In This Issue . . .

Skin Damage by UVA: A Broad-Spectrum Event

Using an experimental human model for chronic skin damage, Lavker *et al* (p. 17) have found evidence that the action spectrum for UVA-induced chronic epidermal and dermal damage extends into longer UV wavelengths. Current concepts about long-term actinic damage are derived primarily from experimental studies of the UVB portion of the ultraviolet spectrum. It is more difficult to assess damage from UVA at usual exposure levels, because it doesn't cause immediate, obvious damage such as a sunburn unless it is administered with a photosensitizer, such as psoralen, but recent evidence from animal and human studies suggests that UVA may also contribute significantly to photodamage. Since photodamaged skin is the result of cumulative solar exposure, both chronic and subacute, the investigators developed a human model for cumulative damage by using repetitive exposures to suberythermal doses of UVA over relatively short durations. Subjects were irradiated with five different UVA wavelengths once daily for 9 days and biopsied, and biopsies were analyzed for epidermal and dermal changes. Chronic epidermal changes were induced more efficiently by the shorter UVA wavelengths (335–345 nm), but the spectrum for chronic dermal photodamage was flat and broad, extending from 335 to 400 nm. These findings strongly suggest that the action spectrum for chronic photodamage differs from the spectrum for acute erythema and includes UVA wavelengths. In order to prevent chronic photodamage, therefore, sunscreens that filter a broad spectrum of UVA extending out to 400 nm and that filter effectively must be developed. This experimental model may be useful in developing a measure of sun protection for UVA sunscreens similar to the sun protection factor, or SPF, used for UVB sunscreens.

Chromosome Abnormalities in CTCL: A New and Better Method of Detection

Karenko *et al* (p. 22) show that chromosomally abnormal lymphocytes found in the blood of cutaneous T-cell lymphoma (CTCL) patients also can be detected in the blood of patients with parapsoriasis en plaque, both by conventional chromosome analysis and also by *in situ* hybridization of blood lymphocytes in interphase. Patients in the later stages of CTCL have a wide spectrum of chromosomal abnormalities. The drawback of conventional cytogenetics has been the need to culture the cells, a process in which the malignant cells are often lost. To look for chromosomal changes early in the course of CTCL, and as a possible diagnostic aid, the investigators compared these methods in conventional chromosome analysis and two different methods of interphase *in situ* hybridization, on peripheral blood lymphocytes. All three methods were in agreement, and findings with the *in situ* method were reproducible at intervals of several months. The level of abnormalities differed in CTCL, parapsoriasis en plaque, and controls, and the development of clones of cells with chromosomal abnormalities was usually found to precede relapse or progression of disease, suggesting that chromosomal *in situ* hybridization methods may be useful in diagnosis and followup. Further studies will be needed to better define the chromosomal regions affected in CTCL and to determine whether chromosomal aberrations in CTCL may reflect genetic instability. The aberrations found in parapsoriasis en plaque by the *in situ* method support the view that a subgroup of large-plaque parapsoriasis is an early stage of CTCL. The new method may replace the much more labor-intensive traditional cytogenetic methods and may facilitate studies of chromosomal abnormalities in CTCL and its clinical precursors.

Complementation Studies in Type II Albinism: A Way to Approach *P* gene Function

The human *P* gene, which encodes a melanosomal membrane protein of unknown function, is one of three genes mutated in the three known types of human albinism. Mutations in the *P* gene produce type II oculocutaneous albinism (OCA2) in humans, and mutations in the homologous *p*-locus in mice cause pink-eyed dilution. In order to begin to discern the function of the *P* gene, Sviderskaya *et al* (p. 30) have produced mouse melanocyte and melanoblast cell lines from mice that were compound heterozygotes for mutations in the *p* locus, lacking a functional *p* gene and hence hypopigmented, a *p*-null mutant cell line. To develop an assay for human *P* gene function, the investigators reintroduced a normal human *P* gene into the *p*-null cells and examined the pigmentation in the transfected cells. Reintroduction of a functional *P* gene complemented the *p*-null mutations and restored both melanin biosynthesis and visible pigmentation in the *p*-null mutant cells, indicating that the transfected human *P* gene was functional and also that the human and mouse genes are functionally equivalent. In experiments to determine to what extent *P* genes from patients with OCA2 could also restore pigmentation to the *p*-null mutants, transfection with each of two OCA2 mutant human *P* cDNAs resulted in only partial complementation, producing pigmentation that corresponded closely with the clinical phenotypes associated with these mutations. The results indicate that the effect of the mutant genes can be assessed even without a direct functional assay for the protein coded by the *P* gene. The complementation assay can be used to distinguish true OCA2 mutations from nonpathologic polymorphisms, to quantitate the effects of these mutations on *P* function, and to begin to determine *in vitro* what types of processes are controlled by the *P* gene. These findings will help to determine the function of the *P* gene.

