Hand eczema is common and multifactorial

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Hand Eczema Is Common and Multifactorial

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Clinicians agree that hand eczema is multifactorial, although there are many uncertainties regarding causative factors. Atopic dermatitis is assumed to be a major risk factor, whereas the role of allergies is overestimated. Twin studies may shed light on the contribution of other endogenous, possibly genetic factors versus the role of exposure to environmental agents, with the latter being amenable to prevention and intervention.

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The term "hand eczema" implies an inflammation of the skin (dermatitis) that is confined to the hands. It is a common condition, with a point prevalence of 1–5% among adults in the general population and a 1-year prevalence of up to 10%, although these high estimates may be based on inclusion of mild cases. Based on a retrospective questionnaire study, the annual incidence is estimated at 5 per 1,000 (Meding and Jarvholm, 2004). The incidence of notified (i.e., usually more severe) occupation-related cases is estimated to be above 0.7 workers per 1,000 per year (Diepgen, 2003). A high prevalence has been documented in specific occupational groups, such as nurses, hairdressers, and bakers. These estimates exclude people affected through housework and many other occupational groups not included in routine surveillance systems. A decreased prevalence has been observed in Swedish adults; it is attributed to decreased occupational exposure to irritants. Hand eczema is twice as common in women as in men, with the highest prevalence in young women. Although genetic factors have been considered a reason for this difference, greater exposure of women to wet work is assumed to be the most likely explanation. Hand eczema has a considerable public health impact because it tends to run a chronic relapsing course, with the vast majority of patients experiencing negative psychosocial consequences. Epidemiology is helpful in trying to understand hand eczema and in dispelling myths about the role of allergy.

> Having been diagnosed with contact allergy . . . had a negligible impact on the role of genetic factors.

Do we know the cause?

Predisposing endogenous and external factors both play a part in hand eczema. Being atopic (commonly, but not precisely defined as having a tendency to develop asthma, hay fever, or eczema) is assumed to be related to the risk of developing and maintaining hand eczema; one third to one half of patients with hand eczema can be considered atopic (Svensson, 1988). Contrary to atopic dermatitis, respiratory atopy is at best only weakly associated with hand eczema, and the association exists mainly because there is partial overlap of respiratory atopy with atopic dermatitis. It is becoming clear that atopy is not the main issue in atopic dermatitis. The role of atopy—i.e., a state of having allergen-specific IgE reactivity toward environmental, mostly respiratory, agents—is challenged in "atopic" dermatitis (Flohr *et al*., 2004); most patients who have the clinical appearance of atopic dermatitis do not have a raised level of allergen-specific IgE.

Although the heritability of atopic dermatitis is obvious, and several chromosomal regions have been linked to it, there is now evidence that genetic factors unrelated to atopy (defined as an innate propensity to develop allergen-specific IgE) may play a role in a subset of patients. A recent study demonstrated a link with mutations in the filaggrin gene, leading to structural defects in the skin-barrier region (Irvine and McLean, 2006). Because the hands take most of the burden of exposure to environmental agents, it is quite possible that this defect plays a role in a number of patients whose hand eczema has been labeled atopic (palmoplantar) dermatitis. Studies on the water barrier of the skin, using transepidermal water loss measurements, have failed to demonstrate that impaired water barrier in unexposed skin is a good predictor of irritant contact dermatitis (Smit *et al*., 1994), although the studies may have lacked power when adjusting for atopic dermatitis. Skin penetration of certain chemicals is increased in atopic dermatitis (McLean and Hull, 2007).

The most common external cause of hand eczema is contact with irritants, or mild toxic agents; water or soaps are typical examples of a contact irritant. A distinction is made between irritant contact dermatitis and allergic contact dermatitis. Allergic contact dermatitis of the hands is much less common than irritant contact dermatitis and occurs only in people who have developed a contact allergy to a specific substance, such as rubber chemicals, nickel, or biocides. Theoretically, identifying and eliminating an allergic contact factor (e.g., allergy to rubber components) could cure hand eczema if this is the

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sole cause. In clinical practice, such cases are rare, because hand eczema is often due to a combination of endogenous factors and irritant and allergic contact factors. Atopic individuals are not more prone to (T-cell-mediated) contact allergy. Nickel allergy is common in hand eczema, but its role as a causative or sustaining agent is challenged. To complicate things, it is possible that atopic dermatitis, especially the accompanying skin-barrier impairment, is an effect modifier of the exposure to irritants.

