Master Molecule, Heal Thyself

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The Early History of DNA Repair

In his nearly three decades of leadership in the natural sciences at The Rockefeller Foundation, Warren Weaver contributed substantially to the mid-twentieth century revolution in biology and agricultural science. A veritable polymath, over a lifetime, Weaver also contributed significantly to mathematics, statistics, physics, and computer science and to various scientific associations (1). In the early 1930s, he persuaded Alexander Hollaender, a highly regarded radiobiologist, to survey the literature and write a report for The Rockefeller Foundation on the biological effects of radiation. In so doing, Hollaender evaluated close to 5000 papers in the field, an effort that lent important impetus to the establishment of federal financial support for radiation biology in the United States. During the Manhattan Project and the ultimate emergence of the atomic bomb, laboratories dedicated to radiation research were established in several parts of the country, with the primary objective of learning how individuals exposed to ionizing (and other types of) radiation might be protected (1).

Following World War II, President Harry Truman designated these entities as national laboratories and placed them under the aegis of the newly created Atomic Energy Commission. In time, the laboratories became the breeding grounds for many early contributors to the emerging fields of DNA repair and mutagenesis. As pointed out in Correcting the Blueprint of Life: An Historical Account of the Discovery of DNA Repair Mechanisms published in 1997 (1), in later years when funding for biomedical research was not always readily available, this situation “did little to endear the community of radiobiologists to the ‘aristocrats’ of molecular biology, who not only labored under restrictive financial conditions, but additionally considered much of the biological research done in these laboratories as frankly pedestrian” (1). This reputation was not totally unwarranted because, for an extended period beginning in the early 1930s, radiobiological research was indeed dominated by simple survival curves, graphs that quantitated the killing effects of exposure to radiation in different cells and tissues in multiple organisms. Although largely descriptive, such meager data generated many bold speculations about the biological effects of radiation exposure.

In time, a number of celebrated investigators interested primarily in understanding how genes function, including Max Delbrück, Salvador Luria, and Hermann Muller, originated experiments that, while continuing to make extensive use of survival curves, led to the discovery that the killing effects of exposure to ionizing radiation or UV light are profoundly influenced by the inactivation of certain genes. Thus, the notion of DNA repair was born (1–3).

By the mid-1960s, mutants of Escherichia coli and of bacteriophage T4 with enhanced sensitivity to killing following exposure to UV radiation had been identified (1–3). Additionally, Richard Setlow, Philip Hanawalt (Fig. 1), the late Paul Howard-Flanders, and others demonstrated that UV radiation-sensitive mutants of E. coli designated uvrA, uvrB, and uvrC had lost their ability to generate acid-soluble DNA products enriched for photoproducts (such as covalently linked adjacent pyrimidines in a DNA strand called pyrimidine dimers) during incubation following exposure to UV light (1–3). These observations prompted the notion that pyrimidine dimers, and likely other photoproducts from UV irradiation, promote cell death by blocking normal DNA replication and that their removal from the genome during post-irradiation incubation constitutes a
DNA repair mode aptly called excision repair, which, in *E. coli*, requires the *uvrA*, *uvrB*, and *uvrC* genes (1, 2).

**Discovering a DNA Damage-specific Endonuclease Activity in Phage T4**

I was born and raised in South Africa and attended the University of the Witwatersrand (Wits) in Johannesburg, where I obtained B.S. and M.B.B.Ch (bachelor of medicine and surgery) degrees, equivalent to the M.D. degree in the United States. Obtaining the B.S. degree as a medical student required an extra year devoted to learning the principles and practice of the scientific method, an education I eagerly absorbed based on my newfound enthusiastic interest in the biomedical sciences.

I had little interest in clinical medicine. After completing medical school, I trained as a pathologist, both at Wits and subsequently at Cleveland Metro General Hospital, a teaching hospital of the Case Western Reserve University School of Medicine in Cleveland, Ohio. Winfield (Win) Morgan, Chief of Pathology at Cleveland Metro, quickly noticed my passion for basic biomedical research and persuaded me to drop my pathology training and execute postdoctoral training in the Department of Biochemistry at Case Western. I owe a debt of gratitude to Morgan for that advice and his subsequent encouragement. While making the rounds in the Department of Biochemistry, chaired by the renowned Harland Wood, I was offered a postdoctoral position with the late David (Dave) A. Goldthwait, himself an M.D.-trained biochemist who had just returned from a sabbatical with François Jacob at the Pasteur Institute in Paris and whose head was buzzing with molecular biology.

