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Shining a Light on Xeroderma Pigmentosum

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Xeroderma pigmentosum (XP) is a rare, autosomal recessive disorder of DNA repair characterized by sun sensitivity and UV radiation–induced skin and mucous membrane cancers. Initially described in 1874 by Moriz Kaposi in Vienna, nearly 100 years later, James Cleaver in San Francisco reported defective DNA repair in XP cells. This eventually provided the basis for a mechanistic link between sun exposure, DNA damage, somatic mutations, and skin cancer. XP cells were found to have defects in seven of the proteins of the nucleotide excision repair pathway and in DNA polymerase η. XP cells are hypersensitive to killing by UV radiation, and XP cancers have characteristic "UV signature" mutations. Clinical studies at the National Institutes of Health found a nearly 10,000-fold increase in skin cancer in XP patients under the age of 20 years, demonstrating the substantial importance of DNA repair in cancer prevention in the general population. Approximately 25% of XP patients have progressive neurological degeneration with progressive loss of neurons, probably from DNA damage induced by oxidative metabolism, which kills nondividing cells in the nervous system. Interestingly, patients with another disorder, trichothiodystrophy, have defects in some of the same genes as XP, but they have primary developmental abnormalities without an increase in skin cancer.

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PROLOGUE FABLE

Imagine it's the late 1800s. An infant is taken outside on the first sunny day of spring. After a short time, the child becomes irritable and starts crying. By the next morning, her skin becomes very red and blistered with eyes swollen shut. Parents wonder what sort of malady this could be? Slowly the skin and eyes heal. But it happens again and again. Strong sunlight seems to bother her eyes that are often red and watering. Just past her first birthday, her skin starts to develop freckle-like spots, mostly in areas not covered by clothing. In older childhood growths develop and turn into tumors that seem to eat through her skin. She doesn't always respond when called as if she were becoming deaf, she is having more difficulty walking and her thinking has become quite slow.

We now know xeroderma pigmentosum (XP) as a rare autosomal recessive disorder of DNA repair, which manifests clinically as photosensitivity, actinic damage to the skin, cancer of UV radiation–exposed areas of the skin and mucous membranes of the eyes and mouth, and, in some patients, progressive neurological degeneration (Table 1). The skin is normal at birth and the disorder may present in two different ways. Some patients have an exaggerated response to UV radiation exposure with pronounced burning and blistering on minimal exposure to sunlight (Figure 1a). Others have a normal acute response to sun exposure. However, they all develop freckle-like pigmentary changes in sun-exposed areas, which eventually appear as poikiloderma (hyperpigmentation, hypopigmentation, atrophy, and telangiectasias). Unlike children in the general population, this freckling (lentiginous hyperpigmentation) typically appears before the age of 2 years (Figure 1b). The average age at onset of first skin cancer is <10 years (Figure 2a).

Our evolving understanding of the puzzling clinical findings of XP have raised many questions related to cell biology, photobiology, photocarcinogenesis, neurodegeneration, and genome stability. Answering the questions has illuminated several areas of biology, but there are still many yet to be clarified.

HISTORY OF XP

The road to our current understanding of XP started in the late nineteenth century with Moriz Kaposi, the Hungarian-born professor of dermatology in Vienna. In 1874, Kaposi described four patients with xeroderma or ''parchment skin'' in the early textbook of dermatology (Hebra and Kaposi, 1874), which he wrote with Professor Ferdinand Hebra, his father-in-law (Kraemer *et al.*, 1987). ''In addition to the parchment-like dryness, thinness, and wrinkling of the epidermis, the checkered pigmentation, and the small dilatations of the vessels, the most remarkable symptoms were the contraction and, at the same time, thinning of the skin'', features designating poikiloderma. His description

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Abbreviations: CS, Cockayne syndrome; NBCC, nevoid basal cell carcinoma; NER, nucleotide excision repair; NMSC, nonmelanoma skin cancer; TCR, transcription-coupled repair; TTD, trichothiodystrophy; XP, xeroderma pigmentosum

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Table 1. Comparison of features of XP, TTD, and CS

Feature	Xeroderma pigmentosum (XP)	XP with neurological abnormalities	Trichothio-dystrophy (TTD)	Cockayne syndrome (CS)	XP/CS complex
Skin					
Skin sun sensitivity	Yes	Severe	Yes/no	Yes	Yes
Lentiginous skin pigmentation	Yes	Yes	No	No	Yes
Sunlight-induced skin cancer	Yes	Yes	No	No	Yes
Eyes					
Photophobia	Yes	Yes	Yes/no	Yes	Yes
Conjunctival growths	Yes	Yes	No	No	Yes
Cancer (anterior eye/lids)	Yes	Yes	No	No	Not reported
Congenital cataracts	No	No	Yes	Yes	No
Pigmentary retinal degeneration	No	No	No	Yes	Yes
Somatic					
Short stature	No	No/yes	Yes	Yes	Yes
Immature sexual development	No	No	No/yes	Yes	Yes
Nervous system					
Progressive sensorineural deafness	No	Yes	No	Yes	Yes
Developmental delay	No	Yes	Yes	Yes	Yes
Progressive neurological degeneration	No	Yes	Unknown	Yes	Yes
Primary neuronal degeneration	No	Yes	No	No	No
Dysmyelination of brain	No	No	Yes	Yes	Yes
Cerebral atrophy	No	Yes	No/yes	Yes	Yes
Cerebellar atrophy	No	Yes	No	Yes	Yes
Calcification (basal ganglia)	No	No	No/yes	Yes	Yes
Disease mechanism					
Reaction to exogenous or endogenous DNA-damaging agents	Yes—severe	Yes—severe	No	Yes	Yes
Developmental defect	No	Yes	Yes—severe	Yes—severe	Yes—severe
Nucleotide excision repair defect	Yes	Yes	Yes	Yes	Yes
Molecular defects	*XPA, XPC, XPD, XPE, XPF, XPG, XP VARIANT (POLH)*	*XPA, XPB, XPD, XPF, XPG*	*XPB, XPD, TTDA, TTDN1*	*CSA, CSB*	*XPB, XPD, XPG*

distinguishes the pigmented lesions from normal as ''dark brown, pigmented spots resembling those of freckles,'' recognizing the clinical distinction between freckles and clinically atypical pigmented lesions (e.g., lentigines; Figure 1b, c, d, and f). He notes (as in Figure 1f) that the ''condition of the skin ceased with an abrupt line of demarcation'' at the upper third of the arm,'' but does not postulate why. He mentions the occurrence of a pear-shaped, red, granulating, fissured tumor that had developed within 1 year, and states ''We recognised the growth to be an epithelioma, and destroyed it in great part.'' However, his puzzlement was evidenced by his statement ''I have no more to say respecting this peculiar disease…''

In 1883, Albert Neisser of Breslau, Germany, reported XP with neurological abnormalities in two siblings who had XP with progressive neurological degeneration beginning in the second decade (Neisser, 1883). At present, it is recognized that ~25% of XP patients in the United States develop progressive neurological degeneration (Bradford *et al.*, 2011; Table 1 and Figure 1d).

