

This Week's Citation Classic

CC/NUMBER 41
OCTOBER 12, 1981

Cleaver J E. Repair replication of mammalian cell DNA: effects of compounds that inhibit DNA synthesis or dark repair. *Radiat. Res.* 37:334-48, 1969.

[Lab. Radiobiology, Univ. California Med. Ctr., San Francisco, CA]

In this paper DNA repair in ultraviolet damaged human cells was measured by the incorporation of labeled thymidine or deoxycytidine during the G₁, G₂, and mitotic stages of the cycle. Three groups of compounds were investigated as to whether they inhibited repair: (1) compounds that inhibit the synthesis of precursors of DNA, (2) compounds that bind to DNA, and (3) compounds acting nonspecifically. [The SC[®] indicates that this paper has been cited over 320 times since 1969.]

James E. Cleaver
Laboratory of Radiobiology
School of Medicine
University of California
San Francisco, CA 94143

April 30, 1981

"It is a most pleasant surprise that this paper has become a most-cited paper in our field of DNA repair in mammalian cells. The key to its frequent citation is that one of the compounds investigated, hydroxyurea, has turned out to be an invaluable adjunct to routine assays of DNA repair. This drug provides a way of specifically inhibiting semiconservative DNA replication without at the same time interfering with DNA repair. Subsequently, it has been found that the blanket assumption that hydroxyurea has no effect on repair is probably wrong. Both hydroxyurea, and cytosine arabinoside, also used in this paper, are found to interfere with late stages of DNA repair and this very inhibition is now used as

another assay for the frequency of repair events.¹

"This early study proved to be one of the first papers in what has now become a vast, extensively worked area of DNA repair in eukaryotic cells that has importance in radiobiology and chemical carcinogenesis. Practical importance has even come out of this early study because measurements of repair are being used for identification of environmental agents that are potentially mutagenic and carcinogenic. DNA repair assayed by thymidine labeling in the presence of hydroxyurea, as first described in this paper, is one of the test systems under current evaluation in the Environmental Protection Agency's Gene-Tox Program.

"This particular study was part of a series of investigations we did leading to the discovery of human diseases which were ultraviolet sensitive with high levels of carcinogenesis because of defects in a DNA repair system. That was first reported in a paper that also became a *Citation Classic*.² The parallel growth of investigations of repair using inhibitors and genetic defects has been invaluable in laying out a role for damage and repair as early events in carcinogenesis from environmental agents.^{3,4}

"This work has been recognized by my receiving both the Radiation Research Society's Award for Research in 1973 and the Lila Gruber Memorial Award for Cancer Research from the American Academy of Dermatology in 1976. The receipt of these gave me great pleasure, as also has the continuous support we have received from the Atomic Energy Commission (now the Department of Energy) for the research carried out from 1966 to the present."

1. Hiss E A & Preston R J. The effect of cytosine arabinoside on the frequency of single strand breaks in DNA of mammalian cells following irradiation or chemical treatment. *Biochim. Biophys. Acta* 478:1-8, 1977.
2. Cleaver J E. Defective repair replication of DNA in xeroderma pigmentosum. *Nature* 218:652-6, 1968.
[Citation Classic. *Current Contents/Life Sciences* 24(30):22. 27 July 1981.]
3. Cleaver J E & Painter R B. Absence of specificity in inhibition of DNA repair replication by DNA-binding agents, co-carcinogens, and steroids in human cells. *Cancer Res.* 35:1773-8, 1975.
4. Cleaver J E. DNA damage, repair systems and human hypersensitive diseases. *J. Environ. Pathol. Toxicol.* 3:53-68, 1980.