Western Reserve was a marvelous place in which to train. The strength of the faculty in the Department of Biochemistry was impressive. Besides Dave, exciting work was being carried out by the legendary Harland Wood, not to mention Merton Utter and Warwick Sakami. The renowned microbiologist Lester Krampitz (recruited to Western Reserve by his longtime friend Harland Wood) was but a floor away. The department was also known for its annual Christmas party, during which some poor soul (usually a graduate student) won the “horse’s ass award” (an engraved plaque on which the rear end of a toy horse was mounted) for the biggest scientific snafu that year! I am proud to state that I never won that “coveted award.”

Dave was then interested in unraveling the biochemistry of genetic recombination in *E. coli*. He had hit on the notion that one or more of the endonucleases, involved in the precise cutting of DNA that must accompany high-fidelity recombination, might recognize specific conformational changes in the DNA backbone as cutting sites. He hoped to mimic such conformational changes by treating DNA with alkylating agents, not realizing of course that the resulting DNA damage might surface an entirely different panoply of endonucleolytic responses, an outcome that, in retrospect, predictably transpired.
I identified and characterized an enzyme from *E. coli* that specifically cut alkylated DNA, which we designated endonuclease II (4–6). Remarkably, only one other endonuclease in *E. coli* had previously been reported. Endonuclease II turned out to have nothing to do with genetic recombination. It was a DNA repair enzyme subsequently shown to be involved in the repair of sites of base loss (so-called apurinic or apyrimidinic sites) in DNA (1, 2). Dave generously offered me the opportunity of presenting my work at the 1968 Cold Spring Harbor Laboratory Symposium, my first such experience and one that terrified me more profoundly than it gratified me! A face among the galaxy of scientific stars that has stayed vividly in my memory (for no reason that I can recall) is that of the late Arthur Kornberg. How odd that forty-six years later, I am writing a biography on Arthur!

While in Dave’s laboratory, I was introduced to Setlow during one of his visits to Case Western and learned more about the groundbreaking studies on DNA repair in UV light-irradiated *E. coli* cells. In these studies, he and Bill Carrier showed that when cells are incubated after exposure to UV light, covalently joined pyrimidines, referred to as pyrimidine dimers, known photoproducts in DNA, appear in the acid-soluble fraction of DNA (1, 2). Setlow correctly postulated that the appearance of acid-soluble pyrimidine dimers reflects their removal from DNA by enzyme-mediated excision (1, 2). I found Setlow to be a knowledgeable and inspiring individual, and my discussions with him brought me to the decision to continue to study aspects of DNA repair if and when I had a laboratory of my own. I had already been offered a junior faculty position in the revamped Department of Pathology at Stanford University under David Korn’s leadership, and I was eagerly anticipating a move to California as soon as my postdoctoral stint with Dave was completed at the end of 1968. However, global events dictated otherwise. The Vietnam conflict was raging fiercely, and shortly before taking up my Stanford appointment, I was drafted into the United States Army Medical Corps.

In theory, I might have been posted anywhere in the Army Medical Corps, so I heaved a huge sigh of relief when I learned that I was to be assigned a research laboratory of my own in the Division of Radiobiology at the Walter Reed Army Institute of Research (WRAIR) in Washington, D. C. There, with the able assistance of a drafted graduate student, Jack King, I went in search of endonuclease activities in extracts of *E. coli* that preferentially attacked UV light-irradiated DNA. These efforts came to naught, as was then the case in multiple laboratories around the world. To be sure, the endonuclease in *E. coli* involved in incising damaged DNA that is indeed encoded by the *uvrA*, *uvrB*, and *uvrC* genes was not identified and characterized until considerably later (1–3).

I elected to switch to the study of excision repair in wild-type bacteriophage T4 by studying an isogenic UV radiation-sensitive phage mutant called T4vI, originally isolated by George Streisinger (1, 2). To my delight, extracts of *E. coli* cells infected with wild-type phage T4 preferentially cut UV light-irradiated DNA (but not native DNA) in an endonucleolytic manner, and this function was defective in extracts of the T4vI mutant (7, 8). These observations were independently made by Mutsuo Sekiguchi (Fig. 2) and his colleagues in Japan at around the same time (9). Both laboratories subsequently purified this apparently UV radiation-specific putative endonuclease (8, 9).

