Itch is an irritative sensation provoking a scratch response that provides at least temporary relief. Itch may protect the skin against potentially harmful or irritating agents. It normally originates in skin and transitional tissues (e.g., conjunctiva, anal mucosa). It can also arise from central or peripheral neurological lesions, as when it follows a stroke or occurs with a peripheral neuropathy.
**ITCH**

- **Acute itch** is the sensation experienced when itch-inducing stimuli ('pruritogens') contact the skin, and usually is relieved by pain (including scratch) in the surrounding area.
- **Chronic itch** is the persistent sensation that results from various causes in which pain does not relieve itch.

**Peripheral Biology of Acute Itch**

- **Pruritogens** stimulate skin receptors and activate the peripheral pathway of itch.

  - This provokes a signaling cascade and action potentials in at least two types of C fibers.

  - These nerve fibers conduct the action potential to the dorsal horn of the spinal cord.

**ITCH**

- Itch may be localized or widespread, commonly outlasts any inciting mechanical stimulus, and is sometimes accompanied by skin changes.
- The scratch phenomenon, which may be painful in other instances, may paradoxically be pleasurable in the setting of itch.
- Psychologic aspects (e.g., induction by thought of irritating stimuli) may be important.

**ITCH**

- Two itch-sensitive afferent pathways exist:
  - a histamine-stimulated pathway that uses **mechanically insensitive C fibers**
  - A cowhage-stimulated pathway primarily involving **polymodal nociceptive C fibers** and A-delta thinly myelinated fibers
Cowhage is a legume that grows wild in the tropics.

It has been used since ancient times to treat Parkinson's disease.

Before the commercial synthesis of levodopa from vanillin, cowhage was investigated as a potential source of it.

The barbed spicules detach easily from the shell of the fruiting pods ("itching powder").

**Encoding of itch in afferent pathways**

- **Specificity theory**: modality-specific receptors and peripheral nerves that constitute a "labeled line" from the skin to the brain.

- **Pattern theory**: somatic sensations including itch are generated by receptors and peripheral nerves that are not specific to the stimulus and that deliver a pattern of signals which is modulated and decoded centrally.

**Evidence for a labeled line for itch**

- Microneurography

- Spinal cord electrophysiology mapping

- Genetic modification techniques.
Evidence for a labeled line for itch

Microneurography

- A histamine-stimulated itch pathway is present, consisting of mechanically insensitive C-fibers that respond with a temporal profile consistent with itch as rated by human subjects.
- These fibers have slowly conducting thin axons with large innervation territories on the skin

Schmelz et al., 1997

Spinal cord electrophysiology mapping:

- A complementary histamine-stimulated central pathway for itch consisting of lamina I spinothalamic tract neurons has been mapped in the spinal cord of cats.
- These neurons have distinct conduction velocities and thalamic projections, differentiating them from pain or temperature projections.

Andrew and Craig, 2001

Genetic modification:

- A subset of dorsal root ganglion neurons release GRP and their receptors (GRPR) are located in lamina I of the cord. When GRPR is genetically knocked out or antagonized pharmacologically, scratching is inhibited.
- A set of MrgrpA3+ (orphan GPCRs) neurons exists in the dorsal root ganglion. They innervate the epidermis and respond to multiple pruritogens. Ablation of these neurons reduces itch behavior; their excitation, regardless of stimulus (even when an algogen), evokes scratch.

Sun and Chen, 2007; Han et al

Itch Mechanisms

- The mechanism probably include both labeled lines and pattern decoding.
- Pain and itch labeled lines interconnect through excitatory and inhibitory interneurons that modulate the activity of each other in the cord.
- If pain and itch fibers are activated together, the sensation of pain alone may emerge because inhibition from interneurons and central descending pathways masks itch sensation.
- In patients with chronic itch, failed crosstalk of these lines creates ‘pro-pain’ and ‘pro-itch’ pathways irrespective of the stimulus
Neurotransmitters such as calcitonin gene-related peptide, gastrin-releasing peptide (GRP), substance P, and glutamate are implicated in first itch synapse. Histamine and cowhage primary afferents do not activate or converge on same secondary neuron, suggesting mutually exclusive dual projections to the spinothalamic tract and descending tract.

At least two separate itch pathways (histamine and cowhage) are involved in a sensation experienced as relatively similar by human subjects. At the molecular level, the division and integration between itch pathways is even more complex. Each pruritogen activates G-protein–coupled receptors (GPCRs) and downstream messengers that interact with other itch- and pain-signaling systems. The dorsal horn synapse likely represents the site of modulation by parallel pain-processing neurons, other inputs, and descending pathways from the brain.

