic
Atopic dermatitis	Chronic renal failure
Contact dermatitis	Primary biliary cirrhosis
Xerosis	Hepatic cholestasis
Psoriasis	Polycythemia vera
Bullous diseases	Mastocytosis
Fungal infections	Hodgkin's disease
Urticaria	AIDS
Lichen simplex chronicus	Hyper- and hypothyroidism
Dermatoses of pregnancy	Carcinoid syndrome
Superficial parasitosis	Malignant neoplasms

nociception, suggesting that common genes underlie variability in sensitivity to those phenomena.

A particularly interesting aspect of the mouse model developed by Kuraishi and colleagues is the scratching behavior induced by exposure to mosquito bites [8]. Just as in humans, ICR mice must be sensitized to mosquito bites over a period of several days before they begin to scratch a new bite. However, also just as in humans, once sensitized, they scratch a new bite even if their sensitizing exposure occurred weeks before. This normal biological behavior provides an important control in support of the mouse model as one that adequately reflects itch-induced scratching behavior. As with animal models of pain, although we do not know for certain that the human and animal sensations are the same, similar behavior supports the validity of the animal model.

Dr. Kuraishi and colleagues have not only provided an extremely valuable animal model of itch, they have also begun to use the model to better understand factors that cause the sensation of itch. As an example, they demonstrated that antihistamines can block scratching induced by histamine but not by mosquito bites [8]. This supports the widely held impression that clinically relevant itch can be divided into two broad categories, histamine-induced and non-histamine-induced itch.

The presence of an animal model in which itch can be studied is crucial to the research community's ability to make progress both in our understanding of the physiology of itch and in the development of strategies to treat clinically relevant itch. The importance of the Kuraishi model is clear, and the research community is already using it in an effort to develop treatments for itch. As an example, a recent report in the *European Journal of Pharmacology* describes the effects of an opioid developed by Toray Industries on itching behavior in the mouse model that was developed by Dr. Kuraishi [9].

A second recent development in our understanding of itch is also likely to enhance opportunities to study and reach a better understanding of the sensation of itch. As summarized by McMahon and Koltzenburg in 1994 [1], there was continuing confusion about how information about the sensation of itch was transmitted from the skin, mucous membranes, and conjunctiva to the central nervous system. Older studies had revealed some details; for example, it could be assumed that itch was communicated from the periphery by small unmyelinated primary afferents because differential nerve block of myelinated fibers did not abolish histamine-induced itching [10]. However, that does not tell us much about the type of fibers or the selectivity of those fibers for itch. One hypothesis was that primary afferents could convey both pain and itch, and that the differences were signaled by differences in the number of action potentials that each stimulus initiated. However, experiments in humans using transcutaneous or intraneural electrical stimulation showed that the number or pattern of action potentials in primary afferents did not change the sensation from pain to itch or from itch to pain [11]. A recent report has provided additional information about the primary afferents that carry information about itch. Using a new computer-controlled method to record from unmyelinated nerve fibers (C fibers) in humans, investigators have identified two classes of slowly conducting fibers that are sensitive to histamine in a way that correlates with human reports of itch following similar histamine application [12]. The number of fibers is quite small and they are all insensitive to mechanical stimulation of their peripheral receptive fields. Some of the fibers respond to non-noxious thermal stimuli and to intracutaneous injection of capsaicin, suggesting that, as with pain fibers, some itch fibers may be polymodal in their ability to respond to several forms of stimulation. For the reader more interested in pain, it is noteworthy that itch is communicated by C fibers, a class of primary afferent that is central to communication of pain information.

That study has provided us with important information about the likely nature of primary afferents that convey information about itch. Although some fibers were weakly activated by histamine, the time course of activation did not match the timing of its sensations in the test subjects. The degree and timing of activation of the histamine-sensitive fibers suggest that there is a population of unmyelinated fibers with a primary responsibility for conveying histamine-induced itch. It will be very interesting to determine whether those same fibers convey itch sensations produced by other itch-producing chemicals.