In 1878, RW Taylor, MD, of New York reported the first few XP patients in the United States at the inaugural meeting

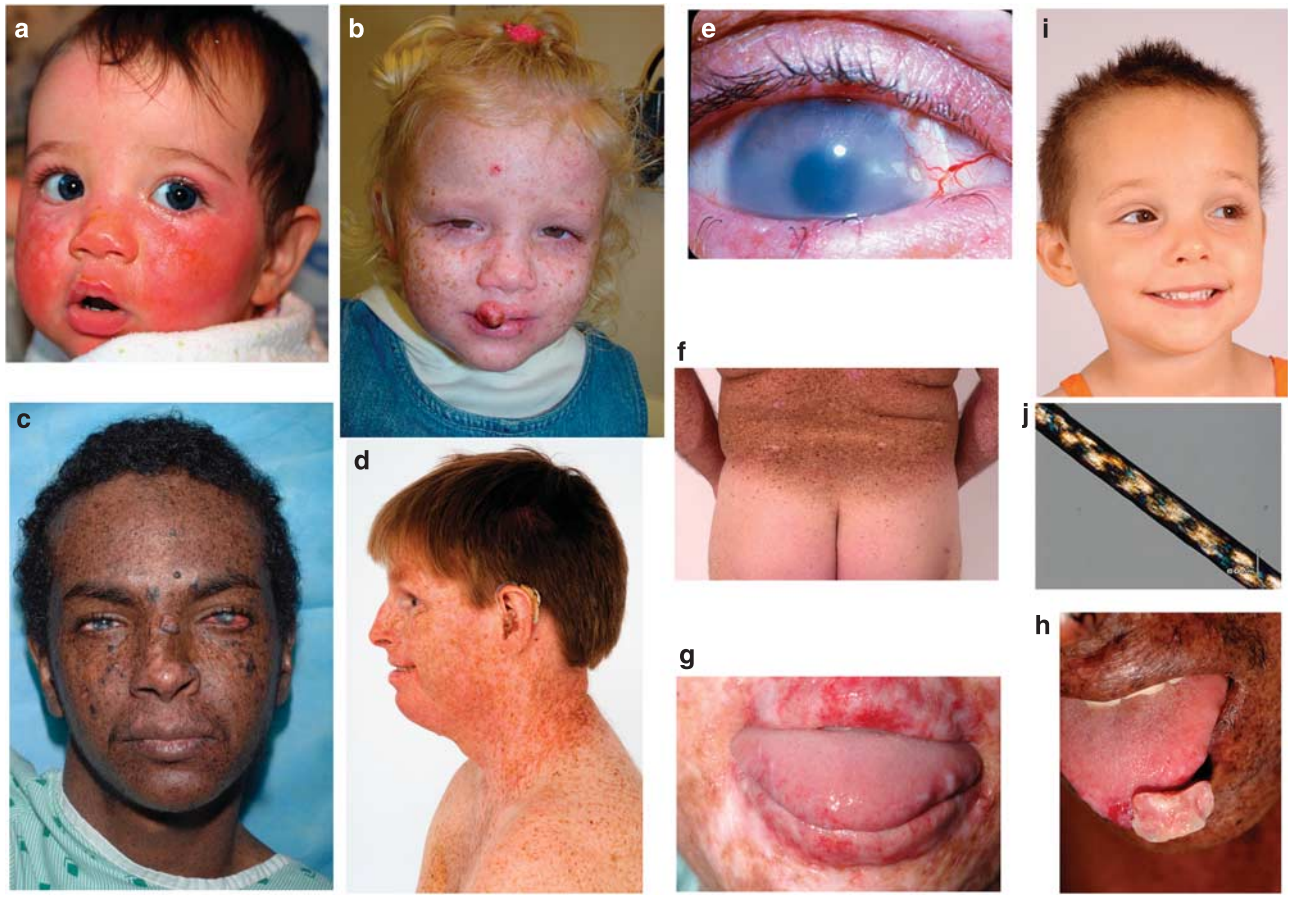

Figure 1. Xeroderma pigmentosum (XP) and trichothiodystrophy (TTD) patients studied. (**a**) Patient XP420BE complementation group X-PD at 9 months of age with severe blistering erythema of the malar area following minimal sun exposure. Note sparing of her forehead and eyes that were protected by a hat. (**b**) Patient XP358BE (XP-C) at the age of 2 years did not sunburn easily but developed multiple hyperpigmented macules on her face. A rapidly growing squamous cell carcinoma (SCC) or keratoacanthoma grew on her upper lip and a precancerous lesion appeared on her forehead. (**c**) Northern African patient XP393BE (XP-C; Mahindra *et al.*, 2008) at the age of 23 years with numerous hyperpigmented macules on his face. Nodular basal cell cancer is present on his left nasal root. Pigmented basal cell cancer is present on his left cheek. His eyes show cornea scarring from unprotected sun exposure. (**d**) Patient XP19BE (XP-A; Robbins *et al.*, 1991) at the age of 35 years with neurological degeneration. He has numerous hyperpigmented macules on sun-exposed areas of his face and neck. Progressive sensorineural deafness requires the use of a hearing aid. Images **a**–**d** are from Bradford *et al.* (2011). (**e**) Corneal clouding, pterygium, contact lens, and loss of lashes on lower eyelid. (**f**) Sharp demarcation between the poikilodermatous changes seen in sun-exposed skin compared with double-covered area of the buttocks of a 35-year-old XP patient. (**g**) Loss of vermillion border of the lips with prominent telangiectasias and scaring of the lips and anterior tongue. (**h**) SCC of the anterior tongue in an African man (from Mahindra *et al.*, 2008). (**i**, **j**) Clinical appearance of TTD. (**i**) A 3-year-old girl with short brittle hair, which is sparse and broken off at different lengths. She rarely has haircuts, except to trim uneven areas. She has a smiling, outgoing personality typical of TTD. (**j**) Tiger-tail banding under polarizing microscopy (original magnification $\times 10$). Images **i** and **j** are from Liang *et al.* (2005).

of the American Dermatological Association. In 1888, he reviewed the world literature and reported a total of 40 cases (Taylor, 1888).

The state of understanding of the disease was proposed in a 1926 report as follows (Per, 1926):

(1) ''Xeroderma pigmentosum is due to an extreme sensitization of the skin to ultra-violet rays of the sun.
(2) This congenital insufficient resistance of the skin to the actinic rays seems to be dependent on the consanguinity of the parents.
(3) Photodynamic substances in the organism (haematoporphyrin) do not play any part in the pathogenesis of this disease.
(4) The actinic rays of the sun produce an unquestionably unfavourable influence on the course of xeroderma pigmentosum.
(5) Medical preventive measures have a high value in this disease.''

