# Old Scratch

It is ironic that one of the Devil's lesser-known aliases, dating from the 18th century, should be "Old Scratch" (an "Old Nick" name, one might say, from the Old Norse *skratte* for goblin or monster), for surely itching is one of the most diabolical of symptoms, whether complicating cholestatic liver disease, azotemia, dermatosis, malignant reticulosis, or any of the other pruriginous disorders.[1–3] To start from scratch, so to speak—borrowing an idiom from horse racing in England long ago, when the starting line was scratched on the ground—"itch" is variously defined as an unpleasant or uneasy sensation of irritation in the skin that provokes the desire to scratch or is relieved by scratching or rubbing. The noun "itch" was first recorded in the 9th century CE (followed by its verb a couple of hundred years later) and was derived from the Old English *gicce* (*gyccae* or *gicche*), which also referred to a contagious disease (probably scabies) in which the skin is covered with vesicles and pustules, and there is severe itching.[4] In the 14th to 15th centuries, the letter before the *i* was scratched and the form *gitch* was contracted to the familiar itch that we know today. *Pruritus*, which also refers to itching of the skin without a visible eruption, is more modern and dates only from the 15th century, from the French verb *prurire* (to itch). Despite such longevity, it is still frequently misspelled as *pruritis* not only by medical students and residents, erroneously after other words ending in "-itis" (for *inflammation*), but alas in current publications too.[5] The idea, often expressed contemptuously, that itch also refers to an uneasy or restless desire, a hankering, or a restive propensity to do something is reflected in the metaphoric itching of various bodily parts—the feet, the lips, and the palms of the hands—which purportedly indicates a craving for travel, a kiss, or money, respectively. Since the 17th century, *itch* has also been considered synonymous with "romantic" desire, as portrayed with tantalizing innuendo in the classic Billy Wilder 1955 Marilyn Monroe comedy movie *The Seven Year Itch*, which was based on George Axelrod's play.

Throughout the ages, itching was commonplace because of the widespread prevalence of lice and scabies, as Fynes Moryson observed during his protracted travels in 17th-century Europe. In the journal of his journeys,[6] he related that "The Italians . . . for the most part are troubled with an itch, witnesse the frequent cry in their streets.. . ." Nonetheless, as long ago as the 2nd century CE itching was recognized as a symptom that accompanies jaundice, as reported by Aretæus the Cappadocian[7] in the days of the Roman Empire, while from the 17th century onward, itching associated with jaundice featured regularly in the classic texts of general medicine[8–11] as well as in books devoted solely to liver disease.[12–14] The preoccupation of the authors of these historic texts was not the pruritus of their yellow patients but the yellowness itself. How to distinguish true from spurious jaundice, what causes jaundice, what is its natural history and prognosis, what factors predict the outcome, and how to treat it were the burning questions of those bygone days.[8–14] Murchison[14] described in detail how to distinguish the various conditions that may be mistaken for jaundice, like the yellow-green countenance of the severely anemic state known then as chlorosis, the grayish-yellow of the cancer patient, the dusky yellow of the chronic malaria sufferer, the weather-beaten outdoors complexion, the bronzing of Addison's disease and what he referred to as the "so-called jaundice of the newborn" that was considered to be a blood disorder because the urine was not dark. Murchison cautioned physicians who enter the public services that jaundice may be feigned by soldiers and sailors desirous of obtaining a discharge by painting the skin with an infusion of saffron, turmeric, rhubarb, broom flowers, or soot, and by coloring the urine by ingesting rhubarb or santonin extracted from the shrubby wormwood *Artemisia cina*.

