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Furthermore, the proportion of normal subjects with anti-Dsg3 IgG increased with increasing proximity of their place of residence to the endemic area. No apparent crossreactivity between anti-Dsg1 and anti-Dsg3 IgG was found in the fogo selvagem patients. Although the authors detected anti-Dsg3 IgG in those patients with fogo selvagem, none of them developed any obvious clinical phenotype of PV, such as oral lesions. It is not clear why those patients with anti-Dsg3 IgG in addition to anti-Dsg1 IgG do not show the clinical phenotype of mucocutaneous-type PV. A part of the reason could be that the quantities of pathogenic anti-Dsg3 IgG were insufficient to induce the PV phenotype, as the authors found that the intensity of immunoprecipitated Dsg3 was less strong than that of Dsg1.

Certainly, fogo selvagem provides a fascinating model in autoimmune diseases. Now we know that an unidentified environmental factor(s) triggers not only anti-Dsg1 IgG but also anti-Dsg3 IgG autoantibodies. This finding offers new insight into the epidemiology of fogo selvagem and provides a framework for better understanding of immunological mechanisms of the onset of autoimmune response against desmogleins in pemphigus.

CONFLICT OF INTEREST

The author states no conflict of interest.

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See related article on pg 2106

Pathways to the Development of Melanoma: A Complex Issue

Marianne Berwick[1]

The investigation of nevus distribution by anatomic site has led to interesting hypotheses of divergent pathways to the development of melanoma. However, such hypotheses must be viewed in all their complexity, and the paper by Randi *et al.* gives additional substance to this complexity.

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In this issue, Randi *et al.* (2006) report on a carefully conducted case-control study of melanoma conducted by a collaborative group, the Italian Group for Epidemiologic Research in Dermatology (GISED), from 1992 to 1994. Dermatologists counted nevi on both cases and controls. The authors state that there was an effect of nevi at all sites, but no site-specific association, except for the posterior trunk. They suggest that their interpretation of the data runs counter to the very interesting hypothesis raised in 2003 by David Whiteman and his colleagues, who suggested different etiologic pathways for melanomas on the head and neck and melanomas on the trunk. Further genetic support for such a hypothesis has been found in the data presented by Curtin and his colleagues (Curtin *et al.*, 2005; Maldonado *et al.*, 2003; Bastian *et al.*, 2003) when they investigated somatic mutations in BRAF. However, it may be best to modify this hypothesis to state that different etiologic pathways may consist of (1) aberrant melanogenesis and (2) cumulative sun exposure among susceptible individuals. The difference here is that the pathways as suggested are similar, but the focus is on biology rather than anatomic site.

In evaluating the difference between the two alternative (although complementary) hypotheses, it is helpful to look at a table of subjects in three epidemiologic studies (Randi *et al.*, 2006; Whiteman *et al.*, 2003; Berwick *et al.*, unpublished data) arranged by anatomical site and to review several differences among the studies (Table 1).

It is immediately obvious that there are important differences in the site distribution of nevi. These differences can in part, but not wholly, be explained by the oversampling used by Whiteman *et al.* (2003), because Randi *et al.* (2006) had a very much larger proportion of individuals with melanoma of the head and neck. In fact, a Spanish study by Ocaña-

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Table 1. Comparison of anatomic distribution of melanoma and median number of nevi in case-control studies in Italy, Australia, and the United States

	Randi *et al.* (2006), Italy	Whiteman *et al.* (2003), Australia	Berwick *et al.*, US
Total subjects	538	231	528
Head and neck	81	77	36
Trunk	219	154	284
Upper extremities	48	—	
Lower extremities	183	—	
Total extremities	231	—	189
Mean/median number of nevi	Mean (trunk, head and neck, and upper extremities): males, 20.2 females, 14.7	Median (trunk, head and neck, and upper extremities): 33	Median (back and arms): 5 Mean: 10.7

Riola *et al.* (2001) reported a similar proportion of head and neck melanomas, whereas both Berwick *et al.* and Cho *et al.* (2005), another American group, had a much smaller proportion of head and neck melanomas. The distributional difference between the United States populations and the Mediterranean populations could possibly be due to genetic factors specific to these populations, differential sun exposure patterns, or selection bias — although the Spanish study was population-based. In any case, the different distribution of melanomas by anatomic site among Mediterranean, Australian, and American populations should be investigated further.

More interesting is the difference in the mean or median numbers of nevi reported. Although the papers report numbers quite differently, the great differences among countries are obvious. Of course, these are also probably due to the wide variation in the methods of counting and the proportion of the body counted. However, in Italy, the highest tertile for nevi on the trunk was ">10" (adding posterior and anterior trunk), whereas, in Australia, 44.8% of the nevi on the trunk and 24.7% on the head and neck were ">60" — a very large difference. A comparison of the median number of nevi in the Berwick *et al.* study and the Whiteman *et al.* (2003) study shows a sixfold difference between Connecticut and Australia, whereas a comparison of the mean number of nevi in the Berwick *et al.* study and the Randi *et al.* (2006) study shows a twofold difference. This is only a very general estimate, given the differences in anatomic sites accounted for. The point, however, should be clear that Australians have many more nevi than Italians and Americans — an unsurprising fact.

Why is that important for the study by Randi *et al.* (2006)? The hypothesis by Whiteman *et al.* (2003) of divergent pathways for the development of melanoma has generated a great deal of interest and enthusiasm. The data of Curtin *et al.* (2005) clearly support this hypothesis. However, it is critical not to interpret these ideas too simplistically — as I fear is happening. True population-based studies and larger studies will bear out the complexity of the issues, but the data of Randi *et al.* (2006) also point out this complexity.

> Different etiologic pathways may consist of (1) aberrant melanogenesis and (2) cumulative sun exposure among susceptible individuals.

The major goal of most epidemiologists working in the area of melanoma is to truly understand its etiology. The problem with the high-profile data presented by Whiteman *et al.* (2003) and Curtin *et al.* (2005) is that they are based on highly selected populations and divide melanomas rather abruptly between those on the head and neck and those on the trunk. Our study (Berwick *et al.*, 2005), using the data cited in Table 1, found that sun-damaged skin, as evidenced by solar elastosis, appears all over the body and is in fact most significantly associated with melanoma on the trunk. Therefore, a paper such as that of Randi *et al.* (2006) is an important contribution to the literature, as it adds the necessary complexity to the important hypothesis put forth by Whiteman *et al.* (2003).

CONFLICT OF INTEREST

The author states no conflict of interest.

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