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Gil Yosipovitch *Editors*

Pharmacology of Itch

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Pharmacology of Itch

 Springer

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Preface

Itching is a remarkably common symptom of dermatologic and systemic diseases and seriously impacts a patient's quality of life. The good news is that there has been a tremendous upsurge in basic itch research over the past decade, galvanized by an influx of molecular biologists and neurophysiologists, and reflected in excellent cutting-edge reviews (e.g., Biró et al. 2007; Han et al. 2013; Roberson et al. 2013; Kremer et al. 2014) and timely books (Yosipovitch et al. 2004; Misery and Ständer 2010; Carstens and Akiyama 2014). The current volume in Springer's well-established Handbook series updates the findings of key researchers and summarizes progress in the itch field through 2014. The scope is comprehensive, encompassing pharmacological advances at all levels from receptor to clinic, and includes historical and veterinary aspects.

Itch is an enigmatic sensation quite distinct from pain and yet, in many ways, still connected. It is multimechanistic and unraveling its molecular underpinnings provides a real challenge for intrepid "itch doctors". The most recent research describes pruritoceptive messages being transmitted by at least two populations of spinal interneurons (natriuretic peptide receptor-A-expressing neurons followed by gastrin-releasing peptide receptor-expressing neurons) before being conveyed to the brain. These academic breakthroughs may prompt the launch of much needed, new antipruritic drugs into the dermatology field.

We wish to express our sincere thanks to the international group of experts who, collectively, have energized this venture with their insightful chapters, enthusiasm, and collegiality. A special nod of appreciation goes to Dr. James Barrett, Chair of the Department of Pharmacology and Physiology, Drexel University College of Medicine in Philadelphia, and champion of all things pharmacological, for initiating the project in his role as Board Member of the venerable Handbook series. Additionally, we acknowledge the professionalism of Susanne Dathe and Wilma McHugh from the supportive Springer team in bringing the volume to completion.

Philadelphia, PA

Alan Cowan
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References

- Biró T, Tóth BI, Marincsák R, Dobrosi N, Géczy T, Paus R (2007) TRP channels as novel players in the pathogenesis and therapy of itch. *Biochim Biophys Acta* 1772:1004–1021
- Carstens E, Akiyama T (eds) (2014) *Itch: mechanisms and treatment*. CRC, Boca Raton, FL
- Han L, Ma C, Liu Q, Weng H-J, Cui Y, Tang Z, Kim Y, Nie H, Qu L, Patel KN, Li Z, McNeil B, He S, Guan Y, Xiao B, LaMotte RH, Dong X (2013) A subpopulation of nociceptors specifically linked to itch. *Nature Neurosci* 16:174–182
- Kremer AE, Feramisco J, Reeh PW, Beuers U, Oude Elferink RPJ (2014) Receptors, cells and circuits involved in pruritus of systemic disorders. *Biochim Biophys Acta* 1842:869–892
- Misery L, Ständer S (eds) (2010) *Pruritus*. Springer, London, UK
- Roberson DP, Gudes S, Sprague JM, Patoski HA, Robson VK, Blasl F, Duan B, Oh SB, Bean BP, Ma Q, Binshtok AM, Woolf CJ (2013) Activity-dependent silencing reveals functionally distinct itch-generating sensory neurons. *Nature Neurosci* 16:910–918
- Yosipovitch G, Greaves MW, Fleischer AB, McGlone F (eds) (2004) *Itch: basic mechanisms and therapy*. Marcel Dekker, New York

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Historical Background of Itch

Elke Weisshaar, Wolfgang U. Eckart, and Jeffrey D. Bernhard

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Abstract

Itch as a disease, and especially as a symptom, was the object of medical and scientific curiosity for centuries. The reluctance of historians to focus on the history of itch relates to its nature as a subjective symptom. After all, how can historians have known what itch really felt like in previous centuries? Since the establishment of dermatology as an independent discipline of medicine in the middle of the nineteenth century, itch has become a subject of investigation in its

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own right. This chapter summarises research we conducted on the medical history of itch in ancient medicine and up through the twentieth century.

Keywords

Itch • Medical history • Prurigo • Pruritus

1 Introduction

Although itch is the most frequent symptom of the skin, surprisingly little is known about its medical history. This chapter offers a selection of information from ancient and more recent medical texts which document characteristic ways of dealing with itch as well as cultural aspects in the centuries leading up to the development of dermatology in Europe. This chapter is based on research described in three previous publications (Weisshaar et al. 2008, 2009a, b). Some of the contents of this chapter are direct quotations from those publications.