The enzyme that Sekiguchi and I isolated was one of just two such enzymes observed in nature to date. The other, the product of a gene in the bacterium *Micrococcus luteus*, was identified by the late Lawrence Grossman (Fig. 3) and his colleagues in the early 1970s (10). Both the phage T4 and *M. luteus* enzymes were shown to facilitate the excision of pyrimidine dimers in a manner mechanistically distinct from that of the endonuclease eventually shown to be the polypeptide products of the *E. coli uvrA*, *uvrB*, and *uvrC* genes (1, 2). Indeed, whereas the endonucleases from phage T4 and *M. luteus* exclusively attacked DNA bearing pyrimidine dimers, the enzyme equivalent in *E. coli* and those in higher organisms, including humans, were shown to be endowed with a much broader substrate specificity, attacking DNA containing many types of helix-distortive base damage caused by a multitude of chemical agents (1, 2). Regardless, the strict substrate specificity of the enzymes that Grossman and I had identified prompted their use as convenient and specific reagents for detecting the presence of pyrimidine dimers in DNA at levels far too small to be observed directly. Exploiting this property led David Clayton, a faculty colleague later at Stanford, and me to establish that mitochondrial DNA is not subject to excision repair (11).

**A Switch to Higher Organisms**

Following my stint at WRAIR, I joined the faculty in the Department of Pathology at Stanford University. In due course, my interests switched to understanding excision repair in higher organisms, especially in individuals afflicted with the hereditary skin cancer-prone disease xeroderma pigmentosum (XP), which is known to be characterized by defective repair of DNA in cells previously exposed to UV light (1, 2) and about which I was...
educated by James Cleaver at the nearby University of California, San Francisco. However, progress toward elucidating the nature of the molecular defect(s) in cells from XP patients gained little traction then.

In the late 1970s, I decided to abandon working with mammalian cells, the use of which was both time-consuming and expensive, and switched to a lower eukaryotic model organism that was genetically and biochemically more tractable, specifically the yeast *Saccharomyces cerevisiae*. The efforts of a postdoctoral fellow, Rick Reynolds (who had trained in Setlow’s Oak Ridge National Laboratory), led to the identification of multiple yeast mutants defective in the excision repair of pyrimidine dimers, thereby defining a robust genetic system amenable to biochemical studies (12–14). Additional contributions by other postdoctoral fellows and a covey of outstanding graduate students in my laboratory eventually led to the identification of multiple yeast *RAD* genes (2).

With the emergence of gene cloning, my colleagues and I were able to isolate and characterize many of the yeast *RAD* genes and purify some of their polypeptide products (15–19, 21). Notable among these studies was the surpris-
ing discovery by a graduate student, Louie Naumovski, that one of these genes, called \textit{RAD3}, is essential for the viability of yeast in the absence of exposure to DNA damage (22). Another notable contribution, this by postdoctoral fellow Zhigang Wang, was the generation of cell-free extracts of wild-type yeast that faithfully supported excision repair of damaged DNA and were defective in extracts of multiple \textit{rad} mutants (23).

**A Link between Transcription Initiation and Excision Repair**

In the late 1980s, I was offered the chairmanship of the Department of Pathology at the University of Texas Southwestern Medical School in Dallas, Texas. I was torn! Not only had I never heard of UT Southwestern, but I also had no particular interest in moving to Dallas. However, after much arm twisting, I agreed to visit the place and met Mike Brown and Joe Goldstein, UT Southwestern’s first two Nobel Laureates (that now number six!). I was sold! I moved to Dallas in 1990, and I continued my research program in DNA repair with the help of a superb cadre of postdoctoral fellows and graduate students, many of whom followed me from Stanford, and also built a significantly sized research-oriented pathology department.

The essential function subserved by one of the yeast genes, called \textit{RAD3}, remained a mystery until a providential visit to my laboratory in the early 1990s by Roger Kornberg from Stanford. While sharing his latest research contributions on transcription in yeast, Roger informed me that his laboratory had recently isolated a large multiprotein complex called transcription factor \textit{IH} (TFIIH) that was essential for RNA polymerase \textit{II}-mediated transcription initiation in yeast. The precise functions of the multiple subunits of TFIIH were unknown. However, Roger idly mentioned that the largest of the subunits was a protein with a molecular mass of \(~100\) kDa. My ears perked up immediately. I related to Roger that, in our own hands, the Rad3 protein was of a size essentially identical to the protein he had identified in yeast TFIIH and that \textit{RAD3} was also an essential gene in our hands. Fully aware that long shots rarely pay off in science, Roger and I nonetheless agreed that it would not take much effort to determine whether the \(~100\)-kDa TFIIH subunit discovered in his laboratory and our Rad3 protein were, in fact, one and the same entity. I vividly remember the excitement in Roger’s voice when, several months after his visit, he informed me by phone that the long shot had indeed yielded a handsome dividend!

