Clinical and cell-culture studies were performed on 15 patients with xeroderma pigmentosum, a hereditary disease characterized by defective repair of DNA damage and by neuromuscular and skin carcinomas; the lesion represented a variant form of the xeroderma pigmentosum (XP) disorder. In the first three cases, a deficiency of XP was seen in our patients while the fourth case was associated with a deficiency of XP. However, the DNA-repair defect might cause the neuronal degeneration in the human nervous system, which led to my appointment in 1965 as a senior investigator in the Dermatology Branch at the National Cancer Institute.

When J.E. Cleaver discovered the defect in DNA excision repair in xeroderma pigmentosum (XP) in 1968, I chose to study XP. I did so not only because of the obviously important relationship between defective DNA repair and the patients' sun-sensitive skin cancers, but also because I speculated that the DNA-repair defect might cause the neuronal degeneration affecting some patients. Accordingly, we brought 15 XP patients to the National Institutes of Health (NIH) for clinical evaluation and tissue-culture studies. Peter Burk and I found the typical DNA-repair deficiency of XP in our first three patients. However, our fourth patient had normal rates of such repair and therefore represented a new form of XP, now commonly referred to as the XP variant form. More than 35 patients with the XP variant form have since been identified, and A.R. Lehmann and coauthors3 have shown that XP variants have defective postreplication repair of DNA. Kenneth Kraemer and I then studied our XP patients with neurological abnormalities and found two new XP complementation groups; this increased the number of groups to four from the two originally described by E.A. de Weerd-Kastelein, W. Keijzer, and D. Bootsma.4

In 1973 we presented these findings at a combined clinical and scientific conference at the NIH. I presented the DNA-repair studies, Kraemer discussed the clinical features and the cell-fusion studies, Marvin Lutzner discussed the effects of ultraviolet radiation on skin, Barry Festoff described the neurological abnormalities, and Hayden Coon discussed his cell-fusion technique and the significance of the resulting somatic cell genetic studies. I am indeed pleased that the edited transcript of this conference has become a Citation Classic.

The paper has been frequently cited for the following reasons: (1) our discoveries of new XP types stimulated research in many laboratories to elucidate their biochemical and biological abnormalities; (2) cells from our patients became widely studied, and many became standards for complementation group assignment in accord with our universally accepted classification system; and (3) the paper was the first comprehensive review of both the clinical and laboratory studies of XP.

The most important contribution of the paper, however, may ultimately result from its conclusions regarding the neurodegeneration in XP. The paper presented my hypothesis that defective repair of neuronal DNA could be the cause of the premature death of the XP nerve cells. In 1978 Alan Andrews, Susanna Barrett, and I provided experimental evidence for the hypothesis, and we concluded that repair of neuronal DNA is required to maintain the integrity of the human nervous system.5 This concept, as recently reviewed,6,7 has led us and others to find evidence for DNA-repair defects in more common neurodegenerative disorders such as Huntington's disease, Friedreich's ataxia, Parkinson's disease, and Alzheimer's disease.