Among the clinical features that were thought to be characteristic of jaundice, such as heat about the nostrils,[7,9] bitter taste,[7–9,14] maldigestion,[12,14] and bradycardia,[11,13,14] only the "jaundiced eye" of poets and philosophers, ". . . which sees all objects clouded with its sickly hue," was regarded with skepticism.[15] Xanthopsia (seeing yellow) was considered to be such a rare symptom in jaundice[12] that the term should be regarded as "poetical license."[16] Vestiges of the ancient humoral theory of disease (popularized by Galen and his followers) as applied to the cause of jaundice lingered on into the 17th and 18th centuries,[8,9] such that some cases of jaundice were still attributed to a quantitative or qualitative excess of yellow bile or black bile decanted and distributed by the liver to the gallbladder or spleen, respectively. Increasingly, however, jaundice was blamed either on biliary obstruction with regurgitation of bile into the bloodstream or on bile constituents that find their way into the blood from the liver itself because of the failure of the liver to secrete, or


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because the liver was unable to separate bile components from the blood.[11–14] The reported prevalence of pruritus in jaundice varied with the experience of the individual author (Frerichs noted only 20%[13]) and with the cause, allegedly being more common in obstructive jaundice than in hepatogenous jaundice,[8,11,14] to which a more modern survey bears witness.[17] Out of 1262 jaundiced patients, 11% had pruritus, but this varied from 9% of nonobstructive cases and 16% in benign biliary obstruction, to as high as 45% in those with obstruction caused by malignancy.[17] Parenthetically it is instructive to reflect that even Osler was confused about the nature of cholestasis, since at the beginning of the 20th century he distinguished jaundice due to biliary obstruction (which he called "hepatogenous") from what he termed "toxemic" jaundice that he assumed to stem from a toxic state of the blood or liver cells, and which he alternatively labeled "hematogenous" jaundice.[11] The insightful observation, in the days before clinical chemistry was available, that pruritus preceded the outward appearance of jaundice in some cases[12–14] is recognized now as a common phenomenon in patients with various forms of biliary cirrhosis,[18] primary biliary cirrhosis in particular,[19] and in other liver disorders.[17] This anicteric presentation of hepatobiliary pruritus suggested that components of bile other than pigment could be the cause of the itching,[12] for which biliary bile acids (salts) were prime candidates[13,16,20] almost since their discovery in the early years of the 19th century.[21] Aretæus himself foresaw this possibility when describing cases of jaundice due to both yellow bile and black bile, for he wrote, "In both cases the whole body is itchy; heat at the nostrils, small indeed, but pungent: the bilious particles are prickly."[7]

Experts on the physiology of itching say that it has nothing in common with the sensations of "prickling" (*i.e.* pins and needles) and "crawling"[1] (*i.e.* formication—a term that is usually remembered well by medical students, for some obscure reason), yet this is precisely how patients with pruritus describe their symptom.[22] Patients sometimes vividly convey the feeling that the sensation that is almost invariably exacerbated in bed at night is like "lying on a bed of cactus."[22] Pruritus at its worst is debilitating and may lead to weight loss and insomnia from the perpetual motion of scratching. The pruritic patient may withdraw from family, friends, and the workplace because of the embarrassment of continually scratching in a society unaccustomed to the itch, unlike that of 17th-century Italy. Pruritus has goaded patients to flirt with suicide[19] and their physicians to recommend liver transplantation because of erosion of the quality of life,[23,24] even when liver dysfunction is otherwise mild and cirrhosis is well compensated. Apart from urticaria, lichen and boils, and bleeding and cellulitis caused by excoriation, habitual scratching can cause fixed eruptions, such as prurigo nodularis that itself perpetuates irritation and leads to a vicious cycle of itch-and-scratch. Repeated skin damage can also lead to postinflammatory hyperpigmentation that is distinct from the green discoloration of the skin that has been attributed to bile pigment deposition at the sweat pores.[25] The contrast that can occur in pigmentation between the areas of skin that are scratched and those that are not is well illustrated in the sign, first reported by Reynolds[26] and confirmed by others,[27] of a "butterfly" of normal pigmentation set on the dark background of skin that has been repeatedly abraded (Fig. 1, top). Patients can be quite inventive in devising methods to scratch the butterfly that is not readily accessible to their groping fingers (Fig. 1, bottom). However, neither scratching nor topical turpentine soap, nor ingested concoctions of rhubarb and aloes, nor measures like galvanic currents, nor rough and harsh exercise such as riding long distances on a hard trotting horse—all of which have been recommended[15]—can be expected to offer anything more than temporary relief. While the use of androgens and other anabolic agents can mitigate pruritus,[19,28,29] this remedy is reserved for otherwise untreatable end-stage disease only, as it is palliative at best and fraught with side effects, including serious deepening of the jaundice.