The discovery that Rad3 protein was essential for RNA polymerase \textit{II}-directed transcription initiation in yeast prompted further collaborative studies with the Kornberg laboratory and led to the demonstration by postdoctoral fellow John Feaver and others that all the subunits of yeast TFIIH are required for both transcription initiation and excision repair in yeast (24–30). Roger and I hypothesized that yeast (and possibly other eukaryotes) may contain distinct multiprotein complexes that share multiple polypeptides and function as “transcriptomes” or as “repairosomes” (24–30). However, to date, no direct experimental evidence has convincingly confirmed or repudiated this notion. Accordingly, although the shared function of TFIIH in transcription and excision repair in yeast (and presumably other eukaryotes) remains unassailable, its precise role during excision repair of DNA remains to be established. The interesting evolutionary question as to whether yeast co-opted the transcription function of TFIIH for excision repair, or vice versa, also remains to be answered.

Other contemporaneous studies in my laboratory around this time led to the discovery of more \textit{RAD} genes and the exciting observation that the yeast \textit{RAD1} and \textit{RAD10} genes encode subunits of a complex that functions as a single strand-specific endonuclease during excision repair in yeast (31), the formal equivalent of the UvABC endonuclease in \textit{E. coli}. Independent studies from Jim Haber’s laboratory at Brandeis University showed that the Rad1/Rad10 endonuclease function is also required for genetic recombination in yeast (32). Further work in both laboratories showed that the Rad1/Rad10 endonuclease specifically recognizes double-stranded/single-stranded DNA junctions during both excision repair and recombination in yeast.

**Cockayne Syndrome, Another Hereditary Human Disease Associated with Defective Biological Responses to DNA Damage**

Cockayne syndrome is a rare hereditary disorder characterized by severe developmental defects and defective DNA repair (2) but without enhanced predisposition to cancer. Two genes associated with the disease have been identified, designated \textit{CSA} and \textit{CSB} (2). The product of the \textit{CSB} gene was shown by several groups be an ATPase/DNA helicase (2). However, the nature of the polypeptide product encoded by the \textit{CSA} gene remained unknown until postdoctoral fellow Karla Henning (in my laboratory at UT Southwestern) cloned the gene and showed that it encodes a predicted WD repeat protein that interacts with CSB protein (33). The precise biological function(s) subserved by a putative CSA-CSB complex, which may well include other subunits, remains unclear at the time of this
writing. The CSA and CSB genes do not appear to be represented in prokaryotes.

**Discovery of DNA Repair Mediated by DNA Glycosylases**

As fully recounted in *Correcting the Blueprint of Life: An Historical Account of the Discovery of DNA Repair Mechanisms* (1), Tomas Lindahl (Fig. 4), a Swedish biochemist who has lived in the United Kingdom for much of his life and at one time served as director of the Medical Research Council Clare Hall Laboratories just outside London, astutely recognized that an important minority of the many covalent bonds in DNA are much less stable than the rest. By determining the rates of hydrolysis of such bonds in DNA as functions of temperature or pH, it became clear to Lindahl that spontaneous hydrolysis of nucleic acids almost certainly occurs at a biologically significant rate under physiological conditions. This led him to the cogent conclusion that DNA repair enzymes yet to be discovered may have evolved to cope with such damage. Accordingly, Lindahl went in search of new DNA repair enzymes and discovered a novel pathway by which the inappropriate base uracil is removed from DNA as the free base. This reaction proved to be mediated by a class of enzymes that Lindahl designated DNA glycosylases because they sever the glycosylic bond linking particular types of damaged or inappropriate bases (such as uracil) to the sugar phosphate backbone of DNA, thereby releasing a free base (2).

