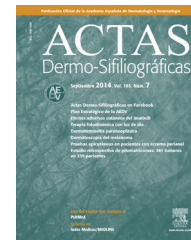




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## HISTORY AND HUMANITIES IN DERMATOLOGY

### Darwinian Medicine and Psoriasis<sup>☆</sup>



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**Abstract** Darwinian medicine, or evolutionary medicine, regards some pathological conditions as attempts by the organism to solve a problem or develop defense mechanisms. At certain stages of human evolution, some diseases may have conferred a selective advantage. Psoriasis is a high-penetrance multigenic disorder with prevalence among whites of up to 3%. Psoriatic lesions have been linked with enhanced wound-healing qualities and greater capacity to fight infection. Leprosy, tuberculosis, and infections caused by viruses similar to human immunodeficiency virus have been postulated as environmental stressors that may have selected for psoriasis-promoting genes in some human populations. The tendency of patients with severe psoriasis to develop metabolic syndrome may reflect the body's attempt to react to environmental stresses and warning signs by triggering insulin resistance and fat storage.

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#### PALABRAS CLAVE

Psoriasis;  
Medicina evolutiva;  
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Síndrome metabólico;  
Escudo químico

#### Medicina darwiniana y psoriasis

**Resumen** La medicina evolutiva o darwiniana entiende algunos procesos patológicos como intentos del organismo por solucionar un problema o generar mecanismos de defensa. Algunas enfermedades pueden haber representado una ventaja en ciertos estadios de la evolución humana. La psoriasis es una enfermedad poligénica con alta penetrancia y una prevalencia de hasta el 3% en las poblaciones de origen caucásico. Se ha descrito que las lesiones de psoriasis generan una mayor capacidad para la curación de las heridas, y de lucha contra la infección. Se ha postulado que, en ciertas poblaciones, los genes promotores de psoriasis han sido seleccionados ante la presión ambiental de ciertas infecciones como la lepra, el sida y la tuberculosis. La tendencia de los enfermos con psoriasis grave al desarrollo de síndrome metabólico puede representar un intento de reacción ante presiones ambientales y señales de alarma que desencadenan resistencia insulínica y ahorro de grasa.

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“Nothing in biology makes sense except in the light of evolution.”

T. Dobzhansky (1900–1975)

Only in recent decades has the theory of evolution been incorporated into our understanding of diseases through the approach known as Darwinian medicine.<sup>1,2</sup> Viewed through the prism of Darwinism, the organism is the product of trial and error and therefore holds within itself certain instructions and functional processes that might prove useful in some environmental conditions but not in others. As a result, certain events, once set in motion, may eventually generate disease. For a condition to fit into this paradigm, it must be prevalent and heritable. Susceptibility must vary and the potential benefits must have exceeded the costs during a prolonged period in the history of the species. Furthermore, the disease must not hinder reproduction.

The example of obesity provides a way to comprehend the Darwinian perspective on disease.<sup>3</sup> Early hominids evolved in an environment in which food was scarce. The better part of our own evolutionary history has continued to take place under conditions of scarcity. A thrifty genotype was therefore favored, but the abundance of high-energy foods in today’s developed world, along with sedentary behaviors, has promoted obesity on a level that has now reached pandemic proportions. Atherosclerosis provides another example, in this case one that shows how certain advantages become disadvantages beyond the reproductive years.<sup>3</sup> Mouse strains with macrophage hyperactivity have been shown to have low rates of infection during the reproductive phase of life. They also display early development of atherosclerosis, however, since macrophages are the main source of foam cells that appear during the initial stages of atheromatous plaque formation. Thus, there is a trade-off between good antimicrobial defenses early in life and the formation of atheromatous plaques later on.

Our reasoning about evolutionary medicine must also take epigenetic mechanisms into account. The environment can affect gene expression and mutations may be heritable. Epigenetics changed the notion that we are merely that which is written in our genes by calling attention to histone interactions with nucleic acid and histone methylation. These processes explain adaptive changes that can take place relatively rapidly—over the course of hundreds of years rather than the millions required for the natural selection of random genotypic variants.

### Analysis of Psoriasis From the Vantage of Darwinian Medicine

The worldwide prevalence of psoriasis has been estimated to be around 2%.<sup>4</sup> A recent study in Spain estimates the prevalence at 2.3%,<sup>5</sup> and a north-to-south gradient can be seen in prevalence rates across all Western countries. Like other autoimmune diseases (Crohn disease, lupus erythematosus, rheumatoid arthritis), psoriasis has many pathophysiological pathways. The pathogenesis of psoriasis is fundamentally genetic: at least 9 loci are implicated (PSORS1–9) through the activation of both innate and

acquired immune pathways. Because the prevalence of psoriasis is high and susceptibility is variable, it is possible to interpret this disease through the framework of evolutionary medicine. Psoriasis is also a systemic disease that is characteristically associated with insulin resistance and inflammation in other organs.