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A Better Way to Diagnose EBA

Chen *et al* (p. 68) have developed an ELISA for rapid detection of anti-type VII collagen autoantibodies in serum, a test that may be very useful in the diagnosis of epidermolysis bullosa acquisita (EBA). EBA, an autoimmune blistering skin disease characterized by IgG autoantibodies to type VII collagen, a major component of anchoring fibrils, can be difficult to distinguish from other blistering diseases, particularly pemphigoid, on clinical grounds. The authors' previous studies had shown that all autoantibodies to type VII collagen in the sera of EBA patients as well as of patients with bullous systemic lupus erythematosus (BSLE), which are also known to react with type VII collagen, recognized four major epitopes localized within the amino-terminal noncollagenous domain, or NC1. Sera from patients with EBA and BSLE reacted with the recombinant NC1 protein in ELISA, but sera from 16 patients with pemphigoid, 11 patients with pemphigus, and a battery of controls did not react. The ELISA appears to be more sensitive than either indirect immunofluorescence or immunoblotting in detecting EBA sera with low titers of autoantibodies. Since the target antigen is fully post-translationally modified and not denatured, it may recognize autoantibodies that bind only to conformational epitopes and not to denatured antigens, for example in an immunoblot. Because of the convenience and widespread availability of the ELISA technology, the new assay can be used widely for screening sera from patients with EBA or BSLE and for following antibody titers to determine whether antibody levels correlate with disease activity.

Why is Borrelial Lymphocytoma So Rare in North America?

Picken *et al* (p. 92) show that borrelial lymphocytoma in European patients can be caused by at least two genomic groups of *Borrelia burgdorferi* sensu lato, one of which is also present in North America. The vast majority of cases of solitary lymphocytoma occur in Europe, and reports from North America are very unusual. This observation, coupled with the presence of three borrelial species isolated from patients in Europe (*B. burgdorferi* sensu stricto, *B. garinii*, and *B. afzelii*), but only one human pathogenic species in North America (*B. burgdorferi* sensu stricto), has promoted speculation that the specific clinical manifestations of Lyme borreliosis may be correlated with specific species of borrelia. This led the investigators to ask whether lymphocytoma isolates of borrelia derived from Slovene patients all belong to the species *B. afzelii* and/or *B. garinii*. Characterization of five isolates obtained over the course of several years showed that four were *B. afzelii*, but the molecular characteristics of the fifth isolate were most similar to those of a rare genomic group, the DN127-group of borrelia, which is closely related to the common North American species, *B. burgdorferi* sensu stricto, and also is found in North America. If these two species, *B. afzelii* and the fifth isolate, represent the only etiologic agents of borrelial lymphocytoma, the paucity of North American cases of lymphocytoma could be explained by the scarcity of DN127-group isolates. Another interpretation of the data, however, is that the specific species of borrelia and the clinical manifestations of Lyme disease are not well correlated, so that one species may cause more than one clinical condition, as has already been shown for both erythema migrans and neuroborreliosis. In this case, reasons for the predominance of solitary lymphocytoma in Europe remain to be elucidated.

Inhibition of S6 Kinase By Rapamycin: A Potential Role in Treatment of Psoriasis?

Many cellular signaling pathways critical to cellular regulation are in turn regulated by kinases, which phosphorylate substrates, for example, changing inactive substrate proteins into active enzymes, and kinase function is often a rate-limiting step. S6 kinase is a participant in a series of protein kinase reactions, or a protein kinase cascade, and regulates translation of specific mRNAs. S6 kinase activity is itself regulated by phosphorylation, which typically occurs in response to growth factors. It was recently discovered that activation of S6 kinase by growth factors is inhibited by the immunosuppressive drug rapamycin, which can be used to treat psoriasis, suggesting that S6 kinase may be involved in the pathogenesis of psoriasis. In this issue, Choi *et al* (p. 98) show, in agreement with this hypothesis, that S6 kinase enzymatic activity is higher in psoriatic lesions than in non-lesional or normal epidermis. S6 kinase mRNA and protein levels were not elevated, indicating that the observed increase in S6 kinase activity rose from activation of S6 kinase rather than from an increase in expression, i.e., in the amounts of S6 kinase mRNA or enzyme. The growth factors EGF and TGF-α, which have been implicated in studies of psoriasis, stimulated S6 kinase activity in cultured human keratinocytes. Rapamycin inhibited TGF-α-stimulated S6 kinase activity and also inhibited keratinocyte growth. The authors propose the following scenario in the pathogenesis of psoriasis: EGF receptor ligands such as TGF-α or amphiregulin, which are known to be elevated in lesions of psoriasis, stimulate the EGF receptor, which increases S6 kinase activity, which is in turn a link in the chain of events leading to epidermal hyperplasia characteristic of psoriasis. Rapamycin may be beneficial in psoriasis by virtue of its ability to interrupt this pathway.