While these experiments were in progress, my own laboratory stumbled on uracil-DNA glycosylase serendipitously by a series of events that led to the independent discovery of the enzyme in *Bacillus subtilis*. Having visited the Setlow laboratory at the Brookhaven National Laboratory, Ann Ganesan, a member of Philip Hanawalt’s laboratory at Stanford and an individual with whom I was in frequent contact, returned to Stanford with perplexing news: the Setlow laboratory had observed that the enzyme from *M. luteus* (discovered by Grossman) that was believed to specifically attack pyrimidine dimers in UV light-irradiated DNA also attacked DNA containing uracil, a base normally present in the genome of a *B. subtilis* phage called PBS2.

A tie in between pyrimidine dimers and uracil in DNA seemed odd. Convinced that Setlow and co-workers had stumbled on a contaminating enzyme activity in their *M. luteus* preparations, my laboratory prepared radioactive PBS2 DNA and observed that it was unaffected by incubation with the purified phage T4 enzyme described above. We therefore concluded that Setlow’s preparations were indeed contaminated with an apparently ubiquitous enzyme that degraded uracil-containing DNA. Accordingly, we proceeded to explore two obvious questions. What is the precise nature of this putative enzyme, and equally interestingly to us, how does the *B. subtilis* phage PBS2 manage to survive and replicate its genome in the presence of the enzyme?

Further experiments revealed that the “endonuclease” in question was in fact the same uracil-DNA glycosylase discovered in the Lindahl laboratory (34–36). The answer...
to the second question was straightforward. Very soon after phage PBS2 infects *B. subtilis*, the phage expresses a specific heat-stable inhibitor of the host uracil-DNA glycosylase. We purified this inhibitor (36), which turned out to be a handy reagent in experiments by others that required the specific inhibition of uracil-DNA glycosylase *in vitro*.

The loss of a free base, such as uracil, naturally leaves a new type of damage in the genome, namely an apurinic or apyrimidinic site, which must undergo further repair to fully restore genetic integrity. Details of this repair were worked out by others and, in *E. coli*, were shown to include a requirement for endonuclease II, the enzyme mentioned earlier that was originally discovered in Dave’s laboratory (2).

In subsequent years, multiple other DNA glycosylases were discovered, all of which were shown to operate in an identical fashion, catalyzing the cleavage of the *N*-glycosyl bond that attaches a particular inappropriate or damaged base to the sugar phosphate backbone of DNA. Surprisingly, both the phage T4 and *M. luteus* pyrimidine dimer-specific enzymes were also shown to function as DNA glycosylases that initiate the excision of pyrimidine dimers from DNA by attacking one of the two glycosyl bonds in a dimer (37, 38). It was now obvious that the term “excision repair” required qualification depending on the specific mechanism involved. I therefore suggested that it would be appropriate to recognize three distinct types of excision repair. Hence, the terms “nucleotide excision repair” (during which, entire nucleotides, typically oligonucleotide fragments ~20 nucleotides in length, are excised) and “base excision repair” (during which, free bases are excised) were introduced to complement the established term “mismatch excision repair,” which addresses the excision of mismatched bases typically generated as errors during semiconservative DNA replication (2).

### A Brief Return to the Skin Cancer-prone Human Hereditary Disease Xeroderma Pigmentosum

Some of the many *RAD* genes identified in yeast were soon shown to have structural homologs in higher organisms (2). In humans, some of these genes had already been shown to be defective in individuals suffering from XP and are designated XP genes A–G. Because it was established that defective XP genes predispose humans to skin cancer when exposed to sunlight, I wondered why these individuals appear rarely, if ever, to manifest cancer in organs that are subject to DNA damage by means other than that caused by exposure to UV light. To address this question, David Cheo in my laboratory exposed mice carrying defective XP genes to known liver carcinogens. Sure enough, livers from XP mice preferentially developed liver tumors (39). We were thus led to the conclusion that the extent of DNA damage in skin cells in human XP subjects exposed to sunlight must far outweigh other types of base damage spontaneously generated in other organs; afflicted individuals die from the effects of skin cancer before cancers in other organs have time to manifest.