A second recent finding about the neurophysiology of itch gives insights into how information about itch is processed by spinal sensory neurons that receive input from primary afferents. The idea that itch and pain are processed by the same second-order neurons can be challenged by the observation that opioids do not block

itch. If itch and pain were processed by the same spinal neurons, we would expect that opioids, especially spinally administered opioids, could inhibit both pain and itch. It now appears that information about itch is conveyed to a small population of spinal dorsal horn neurons that are selectively excited by histamine stimulation of their peripheral receptive fields [13]. This population of cells is associated with the spinothalamic tract and has identified thalamic projections. The report by Andrew and Craig [13] provides evidence of the neurophysiologic pathway that could be responsible for the unique sensation of itch, at least itch produced by histamine. As with the selective primary afferents, it will be interesting to see if other itch-producing substances use those pathways as well.

In addition to specific spinal sensory neurons, it is likely that, as with pain, the sensation of itch is also processed by spinal multireceptive neurons. Most recently Jinks and Carstens have reported that spinal dorsal horn neurons can respond to peripheral receptive field stimulation by chemical substances that produce itch as well as other forms of noxious and non-noxious stimuli [14,15]. It appears, therefore, that as with the sensation of pain, there are spinal mechanisms that employ second-order neurons sensitive to multiple forms of stimulation as well as neurons that are tuned exclusively to itch stimuli. As with pain, a significant amount of work will be required before we fully understand the role that each type of neuron plays.

Understanding the normal physiology of itch may also provide insights into "abnormal" itch sensations. There have been several reports in the literature of itch sensations following CNS trauma [16,17] that would suggest that, as with thalamic pain following stroke, it is possible that some patients could develop itch as a result of CNS trauma. An additional aspect of this kind of itch, with which the anesthesiology community is quite familiar, is the itch seen following the spinal or epidural administration of opioids. That itch appears to be the result of opioid effects on CNS processing of information. One possible explanation is that the multireceptive neurons in the spinal cord receiving information from both itch and pain fibers are capable of being confused in the same way that pain neurons in the spinal cord are confused when the pain signal from myocardial infarction is sent to the spinal cord. During a myocardial infarction the location of the sensory experience is confused, typically resulting in individuals associating pain in their left arm or shoulder with a heart attack. A similar kind of miscommunication may result in spinal dorsal horn multireceptive neurons receiving both pain and itch input. The spinal opioid may blunt the pain message in a way that causes the system to assume that an itch message is being signaled. Much work would need to be done to test such a hypothesis.

Itch is an unpleasant sensory experience. For many of us it is an experience that is relatively short-lived and is usually only associated with an insect bite or a mild exposure to a substance that produces some form of contact dermatitis. However, for others, itch becomes a much greater problem. When we consider the modalities available for the treatment of itch, we quickly recognize that with the exception of steroids, none of the currently available treatments are very efficacious. Antihistamines tend not to work very well and are more likely to produce sedation than to block the sensation of itch. In addition, their continual topical application may cause a contact dermatitis that itself contributes to the clinical problem. Counter-irritants can effectively block the sensation of itch, perhaps by confusing or disrupting interpretation of the itch message when it reaches second-order or higher neurons. It has been known for a long time that the sensation of pain itself can stop itch. However, the counter-irritants can cause skin problems resulting in itch as well. Steroid application, although efficacious in blocking itch, has two obvious problems associated with it. The first is that the onset of the effect tends to be fairly long, so that immediate cessation of the sensation of itch does not occur with steroids. The second and more significant problem is the side effect profile resulting from steroid administration.

A technique of interest to the anesthesiology community is the use of local anesthetics for the control of itch. A recent pilot study demonstrated that the application of EMLA is an effective itch control treatment for postburn pruritus in pediatric patients [18]. The technique is still experimental and has pharmacokinetic and toxicity issues associated with it.

Recognizing that individuals have significant problems with itch and that there are inadequate treatment modalities at present for those individuals, the research community is provided with a unique opportunity to begin to utilize new information about the sensation of itch in an effort to provide better clinical care.

Similarities between the sensation of itch and the sensation of pain, especially in the types of primary afferents and second-order neurons that communicate information, suggest that much that has been learned and will be learned about the signaling of pain may also contribute importantly to our understanding of the sensation of itch. In particular, the increased interest in the neurochemistry of the sensory transduction of noxious stimuli promises to yield important information about unpleasant sensory experiences. Thirty years ago the spinal cord was a focus of research for pain specialists. As that focus moves to include peripheral sites of action, we are likely to uncover information that will assist in the development of better ways to treat itch as well as pain.

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