As recently as 1979, there were only a few paragraphs about itch in the second edition of Fitzpatrick's *Dermatology in General Medicine*, at that time the most important American textbook on dermatology. One might have expected an entire chapter about the most prominent symptom of skin diseases. It may be of some interest to know that when one of the authors (JDB) complained about this to Prof Fitzpatrick, he (TBF) immediately replied: 'OK, you write the chapter'. And so it came to pass (Bernhard 1987).

The exact evolutionary moment at which itch appeared is not known. Suffice it to say that experts believe that all vertebrates experience what we would call itch. This belief is based on the notion that where there is scratch there must be itch. The essential references on the history of dermatology include Pusey's *History of Dermatology* (published in 1933), *Classics in Clinical Dermatology* by Shelley and Crissey (published in 1953) and Crissey and Parish's *The Dermatology and Syphilology of the Nineteenth Century* (published in 1980). To a large extent, the history of itch is intertwined with the biographical history of dermatology, and for that reason, Shelley and Crissey's book is of particular interest, especially if one is sympathetic to the biographical approach to history. Table 1 lists some of the people and some of the major events in the history of itch in the twentieth century.

2 Starting from Scratch: A Note on Terminology

It is important to note that itch is usually not described in a straightforward manner in medical literature composed before the nineteenth century, but is usually found in the context of a localised disease with which it was associated, or sometimes in a chapter dealing specifically with dermatoses. Often one has to rely on textual searches, which makes terminology a major issue.

Table 1 A selection of important events and discoveries in the history of itch in the twentieth century

1922	Von Frey suggests that itch is transmitted by the same network of fibres as pain and may be induced by mechanical, thermal, chemical and thermal stimuli
1939	Bickford proposes that itch is transmitted by fine C fibres (as pain) and is attenuated by cooling
1948	Bishop describes the itch pathway from skin to excitation of sensory nerves and the transfer from spinal cord to thalamus and up to the cerebral cortex
1951	Graham and colleagues describe different sensations of itch and that pain can inhibit itch
1952	Cormia provides a detailed description of histamine-induced itch and a lower itch threshold for histamine in dermatitis or pruritic disorders
1954	Stephen Rothman includes a chapter on pruritus in his landmark book, “The Physiology and Biochemistry of the Skin” (Univ of Chicago Press)
1955,1957	Shelley and Arthur publish results of their studies on the neurophysiology of itch. They identify nerves terminating at the dermo-epidermal junction and determine that mucanian protease(s) is involved in the itch sensation induced by cowhage
1977	Gilchrest and colleagues discover that ultraviolet phototherapy is effective in the treatment of the pruritus of chronic kidney disease
1979	Fjellner and Hagermark publish their work on serotonin and itch
1979	Bernstein and Swift publish the first report on reducing intractable itch with naloxone
1991	Bergasa and Jones employ finger nail transducers to measure scratching and report their work on cholestatic itch and its attenuation with naloxone
1991	Handwerker and colleagues report results of their studies on nociceptors. These results become increasingly important for research on the electrophysiology of itch
1991	LaMotte’s group defines alloknesis and performs psychophysics on itch (Simone et al. 1991)
1997	Schmelz et al. identify a subset of nerves in humans that appears to be itch specific
1999	Bernhard and colleagues report the beneficial effect of systemic gabapentin for the treatment of brachioradial pruritus (Bueller et al. 1999)

In classical Latin, the term *pruritus* refers to itching, irritation or sexual excitement and is thus nearly interchangeable with *prurigo*, perhaps surprisingly given the modern understanding of ‘prurigo’ as describing the specific group of papular dermatoses to which the term is applied today. The Greek term *knêsmos* and related words denote itch, in an irritating or pleasurable sense (tickling). Metaphorical meanings reach from irritation to titillation. From an etymological point of view, *knêsmos* and related words are associated with the notion of scraping or scratching (Weisshaar et al. 2009b).

At the same time, the names of clinical conditions used today have often evolved from the terms employed by ancient authors. However, translations can create a misleading picture of ancient clinical observation. For example, a typical translation of a sentence from the *Corpus Hippocraticum* could run as follows: ‘Leprosy, pruritus, scabies, lichen, vitiligo and alopecia arise from phlegm and are mere blemishes rather than diseases’ (*Affections* 35) (Hippocrates 1988). A more detailed

analysis of the terms used in describing itch and related skin lesions through the centuries remains to be addressed in depth elsewhere. This applies especially to the terms pruritus and itch, which we have used synonymously (Bernhard 1994).

