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Categorization of and comments on isomorphic and isotopic skin reactions

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Abstract *Locus minoris resistentiae (lmr)* can be defined as a site of the body that offers lesser resistance than the rest of the body to the onset of disease. The well-known Köbner phenomenon is itself a clear example of *lmr* in dermatology. The new term *locus maioris resistentiae (LMR)*, a site of the body that offers greater resistance than the rest of the body to the onset of disease, defines the opposite condition. Renbök phenomenon (reverse Köbner's isomorphic response) typically represents an example of *LMR*.

For a long time, it has been well known that all the types of cutaneous scars (subsequent to burns, trauma, or vaccination) are vulnerable sites for the development of neoplasms, infections, and dysimmune reactions. The complex underlying mechanisms have lately been included into the concept of the immunocompromised cutaneous district (ICD). The concept of ICD denotes a regional immune dysregulation caused by lymph flow failure or altered neuropeptide release. The local alteration of the immune response can be either defective (so favoring the outbreak of opportunistic infections or tumors) or overactive (so favoring the outbreak of immune disorders).

Here we propose a newly coined terminology to indicate each specific cause responsible for the occurrence of an ICD. The definitions specifically refer to the morphology and to the diverse causative agents. The new classification of isomorphic and isotopic skin reactions encompasses additional clinical conditions that have not been defined previously. We believe that our new categorization of the disparate causes of an ICD will simplify the understanding of this phenomenon.

Locus minoris resistentiae: An old but still valid way of thinking in medicine

Identifying a vulnerable area of the body has always aroused great interest in humans. *Locus minoris resistentiae* (*lmr*; from Latin, "place of lesser resistance") can be defined as a site of the body that offers lesser resistance than the rest of the body to the onset of disease. Its origins are ancient and can be found in Achilles' and Siegfried's old epic myths, which have offered starting points for the comprehension of the peculiar vulnerability of certain body sites. The *locus minoris resistentiae* concept weaves through many fields of medicine; however, skin transparency makes the understanding of this concept easier than do other organs. There are countless reports of privileged localization of cutaneous

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lesions on injured skin, which represents a typical condition of *locus minoris resistentiae*.[1]

Köbner phenomenon (isomorphic response or isomorphic phenomenon): A classic example of *locus minoris resistentiae*

The well-known Köbner phenomenon, namely the appearance of new lesions pertaining to a previously present skin disorder at the sites of trauma or other insult, is itself a clear example of *locus minoris resistentiae* in dermatology.[1,2]

In 1876 the German physician Heinrich Köbner described this phenomenon in a psoriasis patient who had been bitten by a horse and developed new psoriatic lesion at the site of trauma. Subsequently this skin reaction was named as the "Köbner phenomenon" (reviewed in Kannangara et al[3]).

Cutaneous diseases that may undergo köbnerization are many and multifarious, as are the possible causes of the phenomenon.[4–7] The striking nonspecificity of the Köbner phenomenon suggests the existence of a common pathomechanism at the basis of it. It seems that köbnerization is initiated by epidermal injury, but subsequent dermal events are required for its completion. Microlesions of sensory nerve endings, changes in vascularity along with endothelial mast cell infiltration, and dermal foci of microscarring have all been implicated in generating a sort of tissue vulnerability at the site of injury. The weakened site creates a skin area of dysimmune microenvironment.[1]

Renbök phenomenon (reverse Köbner isomorphic response): An example of *locus maioris resistentiae*

It is strange to note that the opposite of *locus minoris resistentiae* has not been considered so far, though examples of body sites that offer resistance to the onset of disease are not rare. Cochran et al. in 1981 first described a maculopapular drug reaction that spared the sites of previous x-irradiation in a patient who had been treated for Wilms tumor (reviewed in Kannangara et al[3]). In 1982 Bernhard et al. introduced the term *Köbner nonreaction* or *isomorphic nonresponse* to refer the absence of a drug reaction at the site of previous x-irradiation (reviewed in Kannangara et al[3]). In 1991 the Renbök (inverted writing of Köbner) phenomenon was described by Happle et al. as normal hair growth in psoriatic patches noted in a patient with co-occurrence of psoriasis and alopecia areata (reviewed in Kannangara et al[3]). Mansur et al. suggested that a dermatosis sparing another co-existing unrelated previous skin disorder (including Renbök phenomenon) could be defined as a "reverse isotopic response."[8]

The new term *locus maioris resistentiae (LMR)*, a site of the body that offers greater resistance than the rest of the body to the onset of disease, might well define this opposite condition.[2] Renbök phenomenon typically represents an example of *locus maioris resistentiae*.[2]

Isotopic response (Wolf postherpetic isotopic response)

Herpes-infected areas are known to be privileged sites for either harboring or rejecting a wide range of multifarious disorders (infections, tumors, dysimmune reactions).[9] The phenomenon is labeled isotopic response when a new disease occurs on the herpes-infected site *(locus minoris resistentiae)* or isotopic nonresponse when the herpes-infected site is selectively spared by an elsewhere diffuse cutaneous eruption *(locus maioris resistentiae)*.[2,10]

The term *isotopic response* (or *nonresponse*) was mainly used for herpetic infections. Afterward, as a tribute to the first author who had coined the term but also to keep homogeneity of the cases collected, the prevailing term became *Wolf postherpetic isotopic response* or *nonresponse* (*postherpetic* meaning a consequence of a varicella-zoster virus or herpes simplex virus infection); however, the cause of an isotopic response is far from being singular (herpetic infection).[2,10–12]

Sectorial immune default: The immunocompromised district in dermatology

For a long time, it has been well known that all the types of cutaneous scars (subsequent to burns, trauma, or vaccination) are vulnerable sites for the development of neoplasms, infections, and dysimmune reactions. The complex underlying mechanisms have lately been included into the concept of the immunocompromised cutaneous district.[13] This term denotes a regional immune dysregulation caused by lymph flow failure or altered neuropeptide release. The local alteration of the immune response, depending on the neurotransmitters and immune cells each time involved in the immunodestabilized cutaneous site, can be either defective (so favoring the outbreak of opportunistic infections or tumors) or overactive (so favoring the outbreak of immune disorders).[1,2,13]

Although the concept of immunocompromised district was developed only 6 years ago,[13] paradigmatic instances of it, concerning the "opportunistic" onset of malignancies on lymphedematous and immunocompromised lower limbs, had been published as long as 30 years ago. They dealt with cases of Stewart-Treves syndrome, monolateral Kaposi's sarcoma, coexistent basal cell carcinoma, and paucilesional