Per also states: ''However, notwithstanding detailed pathological studies of the disease… no one has succeeded in making clear the obscure pathogenesis of this disease.''

In 1932, de Sanctis and Cacchione described three brothers in the same family with features of XP, mental deficiency, dwarfism, and gonadal hypoplasia with progressive neurological degeneration beginning at 2 years of age

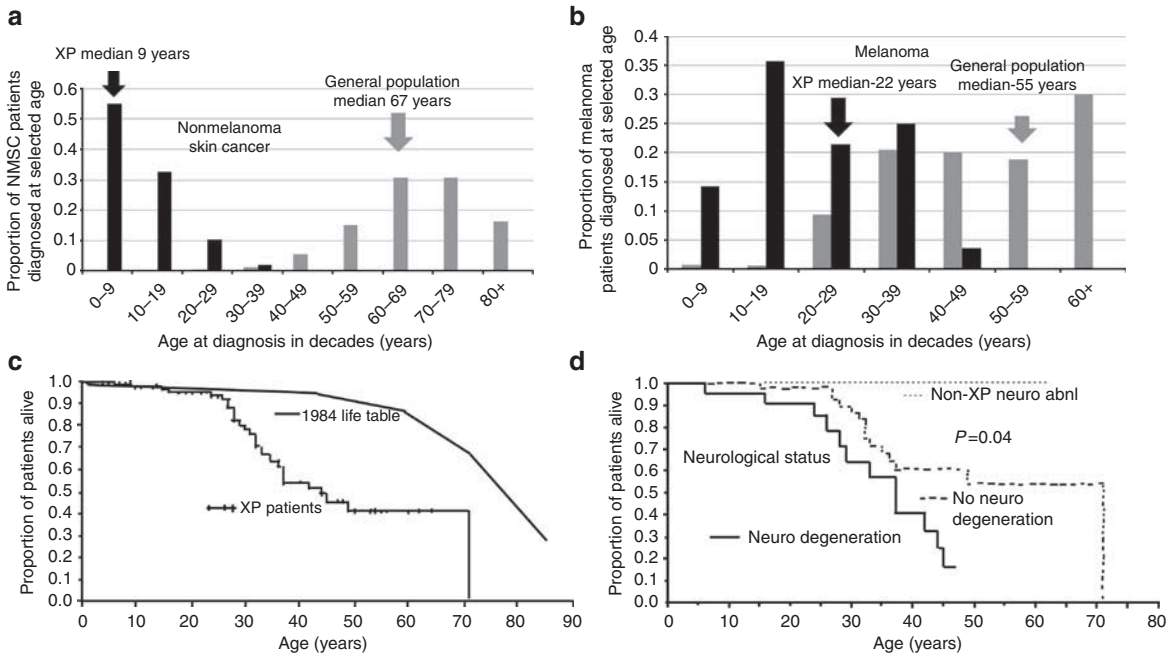

Figure 2. Xeroderma pigmentosum (XP) skin cancer by age at first skin cancer diagnosis and skin cancer type and mortality compared with the US general population. (**a**) Proportion of nonmelanoma skin cancer (NMSC) patients diagnosed at selected ages. (**b**) Proportion of melanoma patients diagnosed at selected ages. XP individuals with both NMSC and melanoma were used for both analyses. General population data taken from Glass and Hoover (1989). (**c**) Kaplan–Meier curve of XP patient survival compared with the US general population: 30% of XP patients had died by the age of 32 years. The survival of the XP patients was significantly less than the general population ($P<0.001$). (**d**) Kaplan–Meier curve of XP patient survival stratified by neurological phenotype. Patients with neurological degeneration had poorer survival rates than those without neurological degeneration ($P=0.04$). Graphs are from Bradford *et al.* (2011).

(de Sanctis and Cacchione, 1932). This severe phenotype is not commonly observed.

XP was described in a black African in 1938 (Loewenthal and Trowell, 1938; Figure 1c) and in an American black in 1940 (King and Hamilton, 1940).

Gartler reported UV radiation hypersensitivity of XP cells in 1964 (Gartler, 1964), but the importance of this report was not recognized for years. DNA repair abnormalities in XP were brought to the attention of the general scientific community by Cleaver's report in 1968 describing deficient excision repair in cultured skin fibroblasts (Cleaver, 1968). Stable DNA photoproducts were identified by Setlow (Setlow and Setlow, 1962). These photoproducts were not removed by XP cells (Setlow *et al.*, 1969; Cleaver and Trosko, 1970). XP cells were reported to be defective in the excision repair pathway by which UV radiation damage to DNA is repaired *in vitro* (Reed *et al.*, 1969) and also *in vivo* (Epstein *et al.*, 1970). The excision repair-proficient form of XP was described in 1971 (Burk *et al.*, 1971) and subsequently named ''XP Variant'' (Cleaver, 1972). Cell fusions studies (1972) demonstrated heterogeneity of the XP molecular defects (De Weerd-Kastelein *et al.*, 1972). Fusion of fibroblasts from different XP patients to form heterokaryons (a cell with nuclei from different patients) was found to exhibit correction (complementation) of the defective repair. To correct the defect, the different nuclei supplied what the other was lacking. This implied that different cells had different defects and led to the characterization of different complementation groups A through G (Kraemer *et al.*, 1975a, b; Arase *et al.*, 1979; Keijzer *et al.*, 1979; Figures 3 and 4). Two decades of research and advances in molecular biology, including generation of rodent cell complementation groups and yeast mutants, finally yielded the genes responsible for the different complementation groups: *XPA* (Tanaka *et al.*, 1990), *XPB/ERCC3* (Weeda *et al.*, 1990a b), *XPC* (Legerski and Peterson, 1992), *XPD/ERCC2* (Flejter *et al.*, 1992a b), *XPE/DDB2* (Dualan *et al.*, 1995), *XPF/ERCC4* (Sijbers *et al.*, 1996), *XPG/ERCC5* (Mudgett and MacInnes, 1990), and XP VARIANT (polymerase η; Johnson *et al.*, 1999; Masutani *et al.*, 1999; Figures 3 and 4 and Table 1).

WHAT HAVE WE LEARNED ABOUT XP AND WHAT HAS XP TAUGHT US ABOUT BASIC BIOLOGY?