3 Medical Histories: Ancient Descriptions of Itch

Cures for itch were sought from the early days of mankind and are documented in sources even more ancient than those of Greek antiquity (e.g. Papyrus Ebers, dating from approximately 1550 BC). The earliest attempt at understanding the mechanisms underlying the complaint, however, was made in Greece around the fifth century BC. Hippocrates is generally seen as the first to introduce rational science into medicine. The *Corpus Hippocraticum* was compiled from the fifth century BC onwards and completed around the tenth century AD. Itch is mentioned in various places in the *Corpus Hippocraticum*. The development of a certain skin lesion is vividly described as follows: ‘Serous fluids appeared in the skin. Having coalesced, they became warm and caused itching. Then they erupted like burn blisters caused by fire, and they seemed to smoulder underneath the skin’ (*Epidemics* 2.1.1). Elsewhere it is noted that a symptom only seen in the Perinthian women suffering from ‘summer fevers’ was ‘roughness of the skin, furfuraceous, similar to the bites of gnats, not very itchy at all’ (*Epidemics* 2.3.1). An extensive case history is documented for a certain Andreas, who ‘before the rising of the Pleiades, displayed shivering, fever, and vomiting’, until among other symptoms, ‘efflorescences appeared on his skin, itching a little, but hot as if caused by fire’ (*Epidemics* 7.43) (Hippocrates 1994). In the *Aphorisms*, a collection of concise clinical observations probably intended for teaching, Hippocrates states that ‘extensive efflorescences’ generally cause less itching (*Aphorisms* 6.9).

In the competitive milieu of Ancient Greek medicine, it was a crucial skill for a doctor to predict the development of a disease. In this, itch served as a prognostic criterion, as can be read in the *Coan Prenotions* containing an extensive sketch of bedside prognostics. Itching of the body preceded by constipation in a patient with consumption is said to bode ill (*Coan Prenotions* 432). Likewise, ‘in all patients, itching will be followed by black stools, and vomiting of curdled masses’ (*Coan Prenotions* 626) [Weisshaar et al. 2008]. As the *Corpus Hippocraticum* is based on the concept of humoural pathology, itch was mostly explained from this point of view which also involved, besides the humours of the body, the influence of external factors such as the weather. Thus, in the *Humours*, it is said that ‘certain forms of leprosy (*leprê*) and joint pain are itchy when rain is impending’ (*Humours* 17).

The Alexandrians succeeded the Hippocratics in the Hellenistic period. The focus of their research shifted to investigative and experimental aspects. Aulus Cornelius Celsus, an encyclopaedist from the first century AD, observed what he calls *scabies*: ‘quite hard, with ruddy skin’ and causes pustules, some of which are ‘rather moist, others more dry’. They emit a serous discharge and proceed to exulcerate, causing itch. The rougher the skin, and the more intense the itch, the

more difficult it is to cure. ‘Therefore, the Greeks call this form of scabies “*agria*”, that is, “the savage one”’. For this disease, Celsus prescribed a salve ‘composed of sublimed zinc oxide, saffron, verdigris, white pepper and a preparation made from unripe grapes’ (Celsus 5.28.16a) (Weisshaar et al. 2009b). Aretaeus of Cappadocia, a Greek physician of the first or second century AD, connected generalised itch to icterus when he discussed two types of jaundice—one ‘light and saffron-coloured’ and the other ‘greyish and dark’—saying that in both, ‘the whole body is itchy’ (Aretaeus 1958).

In the second century AD, Galen of Pergamon developed a synthesis of the medical knowledge of his time and thus became a crucial figure in medical research and practice until the Renaissance and even later times. In his work, *On the Preservation of Health*, Galen explained how to assess a patient’s medical history as an important part for differential diagnosis. Among other things, ‘it is essential to determine whether the patient is one of those who by nature tend to accumulate unhealthy humours. You can find this out by asking him whether he has suffered from a predisposition to scabies (*psôrôdês diathesis*), leprosy (*leprôdês*), whiteness (*alphôdês*) or itching (*knêsmôdês*), or from erysipelas, herpes, the elephant disease (*elephas*), the snake disease (*ophiasis*), the fox disease (*alôpekiasis*), many blisters, ulcerous efflorescences, night rash or any one at all of the symptoms that arise from, or are worsened by, an unbalanced state of the humours’ (Galen *On the Preservation of Health* 4.4.5) (Galen 1823).