### Prevalence and Distribution

Psoriasis has the highest penetrance of all the polygenic disorders. Heritability is estimated at between 60% and 90%<sup>6</sup>; in contrast, the heritability values for Crohn disease and rheumatoid arthritis are 50% and between 40% and 60%, respectively. Psoriasiform dermatoses have occasionally been described in other primates.<sup>7</sup> The relevant genes can also appear in various other species and their expression can be induced in certain animal models, indications that their presence in the genome dates from prehuman evolutionary stages. However, in spite of rare exceptions, psoriasis seems to be a primordial disease of human populations, particularly Caucasians, suggesting that it is an integral part of human rheostasis and highly peculiar to our species.

Psoriasis is not uniformly distributed across populations. The prevalence is so low in 2 ethnic groups—Alaskan Natives (the Inuit and others) and Australian Aboriginals—that the disease is considered practically nonexistent among them. Alaskan Natives also have a low prevalence of inflammatory joint disease, diabetes, ischemic heart disease, and asthma.<sup>8,9</sup> The traditional explanation cites the protective effect of a diet rich in essential fatty acids from blue fish. This diet is also a reliable source of vitamin D, which would not be effectively synthesized in these peoples given their relatively dark skin and the low levels of solar radiation in their traditional habitats near Arctic and Antarctic latitudes. That the traditional Inuit diet is responsible for this protective phenotype would seem to be demonstrated by individuals’ development of the aforementioned diseases on switching to a so-called Western diet. However, all attempts to show a therapeutic effect of fatty acids in psoriasis have failed. It seems that, in addition to environmental factors, there are also specific genetic traits, very probably determined by geographic isolation and genetic drift. Alaskan Natives appear to be representative of the first human migrations across the Bering Strait that led to the colonization of North America.<sup>10</sup>

Australian Aboriginals are the other group in which psoriasis is extremely rare. Recent genetic studies conclude that they are descendents of African hominids who migrated directly to the continent very early.<sup>11</sup> The Aboriginals are therefore a highly homogeneous population from the standpoint of genetics, and they only became influenced by Western lifestyles after the 17th-century colonization of Australia.

Current thinking holds that the lack of psoriasis in such populations is explained by the phenomenon of genetic drift, through which natural selection acted relatively rapidly on certain alleles that provided humans with no advantages in their new environments.<sup>2</sup>

Genetic drift seems to have conserved psoriatic alleles and potentiated their frequency in Caucasian populations,

whose move from Africa occurred later than the migrations of the Native Alaskans and Australian Aboriginals. What benefits could psoriasis have conferred on the highly varied Caucasian populations? *Homo sapiens*, who have inhabited Africa for some 200 000 years, migrated north to colonize the European continent roughly 100 000 years ago during the last major Ice Age. As the glaciers receded about 15 000 years ago, agriculture and animal husbandry began to develop. Until then, the metabolism of European humans had favored insulin resistance in the interest of storing fat for times of scarcity. Also potentiated were physical strength, the ability to walk long distances in search of food, and resistance to cold. The gradual appearance of lighter skin phototypes preserved these humans' ability to synthesize vitamin D under conditions of low solar radiation.

### The Possible Evolutionary Advantages of Psoriasis

Psoriasis flare-ups are triggered by streptococcal infection (guttate psoriasis), psychological stress, local trauma (the Koebner phenomenon), or exposure to certain drugs. From an evolutionary point of view, psoriasis is a cutaneous, articular, and metabolic response to threatening situations.

### The Chemical Shield

Unlike the lesions of atopic dermatitis, psoriasis lesions do not tend to become infected. Rather, they are rich in antimicrobial cells and peptides that serve as a first line of defense.<sup>12</sup> This feature has led authors to posit that the psoriatic plaque provides a protective chemical shield.<sup>13,14</sup> The existence of psoriasis may reflect an aberrant activation of alleles that code for infection control. Patients with the disease have been reported to have certain genetic traits linked to natural killer cell activation and other pathways that are necessary for optimal control of viral infections. One genetic study concluded that seropositive patients with psoriasis have genetic variants that protect against the human immunodeficiency virus.<sup>15</sup>

Another example of the possible anti-infection benefit conferred by psoriasis was observed in the Canadian province of Newfoundland. This territory is populated by a group of genetically isolated individuals descended from early settlers from Ireland, Scotland, and England who arrived some 300 years ago; the half million persons who live in the area have become an ideal model for genetic and epigenetic studies. The prevalence of psoriasis in Newfoundland is 5- to 10-fold higher than in other Caucasian populations.<sup>16,17</sup> Since the founding populations all came from the British Isles, where the prevalence of the disease is roughly 2%, what accounts for the genetic drift observed? The answer must be found in the selective advantages psoriasis provided over the past 300 years and in the incidence of tuberculosis in that period. Early in the 20th century tuberculosis was still the main cause of death in Newfoundland, where mortality was around 348 per 100 000 population, double the mortality in England at the same time.<sup>18</sup> Tuberculosis remained the principal threat until the

1950s, attributable to a harsh climate, poor nutrition, overcrowded living conditions, and isolation.