Genes or environment?

In this issue of the *Journal of Investigative Dermatology* a quantitative genetic epidemiologic study on hand eczema in monozygotic versus dizygotic twins by Lerbaek *et al*. (2007, this issue) gives a closer look at the relative contribution of environmental and genetic factors, while controlling for atopic dermatitis (of which the genetic control is obvious). By analysis of the variance of the correlation coefficients in monozygotic and dizygotic twins, the authors demonstrated that, after controlling for atopic dermatitis, 59% of hand eczema could be attributed to environmental factors. The role of genetic factors in contact allergy to nickel, based on twins with hand eczema, was discussed in an earlier article in the *JID* by the same group, and they concluded that nickel allergy was unlikely to have a genetic basis (Bryld *et al*., 2004). The present study supported these findings by demonstrating that having been diagnosed with contact allergy (a positive patch test) had a negligible impact on the role of genetic factors. The study was unable to address the issue of gene–environment interactions; such interactions may imply that the same exposure has different effects on different genotypes of hand eczema, if such genotypes exist.

The study was entirely questionnaire-based. To study the role of atopic dermatitis the investigators based themselves on self-reported clinical manifestations of eczema. In Scandinavia, questionnaires on eczema seem to have a reasonable sensitivity and a high specificity. The advantage is that this approach may avoid the pitfall of attributing a role to atopy (defined as a specific manifestation of IgE-mediated allergy) and that it includes the atopic dermatitis cases without allergen-specific IgE.

One of the problems that Lerbaek *et al*. (2007) encountered is that there are several not precisely defined types of hand eczema. Irritant contact dermatitis, for example, is supposed to be common, but its diagnosis is based on nothing more than the absence of a positive patch test and a history of exposure to irritants. In addition, there are several types of hand eczema with a distinctive appearance of which the cause is unknown. These types may be referred to as pompholyx, dyshidrotic eczema or dyshidrosis, nummular eczema, tylotic eczema, and hyperkeratotic eczema (the latter is often difficult to distinguish from psoriasis). It is possible that these types tend to be overrepresented among patients with a chronic, debilitating course. For a rare form of autosomal dominant pompholyx, a locus on chromosome 18 has been identified (Chen *et al*., 2006).

Compared with family studies, twin studies are very helpful in separating environmental influence from genetic factors. The results are primarily attributable to twins, and to be representative for the general population the method of recruiting twins is essential. Lerbaek *et al*. (2007) base their findings on 62% of twin pairs who were born in a large region of Denmark. There may be some bias because there was an overrepresentation of females, while younger twins were underrepresented. Because the questionnaire focused on hand eczema, it is possible, as the authors acknowledge, that twins with this disease were overrepresented, inflating the prevalence estimates for the general population: their 1-year prevalence was almost 12%, with a point prevalence of almost 6%. An interesting observation was that high-risk occupations and their accompanying exposure had a higher concordance in monozygotic twins. It is not unusual for monozygotic twins to have similarities in lifestyle, with similarities in environmental and occupational exposure, and this may influence the estimate of a hypothetical genetic impact.

Relevance to public health

In many patients with chronic hand eczema a combination of the factors mentioned above seems to play a role. This has led to the use of many diverse therapies and other intervention strategies to control the disease. Protocols for ongoing systematic reviews of the evidence for these treatments are accessible in the database of the Cochrane Skin Group (http://www.nottingham.ac.uk/~muzd/about/about.htm).

The hands are important organs of communication and expression. Therefore, any visible skin disease on the hands may result in major psychosocial problems, e.g., anxiety, low self-esteem, and social phobia. Itch, fissures, and blisters, in addition to their effect on daily life outside work, can prevent manual work, leading to significant disability and economic loss to both individuals and society. Quality-of-life instruments only indirectly address the impact on employment. A comparison of physician-rated assessments of severity with patient-rated ones demonstrated a poor correlation, indicating that patients value several aspects of their hand eczema differently than physicians.

