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This Week's Citation Classic

Howard-Flanders P, Boyce R P & Theriot L. Three loci in *Escherichia coli* K-12 that control the excision of pyrimidine dimers and certain other mutagen products from DNA. *Genetics* 53:1119-36, 1966. [Radiobiology Labs., Yale University School of Medicine, New Haven, CT]

Mutants of E. *coli* were isolated that were very sensitive to ultraviolet light or mitomycin C, and failed to reactivate UV-irradiated bacteriophages. They were unable to excise pyrimidine dimers from their DNA. The mutations mapped in three widely spaced loci, *uvrA,B,C.* [The *SCI*® indicates that this paper has been cited over 325 times since 1966.]

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"Prior to 1961, the concept that living cells might contain enzymes to repair DNA molecules was no more than a remote possibility that few scientists had even considered. The next five years brought the publication of several papers on the detection of genetic repair processes in microorganisms, and the application of the methods of genetics and biochemistry to their elucidation.[1-4]

"In 1961, there was no very obvious reason to study the effects of ultraviolet light on bacteria. However, multiplicity reactivation and photoreactivation had been discovered. Ruth Hill had isolated a mutant strain of the bacterium *E. coli* B which was of exceptional sensitivity to ultraviolet light and had lost the ability to reactivate ultraviolet irradiated bacteriophages.[5] The only plausible explanation was that bacteria normally contained enzymes for the repair of ultraviolet photoproducts in bacterial or phage DNA and that the sensitive mutant lacked one or more of these enzymes. This concept was novel in the early 1960s, since extensive experiments on radiation mutagenesis in fruit flies had shown X-ray damage in cells and tissues to be almost irreversible. Moreover, the scientific community had been influenced by Watson and Crick, who had discussed the biological implications of their famous model for the structure of DNA, but had not foreseen the possibility that enzymes might repair damaged DNA, or the significance of the complementary structure for the repair of damaged strands

"Our goals were clear enough. We wished to investigate the fate of pyrimidine dimers in the DNA of bacteria, to explore the repair enzymes that act on the damaged DNA, and to study the genetic control of these processes. We also felt the need to bring the methods of biochemistry and genetics to bear directly on these problems, which formerly had been little more than radiobiological curiosities. Since this could not easily be done in strain B, we had to isolate new radiation sensitive mutants from the strain E. *coli* K12 in which fertile males and genetically marked females were available. Fortunately, the main ultraviolet photoproducts in DNA had already been identified as pyrimidine dimers, which could be detected by radio-chromatography, and the methods for genetic mapping in bacteria had been developed. R.P. Boyce and I (and R.B Setlow working independently) found the repair to involve the excision of the pyrimidine dimers from the bacterial DNA (also a *Citation Classic).*[2,3]

"This work had shown bacterial DNA repair enzymes to act on damage induced by ultraviolet light and by mitomycin C, both known carcinogens. Subsequent work by many scientists has shown DNA repair enzymes in man to protect against the effects of environmental carcinogens and radiations, and to be necessary for keeping cancer incidence down to the present levels.[6]

"This paper provided proof that the products of three genes are necessary for excision repair and provided the first comprehensive genetic analysis of excision repair. For more recent work in the field see A. Sancar, *et al.* "[7]

1. **Howard-Flanders P, Boyce R P, Simson E & Theriot L.** A genetic locus in *E. coli* **K12** that controls the reactivation of UV-photoproducts associated with thymine in **DNA.** *Proc. **Nat. Acad.** Sci. **US** **48**:2109-15. 1962.*
2. **Boyce R P & Howard-Flanders P. Release of ultraviolet** light-induced thymine dimers from **DNA** in *E. coli* K-12***Proc. Nat. Acad.** Sci. **US** **51**:293-300, 1964.*
(Citation Classic. ***Current** Contents/Life Sciences* 23(35): 12. 1 September 1980.)
3. **Setlow R B & Carrier W L.** The disappearance of thymine dimers from DNA: an error-correcting mechanism. ***Proc. Nat. Acad. Sci. US** **51**:226-31, 1964.*
4. **Clark A J & Marguiies A D. Isolation and characterization of recombination-deficient mutants** of *Escherichia coli* **K12. *Proc Nat. Acad.** Sci. **US** **53:451-9, 1965.***
5. **Hill R F.** A radiation-sensitive mutant of *Escherichia coli. Biochim. Biophys. Acta* 30:636-7, 1958.
6. **Ts'o P O P & Gelboin H V,** eds. *Polycyclic hydrocarbons and cancer.* New York: Academic Press, 1978. 2 vols.
7. **Sancar A, Warton R P, Seltzer S, Kacinski B M. Clarke N D & Rupp W D.** Identification of the *uvrA* gene product. *J.* Mol. *Biol.* **148**:45-62. 1981.