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This Week's Citation Classic

Cleaver J E. Defective repair replication of DNA in xeroderraa pigmentosum. *Nature* **218**:652-6, 1968. [Lab. Radiobiology, Univ. California Medical Ctr., San Francisco, CA]

Normal skin fibroblasts can repair ultraviolet radiation damage to DNA by inserting new bases into DNA in the form of small patches. Cells from patients with the hereditary disease xeroderma pigmentosum carry a mutation such that repair replication of DNA is either absent or much reduced in comparison to normal fibroblasts. Patients with xeroderma pigmentosum develop fatal skin cancers when exposed to sunlight, and so the failure of DNA repair in the skin must be related to carcinogenesis. [The *SCI*® indicates that this paper has been cited over 610 times since 1966.]

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"In scientific research everyone travels in hope of that lucky break; rarely are we privileged to receive it. This paper, now a *Citation Classic,* describes one of those serendipitous discoveries that has been valuable in defining the role of damage to the genetic material (DNA) in human cancer. It sparked the growth of a large field of currently active, fruitful, and competitive research, and it is this which accounts for the article's frequent citation.

"In 1966-1968, we had the beginning of an interest in the way radiation damages human DNA. One direction was clear; to make significant progress we needed to select mutants that were altered in their capacity to recover from radiation damage. This direction was difficult, and has only recently been successful. The discovery of human mutants started from a most unlikely origin. In April 1967, the *San Francisco Chronicle* ran an article by David Perlman on a hereditary form of skin cancer in man induced by sunlight, xeroderma pigmentosum (XP).[1] From that article I guessed that perhaps XP could be a human mutant of the kind we wanted. The first experiment on XP cells showed that the choice was right, and in just over a year this first report was published, and a second followed the next year.[2]

"The choice of the right disease was everything, because most of the experiments involved routine techniques. Anyone can repeat these first experiments in a matter of a few days, and the rapidity of the competition to harvest the cream from the subject testified to this. Ironically, an earlier report demonstrating hypersensitivity of XP cells to ultraviolet light by Gartler had been completely ignored.[3] That was fortunate for me, because if it had been pursued the pioneering work on XP would have been over before I left graduate school!

"There have been many ramifications from defining XP as a DNA repair deficiency in man. The etiology of a complex human disease involving both genetic and environmental components is clearer. Numerous researchers have been stimulated to search for other diseases that might have similar characteristics. XP studies have become a starting point and justification for many experiments investigating carcinogen action on DNA The role of DNA repair mechanisms in carcinogenesis is a currently active field of research.

"A wide range of human diseases have now been identified that exhibit increases in sensitivity to environmental agents (chemicals, radiations) that damage DNA.[4] These hypersensitive diseases —XP, ataxia telangiectasia, Cockayne syndrome. Fanconi's anemia, etc. — form a diverse class within which XP is a subset involving defective DNA repair. The causes of hypersensitivity in the other diseases are more complex.

"Our work in XP has been recognized by two awards: the Radiation Research Society's Research Award in 1973, and the American Academy of Dermatology's Lila Gruber Award for Cancer Research in 1976. It has been generously supported by the Atomic Energy Commission and its successor, the Department of Energy."

1. **Periman D**. A family pattern in cancer study. *San Francisco Chronicle* 12 April 1967. p. 4.
2. **Cleaver J E.** Xeroderma pigmentosum: a human disease in which an initial stage of DNA repair is defective. *Proc. Nat. Acad. Sci US* **63**:428-35, 1969.
3. **Carrier S.** Inborn errors of metabolism at the cell culture level. (Fishbein M, ed.) *The second international conference on congenital malformations.* New York: International Medical Congress. Ltd.. 1964. p. 94.
4. **Cleaver J E.** DNA damage repair systems and human hypersensitive diseases. J. *Environ. Pathol. Toxicol.* **3**:53-68. 1980.