It has been suggested that psoriasis can confer protection against tuberculosis (Dr. W. Gulliver, personal communication). In addition to the hardships of climate and poor nutrition, it is also possible that large population losses during the colonial period favored the phenomenon known as a genetic bottleneck, referring to the rapid decrease in allelic variants that occurs in genetic drift. We do not know if the selection of psoriasis-promoting alleles is a purely stochastic phenomenon or a true product of epigenetic selection, but the notion that selection for psoriasis is present because it confers protection against tuberculosis is intriguing. In the same line are reports that patients with psoriasis who undergo immunosuppressant or biologic therapies are less likely to develop tuberculosis than those with other related autoimmune diseases such as rheumatoid arthritis.<sup>19</sup> Finally, it is noteworthy that Newfoundland also has the highest incidences of diabetes and Crohn disease in Canada,<sup>20</sup> an observation that gives a certain degree of support to the possibility of selection for individuals with a phenotype tending to autoimmune disease and insulin resistance.

Other authors have made an effort to explain why leprosy and psoriasis behave as mutually exclusive diseases. Bassukas and coworkers<sup>21</sup> hypothesized that the psoriatic genotype plays a role in protecting against Hansen disease, conferring advantages that favored survival in periods when human populations were decimated. The spread of the psoriatic genotype in northern Europe in the late medieval period coincided with the decline of leprosy, recalling the pattern for tuberculosis in Newfoundland. Resistance to infection in psoriasis would be genetically determined, linked to HLA-Cw\*6-associated haplotypes.

### Energy Storage and Systemic Metainflammation

Cutaneous psoriasis has been associated with greater accumulation of body fat, especially around the abdomen, and with the production of adipocytokines produced in adipose tissue.<sup>22,23</sup> Low-grade systemic inflammation in the patient with psoriasis would contribute to cutaneous and articular inflammation as well as the inflammatory state induced by the activation of adipose tissue.

To understand the proinflammatory capacity of the adipocyte we must first recall that liver, adipose, and immune system cells have a homolog in invertebrates, specifically in the fat body of insects.<sup>24</sup> This organ contains a pluripotent cell that is at once an immune, liver, and fat cell. Comparative physiology thus helps us understand how it is that an adipocyte can also behave as a component of the immune system and that some adipocytokines are also mediators of innate immunity, causing inflammation as well as insulin resistance and fat deposition in the liver. Examples of such mediators are lipocalin-2, or neutrophil gelatinase-associated lipocalin; resistin; and adipocyte fatty acid-binding protein.<sup>23</sup>

One theory of the pathogenesis of obesity includes the triggering of an immune reaction against antigens from the cutaneous or intestinal microbiome. The reaction is possibly

led by the innate immune system. The role of the microbiome is also being studied in psoriasis.<sup>25</sup> Individuals with psoriasis have been found to have higher plasma concentrations of lipopolysaccharide-binding peptides (a measure of low-grade systemic endotoxemia); this marker is associated with a higher incidence of metabolic syndrome.<sup>26</sup> It has been speculated that the microbiome can promote the inflammatory response of psoriatic arthritis.<sup>25</sup> This skin-joint-intestinal axis may be based on the activation of type 17 T-helper (T<sub>H</sub>) cells.

## Wound Healing

Psoriasis lesions share certain features present in wounds that are healing. Morhenn and coworkers<sup>27</sup> showed that healing occurred more rapidly in both the psoriasis-involved and uninvolved skin of patients with the disease than in the skin of nonpsoriatic patients. This trait may have represented an advantage for humans of reproductive age in Paleolithic times and possibly points to a putative protective effect of genes that code for psoriatic disease. The hypothesized protective chemical shield against certain infections, which trigger the immune system and warn the organism to prepare to store energy while also promoting rapid healing of wounds, appears to have offered an ideal combination of advantages for Paleolithic humans, who were required to move constantly in search of food, cope with periods of hunger, and fight against predators.

