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## The field and its boundaries

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Evidence-based medicine (EBM) represents the best way of linking and integrating clinical research with clinical practice. The results of clinical research should inform clinical practice. Ideally, whenever there is no satisfactory answer for a clinical question, it should be addressed by clinical research. Since clinical questions are innumerable and resources are limited, the process needs some control, and priorities should be set using explicit and verifiable criteria. The public and purchasers have to be involved at this stage, and health needs and expectations in any given clinical area should be analyzed and taken into account. In many instances, confirmatory studies are needed, and systematic reviews can be used to summarize study results or to explore results in specific subgroups with a view to further research. The results of clinical research should be applied back to the individual patients in the light of their personal values and preferences. Communicational skills and patient understanding are key issues in this respect. In the real world, forces other than those involved in such an ideal process often distort research priorities and questions. For example, strong industrial and economic interests may partly explain the lack of data on rare disorders, or on common disorders if they occur mainly in less developed countries. This book may help identify the more urgent questions that lack satisfactory answers by summarizing for physicians (and patients) the best evidence available for the management of a large number of skin disorders. It may thus provide a starting-point for rethinking the clinical research priorities in patient-oriented dermatology.

### What is special about dermatology

The skin is not a simple, inert covering of the body, but a sensitive dynamic boundary, and it is an important organ of social and sexual contact. Body image, which is deeply rooted in the culture of any given social group, is profoundly affected by the appearance of the skin and its associated structures. The role that skin appearance plays

in any given society is best understood from an anthropological perspective and using a narrative qualitative approach. This area is rather neglected in dermatological curricula.

Extensive disorders affecting the skin may disrupt its homeostatic functions, ultimately resulting in “skin failure,” requiring intensive care. This is rare, but may happen—for example, with extensive bullous disorders or exfoliative dermatitis. The commonest health consequence of skin disorders is connected with the discomfort of symptoms, such as itching and burning or pain, which frequently accompany skin lesions and interfere with everyday life and sleep, and with the loss of confidence and disruption of social relations that visible lesions may cause. Feelings of stigmatization and major changes in lifestyle caused by a chronic skin disorder such as psoriasis have been repeatedly documented in population surveys.<sup>1</sup>

### A vast array of clinical entities

Unlike most other organs, which are usually associated with around 50–100 diseases, the skin has a complement of 1000–2000 conditions, and over 3000 dermatological categories can be found in the International Classification for Disease version 9 (ICD-9). Part of the reason for this is that the skin is a large and visible organ. In addition to disorders primarily affecting the skin, most of the major systemic diseases (e.g., of vascular and connective tissue) have cutaneous manifestations. Currently, the widespread use of symptom-based or purely descriptive terms such as parapsoriasis or pityriasis rosea reflects our limited understanding of the causes and pathogenetic mechanisms of a large number of skin disorders. We still lack consensus on a detailed lexicon of dermatological terms to be used in research and everyday clinical practice.

An effort to improve consensus has recently been taken with three very significant initiatives:

- The *Dermatologischer Diagnosenkatalog* (DDK), published in the German-speaking countries by the *Deutsche*

*Dermatologische Gesellschaft* and published in English by the International League of Dermatological Societies (ILDS).

- The British Association of Dermatologists' Diagnostic Index (BAD Index), first published in 1994 and updated annually since then.
- The Dermatology Lexicon Project, developed with a grant from the U.S. National Institutes of Health, first published in 2005 and now supported by the American Academy of Dermatology.

It is expected that in the not too distant future, a single instrument meeting dermatologists' requirements will become available.<sup>2</sup>

### **Extremely common disorders**

Skin diseases are very common in the general population. Prevalence surveys have shown that skin disorders may affect 20–30% of the general population at any one time. The most common diseases are also the most trivial ones. They include such conditions as mild eczematous lesions, mild to moderate acne, benign tumors, and angiomatous lesions. More severe skin disorders, which can cause physical disability or even death, are rare or very rare. They include, among others, bullous diseases such as pemphigus, severe pustular and erythrodermic psoriasis, and such malignant tumors as malignant melanoma and lymphoma. The disease frequency may vary according to age, sex, and geographic area. In many cases, skin diseases are trivial health problems in comparison with more serious medical conditions. However, as already noted, because skin manifestations are visible, they may distress people more than more serious medical problems do. The issue is complicated, because many skin disorders are not a "yes-or-no" phenomenon, but occur with a spectrum of severity. The public's perception of what constitutes a "disease" requiring medical advice may vary according to cultural issues, the social context, resources, and time. Minor changes in health policy may have a large health and financial impact simply because a large number of people may be affected. For example, most of the campaigns conducted to raise public awareness of skin cancer have led to a big increase in the number of people having benign skin conditions such as benign melanocytic nevi evaluated and excised.