**The Dorsal Horns and Itch**

- Some sensory neurons contain transient receptor potential vanilloid receptor (TRPV1)
- These neurons are activated by a variety of pain, hot and cold, and chemical stimuli
- A neuropeptide—natriuretic polypeptide B (Nppb)—is present in only some of these TRPV1 neurons
- Transgenic mice not expressing Nppb lose the scratch response to an itch-inducing stimulus
- Intrathecal injection of Nppb in Nppb-knockout mice leads to scratch
- Destruction of Nppb receptor-expressing cells blocks itch responses

(Mishra & Hoon, 2013)
Scratching an Itch

Spinal mechanisms help us to stop scratching

- Scratching activates nociceptors. These release glutamate from their intraspinal terminals to excite inhibitory interneurons that suppress itch-signaling neurons
- In mice, intraspinal release of glycine and GABA inhibits the itch-related firing of dorsal horn neurons. In mice, inhibitory interneurons (Bhlhb5 neurons) inhibit itch within the dorsal horn—loss of these neurons leads to persistent itch
- Scratch activates mechanoreceptors and myelinated A fibers, exciting inhibitory neuronal spinal circuits

Itch

- Itch and pain are distinct sensations that interact.
- The clearest differentiation is the effector limb of both—withdrawal for pain vs. scratch for itch
- The interaction between itch and pain is generally antagonistic, with pain dominant over itch
- This is most evident when noxious counter-stimuli on the skin suppress itch sensation, and when opioids inhibit pain but cause itch. The mechanism is probably central

Central Suppression of Itch

Itch suppression by pain is probably central:

- Noxious counter-stimuli may be several centimeters or more away from the itch source, suggesting that different afferent fibers are activated and their signals integrated at the spinal cord level
- Secondary hyperalgesia induced by various noxious stimuli in a skin patch of several centimeters abolishes cowhage or histamine-induced itch in that area, consistent with a central excitatory state that activates pain and blocks itch
But, the relation between pain and itch is not always antagonistic. Herpes zoster can produce:

- chronic pain
- chronic itch, or
- pain plus itch concomitantly
**ITCH & PAIN**

• Many central causes of itch (e.g., spinal cavernous hemangioma) are associated with no reduction in pain despite prominent itch
• Hyperkinesis, in which itch is *augmented* by pain, also implicates a reversal of the traditional model.

**Mechanisms of Chronic Itch**

• **Peripheral sensitization**: decreased activation threshold and increased basal activity of itch-related receptors and nerve fibers (Potenzieri & Undem, 2012).
• **Central sensitization**: neuroplasticity occurs in the spinal cord and brain such that non-pruritic stimuli are perceived as, or augment, itch.

**Causes of Chronic Itch**

<table>
<thead>
<tr>
<th>Dermatologic</th>
<th>Atopic dermatitis</th>
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<tbody>
<tr>
<td></td>
<td>Bullous pemphigoid</td>
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<tr>
<td></td>
<td>Psoriasis</td>
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<tr>
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<td>Urticaria</td>
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<td>Pruritus ani</td>
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<tr>
<th>Systemic</th>
<th>Cholestasis</th>
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<tr>
<td></td>
<td>Uremia</td>
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<tr>
<td></td>
<td>Hodgkin’s lymphoma and other malignancy</td>
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<tr>
<td></td>
<td>Polycythemia vera rubra</td>
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<td></td>
<td>Graves’ disease</td>
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<tr>
<td></td>
<td>Iron-deficiency anemia</td>
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<tr>
<td></td>
<td>Diabetes mellitus</td>
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<tr>
<th>Infectious</th>
<th>HIV infection</th>
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<tbody>
<tr>
<td></td>
<td>Parasitosis (including scabies, trichinosis, ascarisis, and hookworm)</td>
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<tr>
<td></td>
<td>Varicella</td>
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<td>Tinea pedis</td>
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</table>

**Causes of Chronic Itch (continued)**

<table>
<thead>
<tr>
<th>Medication-related</th>
<th>Mu-receptor opioids (histamine related)</th>
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<tbody>
<tr>
<td></td>
<td>Chloroquine (? mechanism)</td>
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</table>

**Neuropathic**

See separate slides

**Psychiatric**

Depression
Delusional parasitosis
Neurotic excoriations

**Other**

Pregnancy
Itch in the elderly
Selected Neuropathic Itch Disorders

LOCALIZATION

Peripheral
(receptors, nerves, roots)
- Itch with polyneuropathy
- Postherpetic itch
- Brachioradial pruritus
- Notalgia paresthetica
- Trigeminal trophic syndrome
- Itch from keloids & burns

EXAMPLES


Post-herpetic itch

Fig. 1. A CT scan of the patient’s head shows a 4 x 6 cm right frontal skull defect, hyperdensity in the underlying brain, and extra-axial fluid. No other lesions were present. The defect was self-induced by scratching an area affected by postherpetic itch after shingles. The scratching was painless.