Relationship of sun exposure to skin cancer

Epidemiological studies in the normal population have been used as evidence to support a role for sunlight as a cause of skin cancer. For example, a higher frequency of skin cancer has been reported in (1) Caucasians with light-colored skin and eyes and frequent sunburns, (2) individuals with large outdoor exposures such as sunbathers and outdoor laborers, (3) association with latitudes closer to the equator, and (4) exposed areas of the body compared with covered areas. However, this relationship is most clearly and powerfully demonstrated in XP patients, where UV radiation damage leads to an early onset and increased frequency of both nonmelanoma skin cancer (NMSC) and melanoma. In XP patients, the median age of first NMSC was 9 years (Bradford *et al.*, 2011) compared with 67 years in the general

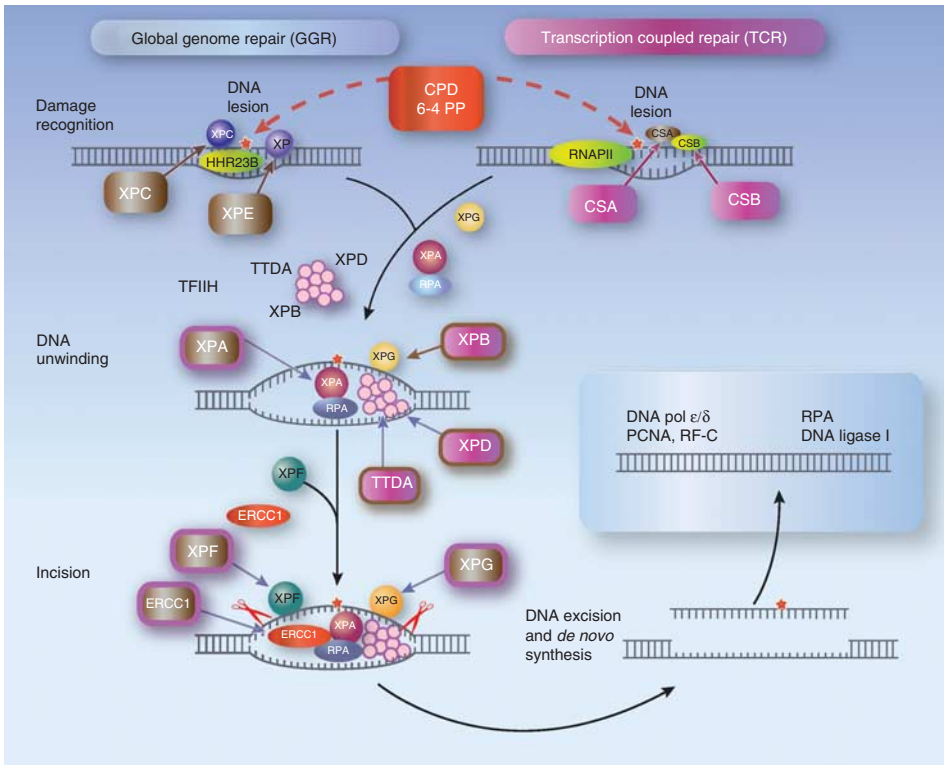

Figure 3. Nucleotide excision repair (NER) pathway. Transcription-coupled repair (TCR) removes damage from actively transcribed genes, whereas global genome repair (GGR) removes damage from the remainder of the genome. In GGR, damage such as UV radiation–induced cyclobutane pyrimidine dimers (CPDs) or 6-4 photoproducts (6-4 PPs) is recognized by proteins including the *XPE* (*DDB2*) and *XPC* gene products. In TCR, the lesion appears to block the progress of RNA polymerase II in a process involving the *CSA* and *CSB* gene products. Following initial damage recognition, the pathways converge. The XPB (ERCC3) and XPD (ERCC2) helicases unwind the region surrounding the lesion along with the *XPA* and *XPG (ERCC5)* gene products, and replication protein A (RPA). The XPF and XPG (ERCC5) endonucleases perform incisions to remove the lesion in a fragment of ~30 nucleotides. The resulting gap is filled in by *de novo* DNA synthesis. This system is coordinated so that if one part of the pathway is mutated the entire pathway fails to function normally. Mutations in the genes in rectangles have been associated with clinical disease. This diagram is modified from Van Steeg and Kraemer (1999) and Kraemer *et al*. (2007). PCNA, proliferating cell nuclear antigen; RF-C, replication factor-C.

population (Figure 2a). Similarly, the median age at onset of the first XP melanoma was 22 years, compared with 55 years in the general population (Figure 2b). This highlights the profound role of an intact DNA repair system in providing protection against skin cancer, in effect, giving the average Caucasian individual more than half a century delay in the onset of skin cancer.

XP patients can develop hundreds of skin cancers. Compared with the general population, XP patients under the age of 20 years have a 10,000-fold increase in the frequency of NMSC, a 2,000-fold increase in melanomas, a 1,000-fold increase in cancer of the sun-exposed tissues of the eye, and a 100,000-fold increase in tongue cancers (Kraemer *et al*., 1994; Bradford *et al*., 2011). The anatomic distribution of NMSC in XP patients is similar to that in the general population, with over 80% occurring on the face, head, and neck (Kraemer *et al*., 1994). The distribution of melanomas is different from that of NMSC in XP patients and in the general population. Melanoma occurs more commonly on the extremities, and in both groups >45% of melanomas were found on the extremities. This suggests that there are different mechanisms involved in the generation of melanoma versus NMSC. The similarity of the distribution of both melanomas and NMSC in both groups suggests that the mechanism of carcinogenesis in XP patients mirrors that in the general population. However, the reversal in median age at onset of NMSC and melanomas in XP patients (9 and 22 years) in comparison with the general population (67 and 55 years; Figure 2a and b) points to a greater role of sun exposure/DNA repair in the induction of NMSC.

The UV radiation–exposed areas of the skin, tongue, and eye have a high cancer risk (Figure 1c, e, g, and h). Although there is an increased risk to the anterior portion of the eye (Ramkumar *et al*., 2011), the lens is a barrier to UV radiation penetration and acts as protection to deeper eye structures. Similarly, the UV radiation–exposed areas of the lips and tongue have an increased cancer risk compared with deeper, more shielded mucous membrane surfaces. The observation that covered areas of the skin and other tissues are highly protected in XP patients (Figure 1f), with lower cancer frequencies, demonstrates the benefit of UV radiation protection in the prevention of sun-induced malignancy.