### **Large variations in terms of health-care organization**

Countries differ greatly in the way in which their health services deal with skin disorders. These variations are roughly indicated by the density of dermatologists—ranging, in Europe, from about one in 20 000 in Italy and France to one in 150 000 in the United Kingdom.

In general, only a minority of people with skin diseases seek medical help, while many opt for self-medication.

Pharmacists have a key role in advising the public on the use of over-the-counter products. Primary-care physicians seem to treat the majority of people among those seeking medical advice. Primary care of dermatological problems is not precisely defined and overlaps with specialist activity. Everywhere, the dermatologist's workload is concentrated in the outpatient department. Despite the vast number of skin diseases, just a few categories account for about 70% of all dermatological consultations.

Generally speaking, dermatology requires a low-technology clinical practice. Clinical expertise depends mainly on the ability to recognize a skin disorder quickly and reliably, and this in turn depends largely on awareness of a given clinical pattern, based on previous experience and on the practised eye of a visually literate physician.<sup>3</sup> The process of developing "visual skill" and a "clinical eye" is poorly understood, and these skills are not formally taught.

### **Topical treatment is often possible**

A peculiar aspect of dermatology is the possible option for topical treatment. This treatment modality is ideally suited to localized lesions, the main advantage being the restriction of the effect to the site of application and the limitation of systemic side effects. A topical agent is usually described as consisting of a vehicle and an active substance, with the vehicles being classified as powder, grease, liquid, or combinations such as pastes and creams.

Much traditional topical therapy in dermatology has been developed empirically with so-called magistral formulations. Most of these products appear to rely on physical rather than chemical properties for their effects, and it may be an arbitrary decision to consider one specific ingredient as being the "active" one. Physical effects of topical agents may include detergency, hydration, and removal of keratotic scales. The border between pharmacological and cosmetic effects may be blurred, and the term "cosmeceuticals" is sometimes used.<sup>4</sup> In addition to drug treatment, various non-drug treatment modalities exist, including phototherapy or photochemotherapy and minor surgical procedures such as electrodesiccation and cryotherapy. Wide variations in the treatment modalities used for the same condition mainly reflect local traditions and preferences.<sup>5,6</sup>

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### **Limitations of clinical research**

As in other disciplines, the last few decades have seen an impressive increase in clinical research in dermatology. However, the upsurge of clinical research has not been paralleled by methodological refinements and, for example, the quality of randomized control trials (RCTs) in dermatology appears to fall well below the usually accepted standards.<sup>7</sup> Innovative thinking is needed in dermatology to

make clinical research address the important issues and not simply ape the scientific design.

### Disease rarity

In at least a thousand rare or very rare skin conditions, no single randomized trial has been conducted. These conditions are also those that carry a higher burden of physical disability and mortality. Many of them have an annual incidence rate of below one case per 100 000 and frequently below one case per million. International collaboration and institutional support is clearly needed, but so far such efforts are very few.

### Patients' preferences

One alleged difficulty with mounting randomized clinical trials in dermatology is the visibility of skin lesions and the consideration that much more than in other areas, patients self-monitor their disease and may have preconceptions and preferences about specific treatment modalities.<sup>8</sup> The decision to treat is usually dictated by subjective issues and personal feelings. Physicians and the public need to be educated about the value of randomized trials to assess interventions in dermatology. Motivations and expectations are likely to influence clinical outcomes of all treatments, but they may have a more crucial role in situations in which "soft end points" matter, as in dermatology. Commonly, more than 20% of patients with psoriasis entering randomized clinical trials improve on placebo independently of the initial disease extension. Motivations are equally important in pragmatic trials that evaluate different management packages, such as the comparison of a self-administered topical product for psoriasis with hospital-based forms of treatment such as phototherapy. Traditionally, motivation is seen as a characteristic of the patient that is assumed not to change with the nature of the intervention. However, it has been argued that it is more realistic to view motivation in terms of the "fit" between the nature of the treatment and the patient's wishes and perceptions—especially with complex interventions that require the patient's active participation. The public is inundated with uncontrolled and sometimes misleading or unrealistic messages on how to improve the body's appearance. It is important to ensure that patient information and motivations are properly considered in the design and analysis of clinical trials on skin disorders.