## Psoriatic Arthritis

Some 30% of patients with cutaneous psoriasis develop characteristic joint disease, which can become incapacitating in its most severe and advanced forms. Some authors believe that the sustained inflammation of cutaneous psoriasis eventually leads to joint inflammation and metabolic syndrome, a process referred to as the psoriatic march.<sup>28</sup> From the vantage of evolutionary medicine, inflammatory joint disease, such as rheumatoid arthritis, is a warning sign that the organism should restrict movement and save energy.<sup>1</sup> Although this strategy seems to create a paradox for the organism's balanced well-being, it is true that energy requirements are reduced when movement is limited, allowing so-called thrifty genes free rein to promote energy storage through fat deposition. Both psoriatic arthritis and rheumatoid arthritis are associated with higher risk for metabolic syndrome because of the low-grade state of meta-inflammation that activates mechanisms involved in insulin resistance,<sup>29</sup> and it seems natural to wonder whether inflammation is the cause or the effect. It is highly likely that the relationship between psoriasis and adipose tissue operates in both directions. However, some metabolic disorders described in psoriasis, such as elevated lipocalin and other adipokine levels,<sup>23</sup> are not fully corrected under antipsoriatic treatments; this finding points to a proinflammatory and proadipogenic genotype or epigenotype that continues to act even when skin lesions have been brought under control. Considered through this evolutionary prism, the individual continues

to have psoriasis even after skin lesions have cleared completely.

## Psoriasis and Reproductive Success

We have left for last our thoughts about an important question: If psoriasis-promoting genes were selected during evolution, once conferring certain evolutionary advantages but eventually promoting the disease prevalent in Caucasians, did psoriasis protect or impede reproduction in the species? Studies of successful gestation and psoriasis offer highly disputed results. A 1987 study concluded that infants born of mothers with psoriasis had higher birth weights,<sup>30</sup> a trait that could confer an evolutionary advantage. However, more recent studies found that infants born of mothers with severe psoriasis, whose gestation takes place under conditions of low-grade inflammation unfavorable to fetal development, more often have low birth weights, which would, in principle, be a disadvantage.<sup>31,32</sup> Furthermore, women with psoriasis have been found to be at higher risk for recurrent miscarriage and cesarean delivery.<sup>33</sup> The unfavorable effect of psoriasis often arises as a result of comorbidity (obesity, hypertension, diabetes, or smoking); complications may also be related to psoriatic treatment.

Pregnancy favors the development of a proinflammatory state in which there is a shift toward a predominantly T<sub>H</sub>2-cell response, rather than the T<sub>H</sub>1- and T<sub>H</sub>17-cell responses that are more closely linked to psoriasis. In the third trimester, however, as delivery approaches, T<sub>H</sub>1 cells once again predominate to play a protective role against infection during birth and the postpartum and neonatal periods.<sup>33</sup>

Finally, there is a curious 1992 study by Traupe and coworkers,<sup>34</sup> who concluded that the offspring of fathers with psoriasis have higher birth weights than the offspring of mothers with the disease. Furthermore, penetrance also depends on the sex of the patient. These findings would suggest genomic imprinting induced by epigenetic changes.

The evidence available to us at this time sheds insufficient light on the relationship between psoriasis, gestation, and fetal health, and it would be useful to design new studies addressing the question. However, any study would have to take into account a possible negative effect of antipsoriatic treatment and comorbidity, which make it quite difficult to analyze psoriasis as a risk factor in itself.<sup>33</sup>

## Conclusions

Darwinian medicine takes up the theory of evolution and applies it, using genetics as a prism to explain disease as an adaptive response to the environment. Darwin's merit lay in having formulated his ideas at a time when the scientific foundations that would come to support them had scarcely been established. Although he was unaware of the existence of genes and their heritability, intuition led him to make a daring proposal, that there were accidental variations that were responsible for changes. Long afterwards, within the framework of the neo-Darwinism of the 1940s, proponents like Huxley and Dobzhansky reinforced Darwin's

theory by linking natural selection to genetics. Today we know that genomic control over the design and function of the organism is an imperfect mechanism. Genes impede or promote conditions that are then classified as diseases or not according to whether they do or do not benefit survival. From this vantage, psoriasis can be considered a disease induced by the expression of a specific set of genes that interact with the environment. In certain periods of the history of human evolution the genetic or epigenetic programming of psoriasis was motivated by a series of needs and provided benefits: energy conservation and the optimization of antimicrobial defense mechanisms and enhancement of wound healing, among other functions such as camouflage and thermoregulation. The genetic basis of psoriasis makes its transformation into a disease inevitable. However, the genome can be shaped and molded, even to the extent that disease expression can be silenced or transformed into an advantage. The coming years will bring another therapeutic revolution in which pharmacogenetics and interventions on gene expression will be applied to autoimmune diseases. It is within our grasp to understand the nature of psoriasis so that we can manage it by modifying both gene expression and lifestyle.

## Conflicts of Interest

The author declares that he has no conflicts of interest.

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