4 The Byzantine Period

The Byzantine period (fifth to fifteenth century AD) is marked by a tendency to compile ancient sources. Alexander of Tralles, writing in the sixth century AD, recommended a remedy for scabby and serous conditions of the head: ‘Crush rue and alum in honey and use them to anoint the shaven head. When the skin has peeled off, boiled leaves of the olive tree should be applied with honey as a poultice’ (Alexander Trallianus *Therapeutics* 1.6). In a fascinating testimony to the broadness with which terms like scabies (*psôra*) were used before systematisation in dermatology, Alexander states that ‘bladder scabies’ (*psôriasis kysteôs*) is present if ‘furfuraceous sediment appears in the urine fluid. This must be distinguished from that carried in the blood vessels’ which arises from excess heat in the body. ‘When the urine is of thin consistency and very acrid, conclude that the furfuraceous sediment has come from the blood vessels. But when the urine is of a thick consistency, conclude that it is bladder scabies’ (Alexander Trallianus 11.5).

In terms of leprosy (*lepra*) and scabies (*psôra*), Paul of Aegina from the seventh century AD states that ‘these diseases have in common the rough appearance together with itching and scratching of the body, which originates from a proneness to black bile’ (Paulus Aegineta 4.2.1). In comparison with leprosy (*lepra*), scabies (*psôra*) is said to be ‘more superficial, adopting various forms, and rendering furfuraceous particles. It is necessary to resort to phlebotomy, if the patient seems strong enough; if not, cleansing should nevertheless be achieved by purging with

substances that expel black bile'. Later, he adds an extensive description of drugs for external application (Paulus Aegineta 4.2.3–5), listing plants, other organic ingredients, metallic components and also some ingredients less familiar for the modern reader, such as goat droppings, which were not uncommon in ancient pharmacopoeias.

Both Paul and Theophanes Nonnos report that 'the itch that comes about in old age' cannot be cured but can be alleviated by a number of procedures and remedies including phlebotomy, baths and salves (Paulus Aegineta 4.4.2–3; Theophanes Nonnos 237) (Paulus Aegineta 1921; Theophanes Nonnus 1794). As these chapters are devoted specifically to itch (*knêsmos*), they may be viewed as an early attempt to define pruritus as a disease in its own right.

5 Medieval Medicine

After the end of the Byzantine empire, ancient medical knowledge continued to be transmitted in the Muslim world and in the Latin West. The tradition of handbooks in Arabic medicine reached its climax in the tenth and eleventh century AD. The physician, Haly Abbas, owes much to the characteristic blend of Byzantine tradition with Persian influences. Scabies and itching arise from 'a mixture of salty phlegm with bilious blood'. If this mixture is 'thin and fine', it soon brings about an itch to promote healing, but if it is coarse, it will 'cause persistent dry itching and scabies'. Especially 'those who do not take warm baths and on whose skin soot accumulates' suffer from itching. Also, 'itch in old age often arises from the weakness of the skin and because salty liquids come about in their bodies'. Haly Abbas adds that 'the characteristic of scabies are intense itch and small nodules, which are first reddened, then suppuration occurs. Scabies is found between the patients' fingers, on their hands, elbows, and on the coccyx' (Weisshaar et al. 2009b).

Another influential author is Avicenna whose medical knowledge is contained in *Kitāb al-Qānūn fi at-Tibb*. He assumes that salty water causes itch and scabies, arguing that it dehydrates the body, draining it of all vigour. First, its effect is cleansing, but later on, it leads to constipation, as it is dry by nature. It spoils the blood and produces itch and scabies. Furthermore, southern winds can promote the curing of itch, for 'they relax the body and open the pores, stimulating the humours and expelling them', and at the same time, however, 'they cause paucity of spirit, festering of wounds, and recidivism. They drain the body of all vigour, promoting ulcers, gout, headaches, dizziness and itching' (Avicenna 1562).

The *Lorscher Arzneibuch* (Lorsch Book of Remedies) was written in Latin in the monastery of Lorsch around 795 AD and is the earliest of its kind in Germany. It documents the role of monasteries in the transmission of medical knowledge. For example, instructions for the preparation and application of drugs for external and internal use in itch and scabies are given: an ointment for 'itching and scabby scalp' based on stinging nettle seeds is recommended, next to the suggestion of inexpensive local medicinal plants (Stoll 1992). Hildegard of Bingen (twelfth century AD),