The opportunity to treat hepatobiliary pruritus physiologically using a simple oral agent and at the same time to test the hypothesis that retained bile acids are the pruritogens presented itself as a result of the development in 1957 by the Merck company of MK135, an undigestible and indigestible nonabsorbable, strongly basic anion-exchange resin with a high affinity for bile acids. Cholestyramine (the chloride form of a quarternary ammonium styrene-divinylbenzene copolymer), as the compound was named, binds bile acids efficiently into an insoluble complex that is excreted in the stools.[35] Further, by eliminating bile acids from the enterohepatic circulation, cholestyramine feeding stimulates cholesterol loss through its metabolism to bile acids, and, as the name is intended to signify, cholestyramine lowers serum cholesterol in experimental animals[30] and in humans.[31] Therefore, since feeding bile acids to patients with medical cholestasis was shown to aggravate their pruritus[19] and the surgical creation of an external biliary fistula to relieve it,[32] the next logical step was to try enteric sequestration of bile acids with cholestyramine as therapy for cholestatic pruritus. The two landmark studies that established the efficacy of cholestyramine as therapy for the relief of itching in jaundiced patients were presented within a month of each other in late 1960 at the respective meetings of the American Clinical and Climatological Association[33] and the

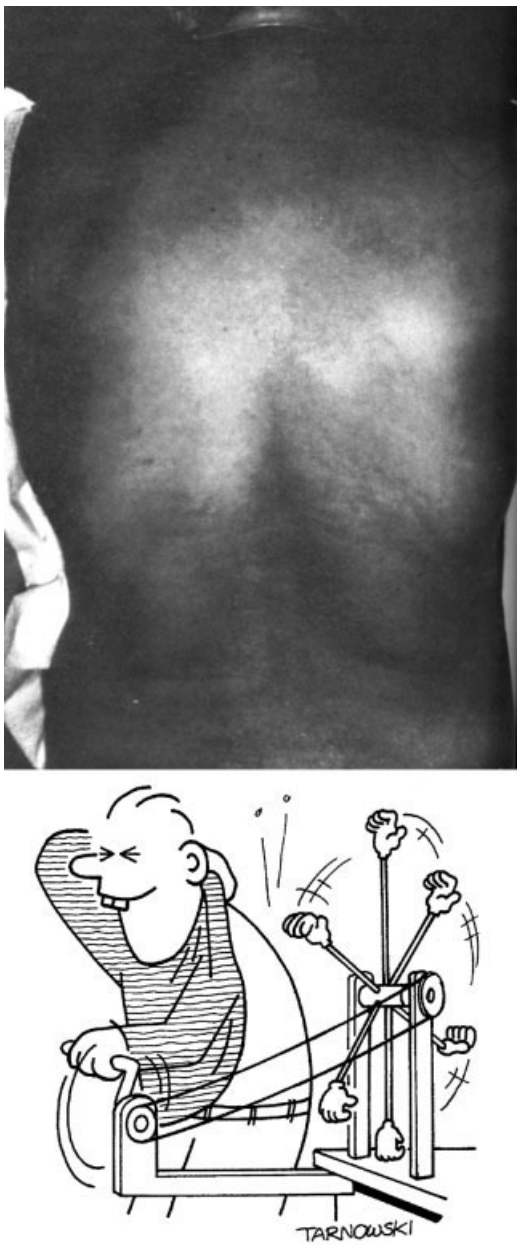


Fig. 1. (Top) The "butterfly" sign of Reynolds[26] showing a characteristic region of relative hypopigmentation on "unscratchable" areas of the back, in a patient with pruritus due to primary biliary cirrhosis. Reproduced with permission from the Archives of Dermatology. (Bottom) Rube Goldberg/Heath Robinson-like contraption that is devised to scratch the "butterfly" area and similar regions within and beyond the pale. Reproduced with permission from www.CartoonStock.com.