For clinicians, the diagnosis and treatment of hand eczema is often a calculated guess. The study by Lerbaek *et al*. (2007) demonstrates the importance of environment and the moderate impact of genetic factors on hand eczema, controlling for atopic dermatitis, which is, at least partially, genetically based. The study calls for a more precise disease definition, including its subtypes and the types that are more likely to have a genetic basis. The environmental component of hand eczema is amenable to intervention. Even if genetically based diminished impairment of the barrier function is an important factor, the accompanying increased susceptibility to environmental agents calls for adequate preventive measures. Chronic hand eczema, whether regarded as a single entity or as a manifestation of different diseases, remains a challenge to researchers and caregivers.

CONFLICT OF INTEREST
The author states no conflict of interest.

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Casting Light on Evidence

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Clinicians are growing inured to the fact that rarely do the results of a single randomized controlled trial (RCT) decisively change clinical practice. Nor should they. In a new RCT, Kirke and colleagues have compared the therapeutic effects of different types of UVB radiation on clearance of psoriasis. Their study is unlikely to be the last word on this topic.

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Not long ago, in an age of optimism (and statistical naiveté), it seemed that you could read the results of a randomized controlled trial (RCT) at the weekend and change your prescribing habits accordingly on Monday morning. It was as though the RCT was a truth machine: you just fed in the patients' details, added a little randomization, mechanically applied some statistical test, and out popped a God's-eye view of how the Universe worked. A veritable epistemological engine. Things do not seem quite so simple anymore. Indeed, in a recent article, Ioannidis (2005) argued cogently, if a little mischievously, that the results of most clinical studies, including RCTs, were mistaken. With this in mind, what are we to make of the report by Kirke *et al.* (2007, this issue) that there is no difference in efficacy between narrowband phototherapy and (selective) broadband UVB lamps for the treatment of psoriasis? Should those recently purchased narrowband cabinets be put to one side?

The use of UVB phototherapy to treat psoriasis has a long history, but it is probably only since the introduction of psoralen plus UVA (PUVA) that interest has focused on how this older modality of therapy could be made more efficacious. Subsequent clinical application has owed more to incremental improvement than to any "eureka" moments. However, if there was an elegant experiment, rather than the brute force of clinical trials, it was that reported by Parrish and Jaenicke in this journal in 1981 (Parrish and Jaenicke, 1981). In this study, Parrish and Jaenicke exposed psoriatic plaques to monochromatic sources and showed that wavelengths less than 290 nm were erythemogenic but had little efficacy. The implication was that it would be better to use lamps of longer wavelengths with the UVC filtered out. Although the exact relative efficacy of different longer UVB wavelengths was unclear, the invention of the 311 nm (Philips TL-01) lamp soon led to their widespread use, at least in Europe. In a pattern common to the way many medical innovations are adopted, an apparent physiological rationale, coupled with a few initial small-scale reports and enthusiasm by early adopters, led to widespread changes in clinical practice. Which is where the exemplary study by Kirke *et al.* (2007) comes into play. Is there anything special about TL-01, or is it just that UVB lamps contaminated with UVC are less efficacious?

Kirke and colleagues (2007) screened 192 subjects in a single university hospital center, of whom 124 were eligible and 24 declined to participate. The remaining 100 were randomized, 50 in each group, to receive either TL-01 or (selective) UVB with UV6 fluorescent lamps. (UV6 bulbs have negligible output in the UVC range; see Kirke *et al.* (2007) for a comparison of the spectra of the two tube types.) The primary outcome was the number of treatments to clearance, and the proportion of patients clearing was also reported. The median number of exposures was 28.4 for TL-01 and 30.4 for UV6. With TL-01, 56% of patients cleared, whereas with UV6, 40% cleared. Neither of these comparisons was significant at the conventional statistical level. So, in the light of the general claims by Ioannidis (2005), how do we interpret the data from this study as evidence? What does it mean?

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