### Translesion DNA Synthesis

Because DNA damage is, in general, a stochastic process, the DNA replication, transcription, and/or recombination machineries may encounter sites of damage before they are repaired. To cope with the deleterious effects of such encounters, cells have evolved a series of biological responses that I designated DNA damage tolerance mechanisms (2). As the term suggests, DNA damage tolerance allows cells to overcome the potentially lethal effects of blocked replication (and possibly blocked transcription) until a time when the damage is removed. Specifically, when the *E. coli* replication machinery is arrested at sites of unrepaird damage, certain proteins can interact with the stalled replication machinery in a manner that facilitates replication past the offending lesion, a process called translesion DNA synthesis (2). Two such genes called *DinB* and *UmuC* were initially implicated in translesion DNA synthesis in *E. coli* (2) and were shown to encode a new family of DNA polymerases designated the Y-family.

A subclass of patients who present clinically with a milder form of XP and who are fully proficient in nucleotide excision repair of DNA had long been designated by James Cleaver at the University of California, San Francisco, as XP-variant individuals (2). However, nothing was known about the pathobiology of the XP-variant form until a mammalian homolog of one of the Y-family DNA polymerases called DNA polymerase (pol) η was shown in Fumio Hanaoka’s laboratory in Japan to be defective in all XP-variant patients examined to date (40).

Thus far, no less than nine distinct translesion synthesis DNA polymerases have been identified (2). Based on the demonstration that pol η apparently evolved for the specific purpose of accurately bypassing unrepaird thymine dimers in irradiated DNA, one presumes that the other eight known DNA polymerases that support translesion DNA synthesis subserve the specific function of accurately bypassing other types of spontaneous or environmentally induced base damage that can arrest normal DNA synthesis.

Consistent with this notion, my colleagues and I identified and isolated a different DNA polymerase required for...
translesion DNA synthesis, which we designated pol κ (41–45). The cognate substrate for replicative bypass by pol κ has not been identified. However, our experiments, sometimes in collaboration with others (44), have demonstrated that pol κ accurately bypasses various types of polycyclic adducts bound to guanine in DNA, many of which are known carcinogens. These observations have led us to the notion that naturally occurring polycyclic guanine adducts, such as the potent carcinogen benzo[\(a\)]-pyrene, may constitute cognate substrates for accurate translesion synthesis by pol κ (43, 44). At the time of this writing, collaborative studies with a colleague at The Johns Hopkins University are in progress to establish whether mice defective in pol κ are unusually predisposed to lung cancer after prolonged exposure to cigarette smoke.

Meanwhile, we and others have made efforts designed to decipher precisely how the process of translesion synthesis transpires. A cogent working hypothesis states that when the replication machinery is arrested at a lesion, it is displaced from its normal primer-template position to allow access of the appropriate DNA polymerase required for translesion DNA synthesis. This DNA polymerase switch promotes accurate replication past the offending lesion, thereby incorporating a single nucleotide (or, in the case of pyrimidine dimers, two nucleotides). When this process is completed, a second polymerase switch transpires during which the replication machinery is restored to its normal primer-template position and continues accurate semiconservative DNA synthesis (2, 42–45).

The precise mechanism(s) by which these postulated DNA polymerase switches transpire is presently a major topic of investigation in multiple laboratories. Much also remains to be learned about other catalytic functions among the family of translesion synthesis polymerases as a whole. For example, recent studies in my laboratory have demonstrated a role(s) of pol κ in the repair of DNA stand breaks (46). Additionally, collaborative studies with Jean-Sébastien Hoffman indicate a requirement for pol κ in checkpoint activation following replicative stress (47). Whereas it is reasonably presumed that the remaining seven known members of the Y-family of DNA polymerases are required for the replicative bypass of other types of naturally occurring base damage, their biological functions remain to be determined.

Most gratifying to me during my long love affair with DNA repair mechanisms is my appreciation of the extent to which the field of biological responses to DNA damage has matured because this phenomenon was first discovered over eighty years ago. It has long shed its reputation of being the “ugly sister” in DNA biochemistry. I am also deeply indebted to a large cadre of graduate students and postdoctoral fellows with whom I enjoyed much pleasure and stimulation in my laboratories both at Stanford and UT Southwestern.

In conclusion, it likely bears mention that, in my later years, I turned to academically and historically based science writing, a passion long neglected! In addition to several editions of a comprehensive textbook entitled DNA...
Repair and Mutagenesis (2), coauthored with Graham Walker, Wolfram Siede, Richard (Rick) Wood, Roger Schultz, and Tom Ellenberger (Fig. 5), this list includes a history of the DNA repair field (1), an examination of Jim Watson’s writing life (48), a history of UT Southwestern (49), and biographies of Sydney Brenner (50) and Paul Berg (20).

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