

This Week's Citation Classic®

Robbins J H, Kraemer K H, Lutzner M A, Festoff B W & Coon H G. Xeroderma pigmentosum: an inherited disease with sun sensitivity, multiple cutaneous neoplasms, and abnormal DNA repair. *Ann. Intern. Med.* 80:221-48, 1974.

[Dermatology Br. and Lab. Cell Biology, Natl. Cancer Inst., and Medical Neurology Br., Natl. Inst. Neurological Diseases and Stroke, Natl. Insts. Health, Bethesda, MD]

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 neurodegeneration and sunlight-induced skin cancer. A DNA excision-repair-proficient form and two new types of the excision-repair-deficient form were discovered. [The *SCI*® indicates that this paper has been cited in over 400 publications.]

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In medical school I became fascinated with the possibilities of relating clinical and pathological manifestations of disease to basic cellular abnormalities amenable to study in tissue culture. These types of relationships were emphasized in my tissue-culture studies of blastogenesis in the human lymphocyte,¹ 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 1968,² I chose to study XP. I did so not only because of the obviously important relationship between defective DNA repair and the patients' sunlight-induced skin cancers, but also because I speculated that the DNA-repair defect might cause the neuronal degeneration afflicting 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 36 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 staff 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 neurodegenerations such as Huntington's disease, Friedreich's ataxia, Parkinson's disease, and Alzheimer's disease.

1. Robbins J H. Tissue culture studies of the human lymphocyte. *Science* 146:1648-54, 1964. (Cited 325 times.)
2. Cleaver J E. Defective repair replication of DNA in xeroderma pigmentosum. *Nature* 218:652-6, 1968. (Cited 805 times.) [See also: Cleaver J E. *Citation Classic*. (Barrett J T, ed.) *Contemporary classics in the life sciences. Volume 1: cell biology*. Philadelphia: ISI Press, 1986. p. 181.]
3. Lehmann A R, Kirk-Bell S, Arlett C F, Paterson M C, Lohman P H M, de Weerd-Kastelein E A & Bootsma D. Xeroderma pigmentosum cells with normal levels of excision repair have a defect in DNA synthesis after UV-irradiation. *Proc. Nat. Acad. Sci. USA* 72:219-23, 1975. (Cited 345 times.)
4. de Weerd-Kastelein E A, Keijzer W & Bootsma D. Genetic heterogeneity of xeroderma pigmentosum demonstrated by somatic cell hybridization. *Nature New Biol.* 238:80-3, 1972. (Cited 105 times.)
5. Andrews A D, Barrett S F & Robbins J H. Xeroderma pigmentosum neurological abnormalities correlate with colony-forming ability after ultraviolet radiation. *Proc. Nat. Acad. Sci. USA* 75:1984-8, 1978. (Cited 100 times.)
6. Robbins J H, Otsuka F, Tarone R E, Polinsky R J, Brumback R A & Nee L E. Parkinson's disease and Alzheimer's disease: hypersensitivity to X rays in cultured cell lines. *J. Neurol. Neurosurg. Psychiatr.* 48:916-23, 1985.
7. Robbins J H, Brumback R A, Polinsky R J, Wirtschafter J D, Tarone R E, Scudiero D A & Otsuka F. Hypersensitivity to DNA-damaging agents in abiotrophies: a new explanation for degeneration of neurons, photoreceptors, and muscle in Alzheimer, Parkinson and Huntington diseases, retinitis pigmentosa, and Duchenne muscular dystrophy. (Woodhead A D, Blackett A D & Hollaender A, eds.) *Molecular biology of aging*. New York: Plenum, 1985. p. 315-44.