### The use of placebo in randomized controlled trials

Too many placebo-controlled RCTs are conducted in dermatology even when alternative therapies exist. As a consequence, a large number of similar molecules used for the

same clinical indications can be found in some areas—e.g., topical steroids. Many regulatory agencies still consider placebo controls as the "gold standard." Criteria are needed for the use of placebos in dermatology. They should be developed with the active and informed participation of the public, and ethics committees and regulatory agencies should consider them. "Pragmatic" randomized trials conducted in conditions close to clinical practice and contrasting alternative therapeutic regimens are urgently needed in order to guide clinical decisions.

### Long-term outcome of chronic disorders

Several major skin disorders are chronic conditions for which a cure does not at present exist. Whenever a definite cure is not reasonably attainable, it is common to distinguish between short, intermediate (usually measurable within months), and long-term outcomes. Long-term results are not simply predictable from short-term outcomes. Many skin disorders wax and wane over time, and it is not easy to define what represents a clinically significant long-term change in the disease status. This is even more difficult than defining the outcome for other clinical conditions, such as cancer or ischemic heart disease, in which death or major hard clinical end points (e.g., myocardial infarction) are of particular interest. In the long term, the way the disease is controlled and the treatment side effects are vitally important, and simply and cheaply measured outcomes applicable in all patients seem to be preferable. These may include the number of patients in remission, the number of hospital admissions or outpatient consultations, and major disease flare-ups. Drop-outs merit special attention, since they may strongly reflect dissatisfaction with treatment.

### Self-control design

Study designs that are often used at a preliminary stage in drug development are *within-patient control studies*—i.e., crossover and self-controlled studies or simultaneous within-patient control studies. In dermatology they are also used, albeit improperly, at a more advanced stage. In a survey of more than 350 published RCTs of psoriasis (unpublished data), a self-controlled design accounted for one-third of all the studies examined and was relied on at some stage in drug development. The main advantage of a within-patient study over a parallel concurrent study is a statistical one. A within-patient study obtains the same statistical power with far fewer patients, and at the same time reduces variability between the populations confronted. Within-patient studies may be useful when studying conditions that are uncommon or show a high degree of patient-to-patient variability. On the other hand, within-patient studies impose restrictions and artificial conditions, which may undermine the validity and generalizability

of results and may also raise some ethical concerns. The wash-out period of a crossover trial, as well as the treatment schemes of a self-controlled design, which entails applying different treatments to various parts of the body, do not seem to be fully justifiable from an ethical point of view. Clearly, the impractical treatment modalities in self-controlled studies or the wash-out period in crossover studies may be difficult for the patient to accept. Drop-outs may have more pronounced effects in a within-patient study than in other study designs, because each patient contributes a large proportion of the total information. The situation is compounded in self-controlled studies, where a patient may drop out from the study having noticed a difference in treatment effect between the parts into which she or he has been “split up.” In this case, given that drop-outs are related to a difference in treatment effect between interventions, the effect of the intervention is liable to be underestimated.

### **The increasing role of industry-sponsored trials**

The influence of the pharmaceutical industry on medical research has increased enormously in recent decades. Dermatology does not appear to be an exception. As indicated by the European Dermatoepidemiology Network (EDEN) psoriasis project, only a quarter of all randomized clinical trials published on psoriasis from 1977 to 2000 were conducted independently of direct pharmaceutical company sponsorship, and the proportion of sponsored trials has been increasing dramatically since then.<sup>9</sup> Systematic reviews indicate that published studies funded by pharmaceutical companies are several times more likely to have results favoring the company than studies funded from other sources.<sup>10</sup> As indicated by the recent development of “biological agents” in psoriasis, placebo-controlled randomized trials and the use of surrogate outcome measures over a short period of time, rather than clinically relevant outcomes over a significant time span, are means of increasing the chances of obtaining favorable results.<sup>11</sup> Selective presentation of scientific data, statements by opinion leaders in sponsored symposia, and involvement of patient organizations in sponsored campaigns are among the promotional strategies adopted to expand the market once limited clinical evidence has been collected on a new agent. Heavy marketing competition has been paralleled by a cycle of increasing dependency between physicians, academic opinion leaders, patients’ organizations, researchers, and industrial interests.<sup>12</sup> In Italy, the recognition of the problems involved with new drug registration and lack of data on effectiveness and safety in situations in which alternative conventional treatments already exist have prompted the launch of post-marketing surveillance programs linking prescription to the provision of patient data at first drug prescription and