Central Society for Clinical Research,[34] followed by definitive publications the following year.[35,36] Although both studies were very small and uncontrolled, the results were undeniable, for within 3 weeks of starting cholestyramine, all 4 primary biliary cirrhosis patients treated in the first study[35] and 4 of the 5 patients in the second study[36] (1 biliary cirrhosis and 3 metastatic liver disease) responded with relief of pruritus and a parallel fall in serum bile acids, whereas the single patient with complete malignant biliary obstruction experienced neither.[36] The triumph of bile acid elimination therapy over pruritus in patients with jaundice was soon confirmed in both short-term and long-term studies,[37–39] lending support to the idea of a causative role for retained bile acids in the itching of hepatobiliary disease. Nonetheless, despite the continuing success in pruritus control of ileal exclusion surgery,[40,41] bile acid sequestration with increased binding efficiency,[42] and novel methods for removing bile acids from the circulation,[43] and the fact that administration of a nonmetabolizable conjugated bile acid analog exacerbates itching in some primary biliary cirrhosis patients,[44] dissension from the notion that bile acids cause itching, has been rife.[45–48] Admittedly, the poor correlation between the presence of pruritus and bile acid levels both quantitatively[45,46,49] and temporally[36] in the blood circulation and quantitatively in the skin,[47] and the fact that cholestyramine treatment improves the pruritus of some nonhepatic disorders too (*e.g.*, azotemia[50] and polycythemia rubra vera[51]) argue somewhat against a bile acid mechanism and in favor of other candidates for the cause of itching in liver disease, such as the endogenous opioid and serotonin systems.[52]

That opioids cause itching was highlighted brilliantly by the experience of the romantic English author Thomas de Quincy (1785–1859) in his sensational autobiography[53] that dwelt so frankly on his opium addiction, and which brought him literary acclaim and recognition when it was first published in the *London Magazine* in 1821. Like other literary figures of the times, de Quincy took laudanum, a sweetened alcoholic tincture of opium, in increasing doses, to which he was led by his physical suffering and mental torture. He wrote, "Upon any attempt obstinately to renew the old doses, there arose a new symptom . . . viz., an irritation on the surface of the skin . . . which soon became unsupportable, and tended to distraction."[53] In this context, Bergasa and Jones have provided a wealth of experimental data and a convincing line of argument in favor of the concept of pruritus being of central origin and possibly mediated by cholestasis-related alterations in opiodergic neurotransmission that could also lead to changes in other neurotransmitter systems.[22,48,52,54] Ever since the initial demonstration that an intravenous opioid antagonist relieved the intractable pruritus of a patient with cholestasis,[55] the experiment has been repeated successfully many times over the past 14 years with various opiate antagonists,[56,57] and indeed with antagonists of the serotonin system,[58,59] cannabinoids,[60] and even with a modifier of circadian rhythm.[61] All told, in global terms, it seems likely that the pruritus of liver disease results from alterations in one or more neurotrans-

mitter systems involving both central and peripheral nervous systems,[62] which in some arcane way may be related to aberrant bile acid activity[63] too.

We have clearly come a long way in our understanding of the pruritus of liver disease since the days of Aretæus and his prickly bilious particles, but there is much to do before finally solving the riddle of hepatogenous pruritus, and here, as Old Scratch would likely boast, the Devil is in the details!

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