XP patients under the age of 20 years have an ~50-fold increase in cancers of the brain and other organs of the

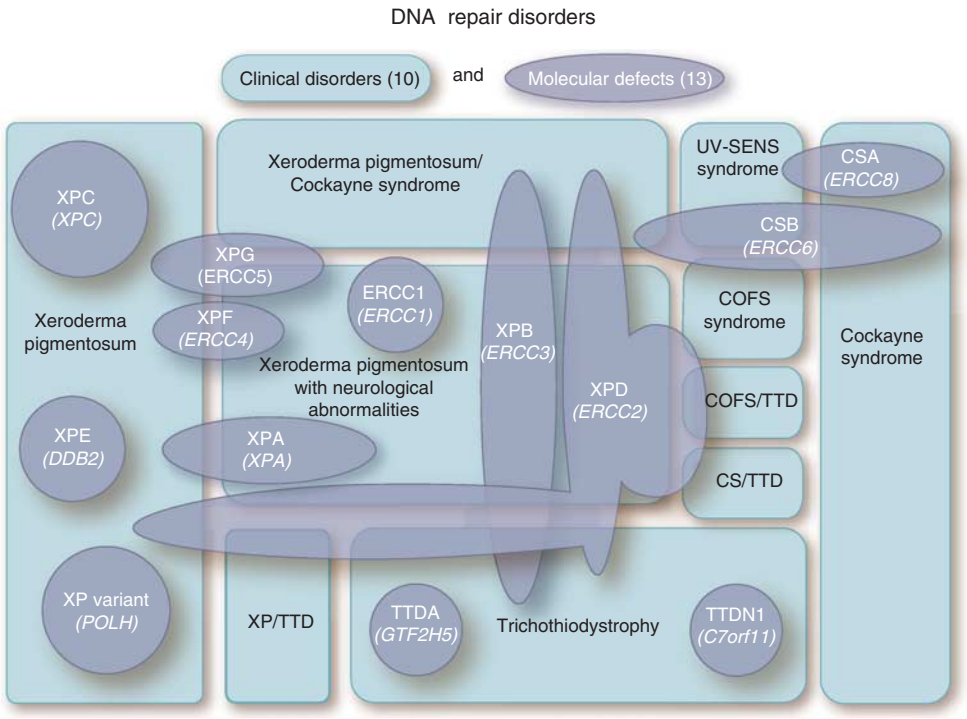

Figure 4. DNA repair diseases—relationship of clinical disorders (light blue rectangles) to molecular defects (dark blue ovals) in DNA repair diseases. A total of 10 clinical diseases and 13 molecular defects are represented. One disease may be caused by mutations in several different genes. Conversely, different mutations in one gene may result in several different clinical diseases. Modified from Kraemer (2004) and Kraemer *et al.* (2007). COFS syndrome, cerebro-oculo-facial-skeletal syndrome; CS, Cockayne syndrome; DDB2, double-strand DNA-binding protein 2; TTD, trichothiodystrophy; XP, xeroderma pigmentosum.

central nervous system (Kraemer *et al.*, 1994). These include brain medulloblastoma (Giannelli *et al.*, 1981), glioblastoma, spinal cord astrocytoma (DiGiovanna *et al.*, 1998), and Schwannoma. These are not sunlight-exposed tissues and the relationship of these cancers to DNA damage is not known. On the other hand, carcinogens in cigarette smoke bind to DNA and cause the type of damage that would be repaired by the nucleotide excision repair (NER) system in normal cells (Maher *et al.*, 1977, 1987). Thus, XP patients are at greater risk of smoking-induced cancer. A 34-year-old smoker with XP died of lung cancer (Kraemer *et al.*, 1994). In a study of 106 XP patients followed up at the National Institutes of Health for almost 4 decades, the median age at death of the XP patients was 32 years, a significant reduction compared with the general population (Figure 2c; Bradford *et al.*, 2011). The median age at death of XP patients with neurological degeneration (29 years) was younger than those patients who had no neurological degeneration (37 years; Figure 2d). Neurological degeneration was second only to cancer in cause of death in XP patients.

Role of sun burning in the development of UV radiation–induced skin damage and skin cancer

Studies in the general population have dissociated the role of acute burning versus chronic lower exposures in the causation of skin cancer. The chronic exposure of light-skinned, outdoor workers has been associated with the development of multiple basal cell carcinomas and squamous cell carcinomas. In contrast, acute blistering burns in childhood have been implicated as a cause of melanoma. However, experience with XP demonstrates that this relationship is more complex. XP typically presents as either of two diverse clinical scenarios. A young child aged 1 to 2 years can develop an alarming blistering or oozing eruption after a short time outdoors in a relatively shady environment (Figure 1a). The onset of the eruption may be delayed for a day or so and may be misdiagnosed as impetigo. After repeated occurrences, the parents learn to rigorously protect the child. Other children with XP do not burn after minimal sun exposure (Figure 1b). However, most XP patients do develop early-onset freckling before the age of 2 years. XP children who do not burn but only freckle may not pay attention to rigorous sun avoidance and paradoxically may experience extensive sun exposure and often develop skin cancers in early childhood (Bradford *et al.*, 2011). It is somewhat surprising that, in the general population, blistering burns are associated with earlier onset of melanoma, whereas in XP this is reversed. XP patients who never burned on minimal sun exposure were found to be significantly more likely to develop skin cancer at an earlier age than those who always or sometimes burned on minimal sun exposure (Bradford *et al.*, 2011).

XP patients with defects in complementation groups A, B, D, and G tend to have blistering burns on minimal sun

exposure, whereas those in groups C, E, and variant do not (Figures 3 and 4 and Table 1). However, all are at high risk of developing early-onset freckling, lentigines, and skin cancers. These observations dissociate the acute burning from the mechanism of UV radiation carcinogenesis and raise important unanswered questions about how the different abnormalities of DNA repair lead to increased cancer risk in all patients, but acute photosensitivity in only some patients. Clearly, the inflammatory reaction of acute burning is not necessary for the development of skin cancer in XP patients.

A model of photoaging?

Photoaging, or dermatoheliosis, describes changes to the skin from chronic exposure to the sun or UV radiation. This includes pigmentary changes and alterations in texture and color. Early damage to melanocytes appears as freckling (tan, symmetrical, round macules) and later as lentigines (colored variable intensity of brown with irregular shapes, sizes, and borders). In contrast, solar elastosis gives the skin a bumpy, yellowed appearance and is thought to be secondary to damage to structural components of the dermis including elastic and collagen fibers. Telangiectasias are the vascular components of UV radiation damage, and atrophy becomes noticeable when the full spectrum of poikilodermatous changes is present. These changes are common in the sun-exposed areas of light-skinned Caucasians in the general population who have sustained excessive, chronic UV radiation damage, where skin laxity, sagging, and wrinkles are prominent. In contrast, although patients with XP develop freckling at an early age, followed by the development of large numbers of lentigos and telangiectasias, they do not develop the skin laxity, sagging, wrinkles, or cutis rhomboidalis of the posterior neck. As described by Kaposi in 1874 (Hebra and Kaposi, 1874), they actually develop skin tightening—the opposite of wrinkling. This contrast dissociates the mechanisms causing the pigmentary and vascular changes (DNA damage in the epidermis and upper dermis) from the causes of damage to structural components of dermal elastic and collagen fibers. This may be explained in part by the absorption of shorter-wavelength, DNA damaging, UVB by the epidermis, and greater penetration of UVA into the deeper dermis with a direct damaging effect on protein. The degree of elastosis may serve as a ''dosimeter'' of the amount of UV radiation reaching the dermis (Robbins *et al.*, 1974). Thus, XP patients demonstrate severe epidermal changes with minimal UV radiation exposure to the proteins in the dermis because of their defective repair of epidermal DNA damage.

