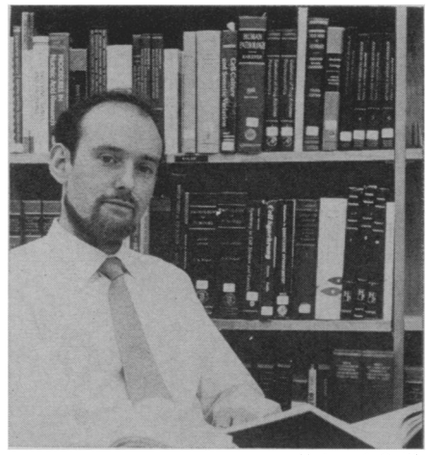
DNA repair

To tune into the subject of cell and molecular repair is to capture the broader essence of molecular biology research today. Molecular biologists operate in Plato's two worlds, the twilight zone between Idea (hypothesis) and Reality (empirical evidence). Testing for repair is a sort of cat and mouse game (now something's here, now something isn't). In other words, researchers are able to draw certain conclusions about repair processes on the basis of changes in cell materials during an experiment, although a cell has never been caught repairing itself, and few of the suspected repair enzymes have been seen or isolated.

Since 1953, when the DNA dogma was proposed (that the basic hereditary information of life is contained in deoxyribonucleic acid and is transmitted by messenger ribonucleic acid and transfer ribonucleic acid into proteins or enzymes)—but especially in the past decade—cellular and molecular repair researchers have been making impressive strides. Several kinds of DNA repair have been discovered. The most common DNA repair, which occurs in cells of all species, is called "dark repair," or "cut and patch." When several pyrimidine bases in a strand of DNA are wedded by ultraviolet light or a chemical into a complex, or dimer, the cell finds this dimer distasteful and wants to chuck it. Thus, with the help of dark repair enzymes (isolated in bacteria, but not in higher animals yet), the cell cuts out the dimer and fills in the broken DNA strands with more DNA bases.

Other processes such as bioenergetics are probably implicated in repair as well. For example, bases may undergo changes before they are used to patch excised DNA. The repair enzymes may need a recognition time before they incorporate these bases into DNA. However, as scientists who attended a first international symposium on cell and molecular repair at Johns Hopkins University pointed out, there are still many pressing questions about repair. Hot controversy centers on whether the base precursor pools for DNA repair differ from those for DNA synthesis; whether repair depends on synthesis; whether a cell can survive if synthesis, but not repair, is cut off, and vice versa.

However ill-defined and provocative repair processes remain at this time, there is accumulating evidence that such processes hold profound implication for everyday life. Resistance to environmental stress agents such as radiation and chemicals, for example, depends on whether cellular and molecular repair tools are intact and honed. A case in point is cited by Dr. James Cleaver of the University of California Medical Center in San Francisco.



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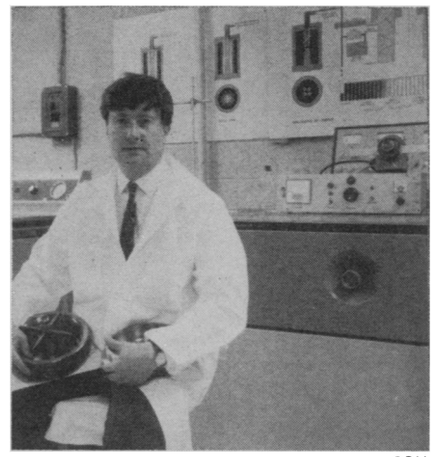
Dr. Cleaver: On repair and cancer.



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Dr. Lett: Can repair prevent aging?

Dr. Cleaver is an authority on Xeroderma Pigmentosum, a rare, inherited disease which causes skin cancer in a person as early as adolescence. His laboratory evidence indicates that persons with Xeroderma lack, or are defective in, an enzyme that excises pyrimidine dimers formed in skin cells by normal exposure to sunlight. Dr. Cleaver is convinced that a missing or defective repair enzyme relates to skin cancer. He offers two explanations: Low pyrimidine excision repair could lead to DNA mutations that could lead to cancer, or low repair could incur lower sensitivity to an environmental stress agent such as a cancer virus. Both possibilities are under investigation. "I opt for the latter," Dr. Cleaver says, "because of strong evidence that cancer is caused by a virus."

There was talk, while the supersonic transport was pending before Congress, that such aircraft might increase the incidence of skin cancer in the population. Such a claim could have foundation, Dr. Cleaver explains, because a disturbance of the ozone layer by supersonic aircraft might lead to more ultraviolet radiation on the earth's surface and in turn could place greater stress on the excise process. The SST controversy aside, evidence of genetic damage in mice by radiation, and repair of this damage, has been gathered, over a period of years, by Dr. W. L. Russell of the Oak Ridge National Laboratory.

Yet even when a cell possesses the necessary DNA repair enzymes, it may not necessarily resist radiation damage, according to Dr. J. M. Boyle of Christie Hospital, Manchester, England, because radiation probably shuts down cell respiration, turning off RNA and protein synthesis. A chemical compound called Fluorouracil helps a cell breathe, Dr. Boyle has found, and in turn the cell does a better job of excising unwanted dimers and repairing DNA. Since Fluorouracil is one of the currently more successful drugs for cancer therapy, drugs could conceivably engineer the repair of cells and molecules.

Surgical alteration of a defective repair enzyme is still something out of science fiction, as is enzyme replacement. "It's hard enough to get a cell to accept foreign chemical material injected into it," a researcher wryly pointed out at the Johns Hopkins conference, "let alone force a cell to swallow a foreign enzyme whole." Nonetheless enzyme alteration or replacement therapy possibilities are keeping many a scientist tossing and turning at night, because a host of diseases could probably be arrested, and DNA repaired, by such methods.

Meanwhile repair research may shed light on the elusive process of aging. Dr. John Lett of Colorado State University at Fort Collins is looking at radiation damage and DNA repair in dog brain cells. He is trying to see whether the number of breaks in DNA strands accumulates with age, either because rejoining mechanisms are absent from such tissues, or because repair mechanisms deteriorate with age. A special centrifuge rotor had to be created for him so he could detect DNA breaks and repair in nondividing brain cells. Normally DNA can be made radioactive and spotted that way in the centrifuge, as long as the cells are undergoing synthesis.

In the absence of more definite evidence on repair and aging, other scientists concur that a breakdown in cell repair could contribute to aging, but is probably not the entire story. Yet other theories of aging, that antibody production slacks off in old age lowering disease resistance, or that cell reproduction mechanisms go haywire, touching off cancer, undoubtedly tie in with defective DNA repair, Dr. Lett says. □