See related articles on pages 56, 99, 104

In this Issue: Defined Patient Populations are Required to Establish Genetic Pathogenesis

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DEFINED PATIENT POPULATIONS

Despite enormous progress in the basic sciences and substantial progress in identifying biochemical and genetic mechanisms of many skin diseases, it is the clinical scientist who now holds the key to unraveling most of skin's mysteries. Knowledge about the genetic code and sequencing the human genome have not replaced the physicians who take care of patients. Until now, and for patients with single gene defects, biologic samples from a limited number of patients have allowed laboratory scientists to identify those diseases that are caused by defects in single genes. As examples, sex-linked ichthyosis (OMIM #308100 ICHTHYOSIS, X-LINKED) and keratosis follicularis (OMIM #124200 DARIER-WHITE DISEASE) come to mind. On the other hand, for genetically complex diseases, which affect the majority of patients who seek care from physicians who know about skin, the issues are much more difficult. In this issue, the paper by Alamartine and colleagues from the Renal Transplantation and Dermatology Services in Saint Etienne, France illustrates this issue well (page 99). These investigators sought to identify genetic factors that might contribute to the high frequency of skin cancer that follows immunosuppression, as is required to protect allograft kidneys after transplantation. Their search began with knowledge that the cytokine Interleukin-10 (IL-10) plays roles in ultraviolet radiation-mediated immunosuppression, and it was complemented by an older, established literature about the critical role of immunosuppression in cutaneous carcinogenesis. Their aim was to search for IL-10 gene promoter polymorphisms in the patients who had developed skin cancer. Key to the experimental work were 70 kidney transplant recipients who developed squamous cell or basal cell carcinomas, matched with 70 healthy control subjects and with 70 transplant patients who had not developed cancer. The idea of a polymorphism is that patients with cancer might be more likely to have a 'minor' difference in the genetic sequence that regulates the expression of the gene and consequently the expression of the IL-10 protein. After the genetic studies were performed, the investigators then examined IL-10 secretion capability in a subgroup of 40 patients by *in vitro* stimulation of peripheral blood mononuclear cells. It is the nature of scientific reporting that we would not be discussing this article if the answer had not been informative. In fact, IL-10 genotypes were differently distributed in the kidney transplant recipients who developed a skin carcinoma, but especially in those who developed squamous cell carcinomas. Moreover, secretion of IL-10 was strongly correlated with the predicted phenotype, and tended to be higher in patients who had developed squamous cell carcinomas. And what this means is that a genetic factor beyond that of pigmentation in transplant recipients plays a major, and perhaps even a dominant, role in conferring susceptibility for skin cancer. Obviously, the expression of IL-10 may not be the only factor that controls this susceptibility. Perhaps we are closer to being able to identify those patients who are most at risk for this preventable complication of immunosuppression. But it was the availability of a relatively homogeneous population of patients with skin cancer that made this study possible.

THERE ARE ANTIBODIES AND THEN THERE ARE ANTIBODIES

It is possible to define scientific progress as the process by which an individual (the scientist) determines how to make finer and finer discriminations among observations. For example, in the physical world, at first there was matter (such as water, identified through direct observation), and then molecules (H_2O, identified through chemistry) and eventually particles (neutrons, protons, and electrons, identified through physics). This process of making finer and finer distinctions has typified 19th, 20th, and now even 21st Century science, and it has obviously occured in medical science, as well. In this issue Luis Diaz and his several colleagues from all over the Western Hemisphere have added one more important step in our understanding of pemphigus by using an important distinction in the discipline of cutaneous immunology (page 104). They have worked with a special cohort of patients in a focus of endemic pemphigus in Limao Verde, Brazil, where disease prevalence is 3.4%. (See comments above about the importance of physicians who care for patients, and the role of these physicians in assembling well-characterized population of patients.) Endemic pemphigus foliaceus, like the sporadic form seen in the developed world, is mediated, at least in part, by IgG antibodies to desmoglein-1. The investigators had previously detected IgG antibodies to desmoglein-1 in 97% of their patients, but IgG antibodies were also present in 55% of normal subjects who lived within the endemic focus. Moreover, there were progressively lower levels of such antibodies in normal subjects in the surrounding areas. Thus, there was uncertainty about the role of such antibodies in the patients with the disease, when compared with the subjects without the disease. The key to the study was knowledge that IgG antibodies do not constitute a single population, but, rather there are important subtypes (IgG_1 through IgG_4), each with differing capabilities. The investigators went ahead and developed a highly selective assay to quantitate the subclasses of IgG antibodies. They now report that the normal subjects did have both IgG_1 and IgG_4 responses, and that the patients had similar levels of IgG_1, but much higher (19.3-fold higher) IgG_4 responses. Patients in remission had weak IgG_4 responses, but 74.3-fold higher IgG_4 responses were associated with active disease. Finally, in 5 patients in whom they had taken blood samples before and after the onset of clinical disease, a mean 103.1-fold rise in IgG_4 was associated with its onset. The conclusion is clear: it is not the IgG response against desmoglien-1 that is important, but

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the IgG_4 response. Not only do we need well-defined populations of patients to make such distinctions, we still need basic scientific information to tell us how to look.

SHEDDING LIGHT ON LASER LIGHT

A growing literature documents the concept that exposure of skin and the cells within skin to laser light at fluences below that which produce destructive thermal effects may have relatively specific effects on cellular function. This fact is now making the transition from a largely unanticipated observation to laboratory and clinical usefulness. And it is through knowledge of mechanisms of action for these effects that one may make refinements that lead to even greater specificity. Progress is reported in this issue by Yu, Hsin-Su and colleagues from the Kaohsiung Medical University in Taiwan (page 56). As noted above, it had been known that low-energy lasers are capable of producing energy densities so low that biologic alterations are the result of a direct irradiation effect, not thermal events, with temperature elevations in irradiated tissues limited to less than 0.1–0.5 C. Recently, *in vitro* studies had shown that low-energy lasers induce biostimulatory effects on cultured cells, inducing macrophages to release factors that stimulate fibroblast proliferation and fibroblasts to increase the production of pro-collagen, collagen, basic fibroblast growth factors and rates of proliferation. He–Ne laser treatment had been reported to stimulate IL-8 and IL-1 release from cultured keratinocytes and to induce an increase in the rate of keratinocyte migration and proliferation. Importantly for the study that follows, earlier reports had indicated that low-energy laser treatment might induce repigmentation in patients with vitiligo. Three important observations are reported in the article that follows: (1) The He–Ne laser induced a significant increase in basic fibroblast growth factor release from both keratinocytes and fibroblasts and a significant increase in nerve growth factor release from keratinocytes. (2) Media from He–Ne laser irradiated keratinocytes stimulated thymidine uptake, proliferation, and migration by cultured melanocytes. (3) More than half of the 30 patients with segmental-type vitiligo treated once or twice weekly experienced significant repigmentation. We agree with the investigators that it is reasonable to propose that He–Ne laser irradiation does stimulate melanocyte migration and proliferation through the relatively specific release of melanocyte growth factors and chemotactic agents, thereby providing a microenvironment suitable for repigmentation.