A model for clinical research: chemoprevention of skin cancers

Because of the high frequency of skin cancers in XP patients and the associated morbidity, effective chemoprevention approaches would convey enormous benefit. In fact, XP has been used as a model for skin cancer chemoprevention studies. As each patient may develop large numbers of new skin cancers, significant differences may be observed with small numbers of patients. A trial of oral isotretinon conducted with only seven XP patients demonstrated a statistically significant (63%) reduction in new skin cancers compared with the 2-year interval before treatment (Kraemer *et al.*, 1988). This controlled clinical trial was one of the first to conclusively demonstrate effective chemoprevention of any cancer in humans. At present, isotretinoin and the related retinoid acitretin are widely used in patients at high risk of developing new skin cancers who have other predisposing conditions including post-transplantation and the NBCC syndrome. T4 endonuclease V, a bacterial DNA repair enzyme, was also tested in a double-blind study of 20 XP patients and was found to lower the rate of actinic keratoses and basal cell carcinoma (Yarosh *et al.*, 2001).

Specificity in sensitivity to damaging agents

One of the lessons learned from XP is that patient hypersensitivity to damaging agents is specific. Although XP cells are hypersensitive to killing by UV irradiation, they have normal killing after X-rays. In normal cells, the bulky DNA damage caused by UV radiation is repaired by the NER system, which is defective in XP patients (Figure 3). Most of the X-ray damage is different and the X-ray repair systems are normal in XP cells. In fact, patients with XP who develop inoperable eye or internal tumors such as brain or spinal cord tumors have been treated with high-dose X-irradiation as therapy and have tolerated the treatment well (Grier, 1919; Giannelli *et al.*, 1981; DiGiovanna *et al.*, 1998). This is in contrast to patients who are hypersensitive to X-irradiation, such as patients with the NBCC syndrome. NBCC patients have a germline mutation in the PATCH gene, and their cells retain only one of the two normally present functional alleles. Basal cell carcinomas result when NBCC cells sustain a second hit, which can be the result of X-irradiation. NBCC patients who develop neuroblastoma at a young age and receive treatment with radiation therapy frequently develop a large number of basal cell carcinomas in the radiation port, where they may also be at risk for development of additional central nervous system tumors (Kleinerman, 2009). These observations clearly highlight the differences in the mechanisms of repair of UV irradiation-induced versus X-irradiation-induced DNA damage.

DNA repair—molecular mechanisms of carcinogenesis

The skin of XP patients is hypersensitive to sun exposure, and this is reflected in a hypersensitivity of cultured skin fibroblasts following exposure to UV radiation (Ruenger *et al.*, 2008; Kraemer and Ruenger, 2008). Thus, examination of cultured cells from XP patients provides an opportunity to obtain insights into detailed mechanism of the relationship of UV radiation damage to carcinogenesis. For example, cells from XP patients are hypersensitive to killing by UV radiation and by UV radiation–mimetic chemical compounds such as benzo-a-pyrene in cigarette smoke (Maher *et al.*, 1977, 1987; Kraemer and Ruenger, 2008). In addition, XP cells are hypermutable following UV radiation exposure, thereby linking sun exposure to somatic mutations.

UV radiation exposure of DNA produces several types of stable dipyrimidine nucleotide photoproducts (Kraemer and Ruenger, 2008). The major photoproduct is the cyclobutane pyrimidine dimer of adjacent thymines (T), cytosines (C), or

mixed T and C. Also formed are 6-4 pyrimidine-pyrimodone TC photoproducts (6-4PPs). These DNA lesions serve as substrates for the nucleotide excision repair pathway (Figure 3). In normal cells, the DNA-distorting 6-4PPs are repaired more rapidly (within 6 hours) than the cyclobutane pyrimidine dimer (~50% removed by 12 hours). Neither photoproduct is repaired by XP cells. Unrepaired photoproducts are premutagenic lesions. During replication, a DNA polymerase meeting an unrepaired photoproduct can stop replication—leading to cell death. As the photoproduct distorts the nucleotides, they do not code properly. Polymerases that bypass the photoproducts frequently incorporate the incorrect nucleotide (e.g., incorporating a T in place of a C that is involved in a TC photoproduct; Lange *et al.*, 2011). This leads to a C-to-T mutation, which is characteristic of UV radiation mutagenesis. In cultured XP cells and UV radiation–treated plasmids grown in XP cells, these C-to-T or CC-to-TT ''UV signature mutations'' are frequently found after UV radiation exposure (Bredberg *et al.*, 1986; Gozukara *et al.*, 1994).

If purified plasmid DNA is exposed to UV radiation and transfected (introduced) into cells, the plasmid DNA is subject to repair by the DNA repair processes of the cell. The efficiency of repair can be assessed by the use of a plasmid that codes for a marker gene. The DNA damage in the plasmid can be measured or modified before introduction into the cells and then the effect can be measured (Emmert *et al.*, 2002). We used this assay to demonstrate that one UV radiation photoproduct in the coding strand of the marker gene was sufficient to block its transcription in sensitive XP cells (Protic-Sabljic and Kraemer, 1985), thereby demonstrating the importance of DNA repair in removal of DNA damage that blocks transcription. Similarly, replicating plasmid coding for a suppressor transfer RNA marker that is assessed in bacteria revealed that the XP cells introduce a high frequency of mutations into the plasmids. Sequence analysis of the recovered plasmids showed that the mutations following UV radiation exposure of the plasmid are frequently at sites of dipyrimidine photoproducts and lead to C-to-T mutations (Bredberg *et al.*, 1986). This is strong direct evidence of the role of UV radiation in mutagenesis. These cellular studies have provided a molecular foundation for demonstration of the UV radiation–induced origin of mutations found in NMSC (Giglia *et al.*, 1998; Couve-Privat *et al.*, 2004) and melanomas (Daya-Grosjean and Sarasin, 2005; Wang *et al.*, 2009) in cancer-suppressing genes (*p53*, *PTCH*, and *PTEN*) in XP patients. This CC-to-TT UV radiation ''signature'' has been used to link sun exposure to mutations in many other cancer-related genes in melanomas and other skin cancers in the general population (Prickett *et al.*, 2009; Pleasance *et al.*, 2010; Wei *et al.*, 2011).