regularly thereafter during a predefined follow-up period. One example of such a program on psoriasis is the Psocare program ([www.psocare.it](http://www.psocare.it)).

### **The limitations of systematic reviews**

The large number of clinical studies in dermatology and the lack of consensus on the management of many skin disorders suggest systematic reviews as a way of improving the evidence and guiding clinical decisions. However, systematic reviews alone cannot be expected to overcome the methodological limitations in dermatological research described above. On the contrary, it seems that systematic reviews, if not properly guided by important clinical questions, may amplify the unimportant issues and may result in a rather misleading scale of evidence to guide clinical decisions. Since most RCTs are performed by pharmaceutical companies, data-driven systematic reviews might well reflect the priorities of pharmaceutical companies and not necessarily those of the public and clinicians. Without a change in regulatory procedures, pharmaceutical companies will continue to pay little attention to comparative RCTs and will continue to assess drugs for lucrative indications, neglecting rare but clinically important disorders.

Systematic reviews alone cannot fill the gap, and we urgently need primary research and high-quality and relevant clinical trials.

### **Evidence-based medicine: where do we go from here?**

An EBM approach should permeate medical education and inform academic medicine. It is only if such a change is promoted that EBM can become central to clinical practice and not trivialized to become “cookbook” medicine. If EBM is successfully integrated into everyday practice, it may become easier to conduct primary clinical research based on clinical needs rather than on commercial interests.

In primary research, more imaginative and effective research instruments are needed, and research strategies should be developed that take account of the peculiarities of dermatology as compared with other disciplines. Qualitative research should not be neglected. It is the key to understanding intercultural variations in body image and of the ways in which health needs for skin diseases are expressed and perceived in different situations.

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## References

- 1 McKenna KE, Stern RS. The outcomes movement and new measures of the severity of psoriasis. *J Am Acad Dermatol* 1996;**34**:534–8.
- 2 Papier A, Chalmers RJG, Byrnes JA, Goldsmith LA. Framework for improved communication: the Dermatology Lexicon Project. *J Am Acad Dermatol* 2004;**50**:630–4.
- 3 Webster GF. Is dermatology slipping into its anec-dotage? *Arch Dermatol* 1995;**131**:149–50.
- 4 Vermeer BJ, Gilchrist BA. Cosmeceuticals: a proposal for rational definition, evaluation, and regulation. *Arch Dermatol* 1996;**132**:337–40.
- 5 Peckham PE, Weinstein GD, McCullough JL. The treatment of severe psoriasis: a national survey. *Arch Dermatol* 1987;**123**:1303–7.
- 6 Farr PM, Diffey BL. PUVA treatment of psoriasis in the United Kingdom. *Br J Dermatol* 1991;**124**:365–7.
- 7 Williams HC, Seed P. Inadequate size of “negative” clinical trials in dermatology. *Br J Dermatol* 1993;**128**:317–26.
- 8 Van de Kerkhof PCM, De Hoop D, De Korte J, Cobelens SA, Kuipers MV. Patient compliance and disease management in the treatment of psoriasis in the Netherlands. *Dermatology* 2000;**200**:292–8.
- 9 Naldi L, Svensson A, Diepgen T, *et al.* Randomized clinical trials for psoriasis 1977–2000: the EDEN survey. *J Invest Dermatol* 2003;**120**:738–41.
- 10 Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality. *BMJ* 2003;**326**:1167–70.
- 11 Naldi L. A new era in the management of psoriasis? Promises and facts. *Dermatology* 2005;**210**:179–81.
- 12 Williams HC, Naldi L, Paul C, Vahlquist A, Schroter S, Jobling R. Conflicts of interest in dermatology. *Acta Derm Venereol* 2006;**86**:485–97.