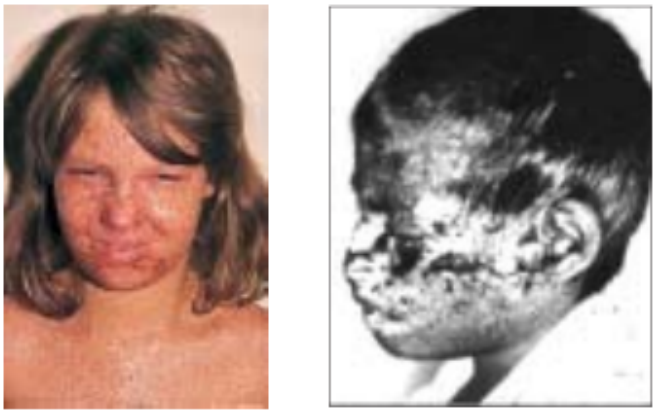
Xeroderma Pigmentosum

Xeroderma pigmentosum (XP) is a heterogeneous group of genetically determined skin disorders due to unusual sensitivity to ultraviolet light. They are manifested by dryness and pigmentation of the exposed regions of skin (xeroderma pigmentosum=“dry, pigmented skin”). The exposed areas of skin also show a tendency to develop tumors. The causes are different genetic defects of DNA repair. Repair involves mechanisms similar to those involved in transcription and replication. The necessary enzymes are encoded by at least a dozen genes, which are highly conserved in bacteria, yeast, and mammals.

A. Clinical phenotype

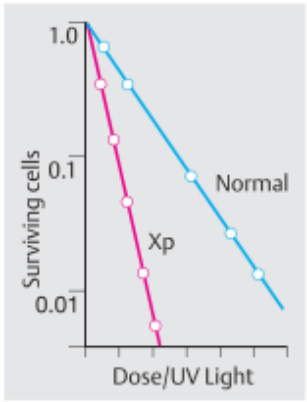
The skin changes are limited to UV-exposed areas (2). Unexposed areas show no changes. Thus it is important to protect patients from UV light. An especially important feature is the tendency for multiple skin tumors to develop in the exposed areas (3). These may even occur in childhood or early adolescence. The types of tumors are the same as those occurring in healthy individuals after prolonged UV exposure.



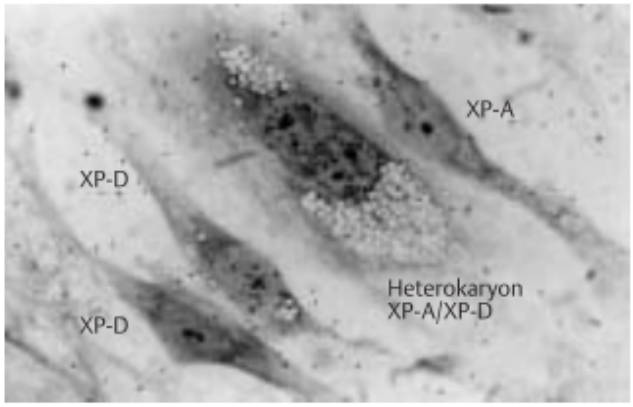
Clinical phenotype

B. Cellular phenotype

The UV sensitivity of cells can be demonstrated in vitro. When cultured fibroblasts from the skin of patients are exposed to UV light, the cells show a distinct dose-dependent decrease in survival rate compared with normal cells (1). Different degrees of UV sensitivity can be demonstrated. The short segment of new DNA normally formed during excision repair can be demonstrated by culturing cells in the presence of [3 H]thymidine and exposing them to UV light. The DNA synthesis induced for DNA repair can be made visible in autoradiographs. Since [3 H]thymidine is incorporated during DNA repair, these bases are visible as small dots caused by the isotope on the film (2). In contrast, xeroderma (XP) cells show markedly decreased or almost absent repair synthesis. (Photograph of Bootsma & Hoeijmakers, 1999).



1. UV sensitivity



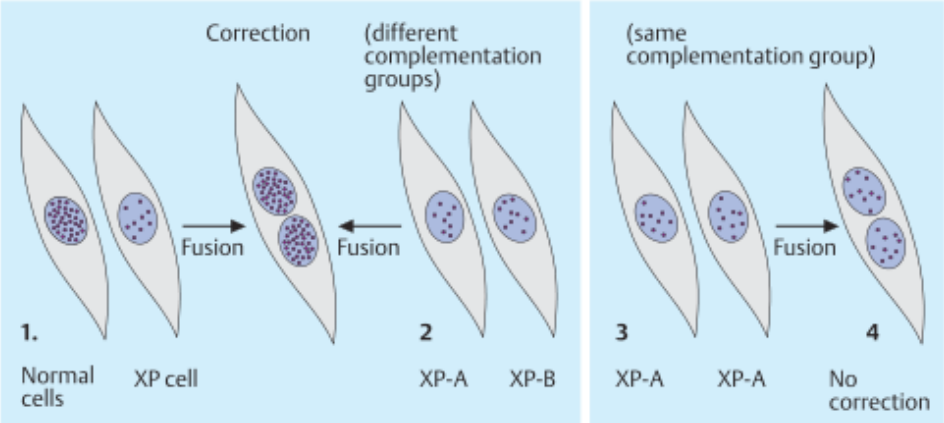
2. Complementation following fusion of XP-A and XP-D cells

Cellular phenotype

C. Genetic complementation in cell hybrids

If skin cells (fibroblasts) from normal persons and from patients (XP) are fused (cell hybrids) in culture and exposed to UV light, the cellular XP phenotype will be corrected (1). Normal DNA repair occurs. Also, hybrid cells from two

different forms of XP show normal DNA synthesis (2) because cells with different repair defects correct each other (genetic complementation). However, if the mutant cells have the same defect (3), they are not be able to correct each other (4) because they belong to the same complementation group. At present about ten complementation groups are known in xeroderma pigmentosum. They differ clinically in terms of severity and central nervous system involvement. Each complementation group is based on a mutation at a different gene locus. Several of these genes have been cloned and show homology with repair genes of other organisms, including yeast and bacteria.



Genetic complementation in cell hybrids