XP cells are defective in NER (Figure 3; Van Steeg and Kraemer, 1999). This system serves to recognize DNA damage, excise the damage, and replace the damaged region with undamaged DNA. Global genome repair serves to identify DNA damage in the 99% of the DNA that is not involved in transcription. Transcription-coupled repair (TCR) is triggered by a stalled RNA polymerase that contacts DNA damage in actively transcribed genes comprising the remaining 1% of the DNA. DNA photoproducts in the global genome are recognized by several proteins acting in tandem, including double-strand DNA–binding protein 2 (DDB2) and XPC. TCR-related proteins include Cockayne syndrome A and B. After recognition, the DNA is unwound by XPB and XPD helicases, which are part of the 10-subunit basal TFIIH (transcription factor IIH). These proteins are thus involved in both DNA repair and transcription of many other genes. The XPA protein maintains the open DNA region containing the damage, which is then cut out by XPF/ERCC1 and XPG endonucleases as part of an ~30-nucleotide single-stranded fragment. The resulting gap is filled in by DNA polymerase and ligase. The TCR pathway acts more rapidly than the global genome repair pathway and in fact shows strand-specific repair with preferential repair of the transcribed strand. The NER pathway is closely coordinated so that if one of the proteins is defective, the entire pathway does not function correctly. Thus, mutations in any of the above proteins lead to clinical diseases (Figures 3 and 4). The ''XP variant'' form of XP has normal NER. These patients have clinical XP with increased skin cancer susceptibility. Their cells are deficient in an error-prone DNA polymerase, polymerase η, which normally serves to permit DNA replication past unrepaired photoproducts. Identification of this class of bypass polymerases provides insights into the varied mechanisms that organisms have developed to cope with DNA damage (Lange *et al.*, 2011).

XP neurological degeneration

Approximately 25% of the XP patients have progressive neurological degeneration (Bradford *et al.*, 2011). These patients often have defects in the *XPA*, *XPB*, *XPD*, or *XPG* genes (Table 1 and Figure 4). They are usually born with normal size and weight. The earliest clinical abnormalities are frequently absent deep tendon reflexes and high-frequency hearing loss, and these can act as screening tests. Affected individuals may have delayed developmental milestones. The age at onset and rate of progression of the neurological abnormalities is variable among patients. Typical involvement includes sensorineural hearing loss, progressive intellectual impairment, which may progress in severe cases to slurred speech, loss of ability to walk, difficulty in swallowing, and requirement for the use of a feeding gastrostomy. Imaging studies show thinning of the cortex of the brain with concomitant dilation of the ventricles, and thickening of the skull bones. The pathology is a primary neuronal degeneration without evidence of inflammation or infiltration by other cells. XP patients with neurological degeneration have a high mortality (Figure 2d; Bradford *et al.*, 2011).

Relationships within the family of DNA repair disorders

There are three related, clinically defined disorders of DNA repair that can be used as archetypes to understand the spectrum of genotype–phenotype relationships within this group (Table 1 and Figure 4; Kraemer *et al.*, 2007). Photosensitivity, neurological/developmental abnormalities,

and skin cancer are important pathological features that can be used to distinguish between these three archetypes: XP, trichothiodystrophy (TTD), and Cockayne syndrome (CS). In addition, there are several related or overlapping disorders with similar features that form a family of syndromes involving neural, oncologic, cutaneous, developmental, and other abnormalities. Table 1 lists detailed clinical features that may be useful in distinguishing between XP, XP with neurological disease, TTD, CS, and XP/CS complex. Although photophobia and skin sun sensitivity may be seen in all of these conditions, lentiginous hyperpigmentation is seen in XP but not in TTD or CS. Pigmentary retinal degeneration is seen in CS, but not in XP or TTD. More precise clinical delineation has permitted the identification of subtle overlap syndromes in patients with features of two of these disorders. Figure 4 diagrams the current state of the evolving genotype–phenotype relationships within this group. Phenotypes representing the clinical disorders are shown in light blue and molecular defects are shown in gray, with the overlapping patterns showing the underlying molecular defect identified in patients within each phenotypic group. XP can be diagnosed on the basis of clinical criteria based on the presence of acute burning on minimal sun exposure, early-onset freckling before the age of 2 years, and skin cancer. Although XP patients usually do not have developmental abnormalities, ~25% of XP patients develop progressive neurological degeneration. TTD is a disorder characterized by short, brittle hair and multisystem abnormalities (Figure 1i–l). TTD developmental abnormalities may be evident in the pregnant mother carrying a TTD-affected fetus. These pregnancy abnormalities may include abnormal triple screen test results, preterm delivery, preeclampsia, placental abnormalities, or HELLP syndrome (Moslehi *et al.*, 2010; Tamura *et al.*, 2011). The newborn may present with a collodion membrane, short stature, micrognathia, and have increased risk of infections, growth and developmental delay, congenital cataracts, and other abnormalities. Although patients frequently have photosensitivity, they do not develop skin cancer or the freckle-like pigmentary abnormalities of XP. In contrast to XP, the neurological involvement in TTD patients is usually not one of progressive decline. CS has features of both disorders with photosensitivity and both developmental delay and progressive growth and neurologic decline, but not skin cancer. Cerebro-oculo-facial-skeletal syndrome is a severe variant of CS, with abnormalities beginning *in utero*. Infants are born with contractures (arthrogryposis), thought to be due to decreased fetal movement, extreme microcephaly, congenital cataracts, and facial dysmorphism (Laugel *et al.*, 2008, 2010). Careful and precise assessment of clinical features of each disorder has led to the identification of patients with several overlap syndromes. Patients with XP/TTD have features of both diseases, although mildly attenuated. They have tiger-tail banding and hair shaft defects, but less prominent than those that occur in TTD, leading to longer hair. They are at risk for skin and possibly internal malignancies, but at a lower frequency than seen in XP. Similarly, overlap syndromes of XP/CS, CS/TTD, and cerebral-ocular-facial-skeletal syndrome (COFS)/TTD have been described (Figure 4). Different mutations in the *XPD* gene have led to the greatest heterogeneity in clinical phenotype. Patients with the rare UV-sensitive syndrome have mild photosensitivity without pigmentary abnormalities or apparent defects in the central nervous system (Itoh *et al.*, 1996). Their cells have the same transcription defects as CS cells and have been reported to have defects in the *CSA* or *CSB* genes (Horibata *et al.*, 2004; Nardo *et al.*, 2009; Figure 4). This suggests that the defect in the central nervous system in CS patients may be related to an additional property of the CS proteins.

HOW HAS XP HELPED US UNDERSTAND THE BASIC BIOLOGY AND MECHANISMS UNDERLYING OTHER DISEASES?

