DIR RESEARCH UPDATE

The Consequences of DNA Replication Infidelity to Human Health

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"It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material."
Watson and Crick, Nature, 1953

In the years since this remarkable understatement, we have come to realize the enormous complexity of the cellular machinery devoted to replicating DNA with the accuracy needed to maintain genetic information over many generations, balanced by the need for mutations on which selection can act. This complexity is strongly driven by the need to remove or tolerate a wide array of cytotoxic and mutagenic lesions in DNA generated by environmental stress. This presentation will briefly consider the fidelity with which undamaged and damaged DNA is replicated by the many DNA polymerases now known to exist. Some of these polymerases seriously violate Watson-Crick base pairing rules such that, depending on the polymerase, the composition and location of the error and the ability to correct errors (or not), DNA synthesis error rates can vary by more than a million-fold. This offers the potential to modulate rates of point mutations over a very wide range, with consequences that can be either beneficial or deleterious to human health. Several environmental health consequences of replication infidelity will be described, within the context of Goals 1, 2 and 3 of the new NIEHS Strategic Plan.