Fig. 2. POP-95 transillumination of nerve fibers in pouch skin biopsies. The epidermis is over the top and the superficial dermis is below. Representative labeled vertical sections from (A) a normal area of the patient’s scalp showing some contructing up into the epidermis, and (B) genistein-stained skin are shown.
Weeks after zoster ophthalmicus, patient developed trigeminal trophic syndrome (triad of dysesthesias, anesthesia, and ulceration).

Trigeminal Trophic Syndrome

- **Ulceration** of face, especially of the ala nasi, occurs in a territory of the trigeminal nerve that is anesthetic from a surgical or other process involving CN V or its central sensory connections.
- Usually a history of paresthesias and self-induced trauma to the area.
- **Causes** include surgical trigeminal ablation, injection of gasserian ganglion, brainstem vascular lesions, acoustic neuroma, postencephalitic parkinsonism, and syringobulbia.
- **Treatment** unhelpful. Try protective devices. Excision.

Brachioradial Pruritus

- Neuropathic itch on dorsolateral surface of upper arm or forearm.
- Has been related to exposure to sunlight.
- Exam is normal apart from a few scratch marks.
- **EMG/NCS normal**
- Skin biopsy: reduced skin innervation.
- Helped by local ice and certain AEDs.
Notalgia Paresthetica

- Itch, usually left-sided, subscapular.
- May be accompanied by pain, paresthesias, or hyperesthesia.
- Hyperpigmented skin patch in the affected area.
- Due to spinal nerve impingement.
- Treatment: LA, steroid cream, capsaicin, Botox.

"The posterior rami of spinal nerves arising in T2 through T6 are unique in that they pursue a right-angle course through the multifidus spinae muscle, and this particular circumstance may predispose them to harm from otherwise innocuous insults of a varied nature."

(Plete and Massey, 1970)

Fig 1. Patient 20 with the characteristic hyperpigmented patch on her back covering dermatomes T6-8.

### Selected Neuropathic Itch Disorders

<table>
<thead>
<tr>
<th>LOCALIZATION</th>
<th>EXAMPLES</th>
</tr>
</thead>
</table>
| Spinal cord  | * Transverse myelitis  
* Neoplasms e.g. NFs  
* Cavernous hemangiomas  
* Other vascular malformations  
* Post-traumatic B-S syndrome  
* Post-herpetic? |

May be segmentally unrelated. \( ? \) Relates to irritation of C fibers, loss of inhibitory neurons, etc.

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### Spinal Cavernous Hemangioma

Central neuropathic itch as the presenting symptom of an intramedullary cavernous hemangioma.

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### Selected Neuropathic Itch Disorders

<table>
<thead>
<tr>
<th>LOCALIZATION</th>
<th>EXAMPLES</th>
</tr>
</thead>
</table>
| Brain        | * Subcortical/brainstem stroke  
* Demyelination  
* Neoplasms or abscess  
* Paraneoplastic disorders  
* Creutzfeldt-Jakob disease |

Usually contralateral but precise location varies. Occurs in absence of pain and with variable motor and sensory involvement. Unrelated to seizures.
• Exact mechanism unknown (? spontaneous firing of thalamocortical neurons or loss of inhibitory neurons)
• Hemilateral pruritus, then generalizing, is reported as a paraneoplastic consequence of Ca prostate. Antigenic target unclear.


TREATMENT OF NEUROPATHIC ITCH

• Behavioral interventions (e.g., skin protection). Cold packs provide temporary relief.

• Antihistamines, steroids, and most analgesics are usually ineffective.

• Stepwise trials
  • topical agents (e.g., capsaicin),
  • antiepileptic drugs (e.g., gabapentin),
  • thalidomide
  • injection of other agents (e.g., botulinum A toxin),
  • neurostimulation techniques (e.g., cutaneous field stimulation).

Botox and Itch

Botulinum toxin type A for neuropathic itch in a patient with notalgia paresthetica.

Wallengren and Bartholom (2016).
Cutaneous field stimulation


Figure 1. Cutaneous field stimulation (CFS) device consisting of a flexible electrode rubber plate (8 x 8 cm) to be fastened on the itchy patch or the area to be tested, a flat reference electrode (5 x 5 cm) to be placed on the same part of the body, and a stimulator (9 V battery). The pulse amplitude is adjustable from 0 to 18 A to control stimulus intensity.

Stepwise approach to treatment of neuropathic pruritus. Antihistamines usually ineffective but occasionally do help in treating pruritus and have a benign side-effect profile. However, there are no RCTs to support their use.

My time is up......

Thank you!