When the genes that are defective in XP patients were identified, the homologous genes were soon identified in mice. Knockout mice with many of these defects have been generated (see Mouse Mutation Database v5 at http://pathcuric1.swmed.edu/Research/research.htm) and serve as models for probing the role of these genes in carcinogenesis. For example, mice with defects in *XPA* and *XPC* have increased susceptibility to UV radiation–induced skin cancer (deVries *et al.*, 1995; Sands *et al.*, 1995; Cheo *et al.*, 2000; Tanaka *et al.*, 2001). XP heterozygous mice also have an increase in cancers of both the skin and internal organs (Cheo *et al.*, 2000). This suggests that humans who are heterozygous for XP disease–causing mutations—such as 1 million Japanese people who are carriers of an XPA founder mutation (Hirai *et al.*, 2006)—may be at increased cancer risk. However, mice are not perfect models for these diseases as TTD and CS patients do not have increased skin cancer susceptibility, but mice with TTD and CS mutations do have increased post-UV radiation cancer frequency (van der Horst *et al.*, 2002).

Single-nucleotide polymorphisms are variants in the DNA sequence that occur with a frequency of at least 1% in the general population. Single-nucleotide polymorphisms may affect gene function, or, more commonly, act as markers of genetic differences to which they are linked elsewhere in the genome. A polyA-T polymorphism in intron 9 of the *XPC* DNA repair gene was found to be linked to an A-to-C single-nucleotide polymorphism in exon 15 that changed amino acid 939 from Lysine (AAA) to Glutamine (CAA) but did not alter the *XPC* function (Khan *et al.*, 2000). The polyA-T polymorphism was also linked to an *XPC* intron 11 –5C/A single-nucleotide polymorphism that altered the frequency of alternatively spliced *XPC* mRNA, which was shown to have reduced DNA repair ability (Khan *et al.*, 2002). This *XPC* polyA-T polymorphism was associated with increased susceptibility to head and neck squamous cell carcinoma (Shen *et al.*, 2001) and to cutaneous melanoma (Blankenburg *et al.*, 2005). The use of polymorphisms in the *XPD (ERCC2)* DNA repair gene as an indication of cancer susceptibility has been questioned (Clarkson and Wood, 2005). However, recent meta-analysis of 13 case–control studies of bladder cancer (Stern *et al.*, 2009) and 56 case–control studies of several types of cancer (Wang *et al.*, 2008) found a weak but consistent association with several polymorphisms in the *XPD* gene.

Interestingly, wild type rodent cells have normal post-UV radiation survival despite an apparent defect in NER as indicated by some DNA repair assays. These cells have a defect in the *DDB2* NER gene in the dermis with defective global genome repair but normal TCR. A ''humanized'' mouse was developed that had addition of the *DDB2* gene, and it showed increased DNA repair (Alekseev *et al.*, 2005). Interestingly, mouse keratinocytes have a higher level of *DDB2* and greater repair than fibroblasts (Pines *et al.*, 2009).

Although patients with defects in some of the NER genes show profound, progressive neurological abnormalities, mice with defects in XPA or CS do not. However, crossing of Xpa or Xpc mice with Csb mice does result in mice with severe neurological abnormalities (Murai *et al.*, 2001; Laposa *et al.*, 2007). The XPG mutant mouse does show neurological abnormalities. These mouse model systems have been used to mimic some features of neurological degeneration in the general population. A major theory of neurodegeneration involves generation of free radicals by oxidative processes involving the mitochondria. These have been studied in mice with NER defects. Treatment with antioxidants is assessed in these mice.

XP cells have been used as reagents to determine the mechanism of action of chemotherapeutic agents. For example, XP cells with defective TCR are hypersensitive to killing by cisplatinum, but XPC cells with a global genome repair defect have a normal response (Furuta *et al.*, 2002). This indicates that the TCR pathway has a role in the action of platinum and suggests that tumors that are resistant to platinum may have alterations in their TCR-related genes. Interestingly, the use of XP cells determined that a toxin from the sea squirt, ET743, was activated by this TCR machinery to induce lethal DNA strand breaks (Takebayashi *et al.*, 2001). This agent is currently in clinical trials for cancer therapy.

Immune diversity is generated by hypermutability of Ig variable genes in maturing B lymphocytes. The spectrum of mutations in B cells from XP variant patients with defects in the DNA polymerase η were found to show a deficiency in the frequency of A–T mutations and a concomitant rise in G–C mutations. These data indicate that polymerase η in involved in generating mutations in Ig variable genes (Zeng *et al.*, 2001).

EPILOGUE

We are in the second decade of the twenty-first century. A young child is taken out on the first sunny day of spring in a modern umbrella stroller, but the child becomes irritable. By the next morning, her skin becomes red and blistered, necessitating a trip to the emergency room. The pediatrician thinks this is a sun burn, but is concerned about how parents could have let this happen. After a second episode, an astute dermatologist recognizes acute burning on minimal sun exposure, begins a work-up for photosensitivity disorders, and instructs the parents to immediately start measures for aggressive sun protection. The child will not burn again. We have learned a great deal in the ~140 years since Kaposi's description in 1874 (Hebra and Kaposi, 1874). We now know that the skin changes of XP are the result of UV radiation exposure. Once a diagnosis is made, the family can be guided to sources of skin and eye protection (e.g., sun blocks, protective clothing, window tinting), an easy-to-use UV radiation meter, and instructional materials for the school, and all of this may be facilitated through contact with patient support groups that can be helpful in identifying resources for the family (Tamura *et al.*, 2010). We know many, but probably not all, of the disease-causing genes. Genetic testing may be available for confirmation of diagnosis not only in patients but also *in utero* and for future pregnancy planning. Vitamin D supplementation will prevent deficiency. Monitoring for possible neurological involvement will permit early detection and management (e.g., hearing aids). The Americans with Disabilities Act (ADA) requires a safe, UV radiation–protected school environment, and mandated individualized educational plans assist in education.

This child may develop freckles and lentigines, but the family should have the knowledge and tools to avoid most of the damage that UV radiation can cause in XP. If a skin cancer develops, advanced topical and surgical management can provide a cure with minimal discomfort and cosmetic alteration. Patients now can live healthy fulfilling lives well into adulthood despite having many types of skin cancers (Oh *et al.*, 2011). Although we have reached this far, we still have a long way to go. Many patients are unable or unwilling to use extreme sun protection, and thus better methods are needed. Genetic testing is not readily available. We do not have effective intervention for neurological decline. In addition, we often have too long a delay in diagnosis. Individuals who do not have extreme sun sensitivity may not be diagnosed early, leading to substantial sun damage at a young age. Although all XP patients are at high risk for the development of skin cancer, we do not understand why some patients burn and others just freckle. We do not have a method to reverse the damage. Also, why don't patients with TTD who have photosensitivity and abnormal NER develop skin cancer? While we can diagnose, treat, prevent damage and understand some of the pathophysiological mechanisms in XP patients, there is still much more to learn.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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