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DNA Fragility and Repair: Some Personal Recollections

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Abstract

In this autobiographical article, I reflect on my Swedish background. Then I discuss endogenous DNA alterations and the base excision repair pathway and alternative repair strategies for some unusual DNA lesions. Endogenous DNA damage, such as loss of purine bases and cytosine deamination, is proposed as a major source of cancer-causing mutations.

Contents

BACKGROUND

The identification of DNA as the carrier of genetic information in cells and organisms by Oswald Avery and collaborators suggested that DNA should be a chemically very stable molecule to avoid the generation of large amounts of mutations. But this hypothesis was not confirmed in my biochemical investigations of the instability of the primary structure of DNA. The Watson–Crick double-helical structure of DNA provides some protection, especially against deamination damage, but this seems far from sufficient to avoid intolerable mutation frequencies. The dilemma can be explained by postulating continuous in vivo DNA repair of endogenously generated DNA damage, usually by the DNA base excision repair (BER) pathway. Since these investigations have been reviewed previously (1–12), I do not describe them in detail here. Instead, I attempt to propose some different concepts and ideas in the field of DNA damage and repair and describe tangential projects that have fascinated me, but first I comment on my background.

I was born in Stockholm in 1938, and I am of Swedish middle-class origin on both my father's and mother's sides for hundreds of years. In spite of the unfortunate Brexit situation, and having worked in the United Kingdom for the second half of my life, I have remained a European and Swedish citizen. Neither of my parents were scientists, and I have described my immediate family and early scientific career elsewhere (8). But I am sometimes asked about any scientific inheritance that might have inspired me, and in that regard, it is of relevance that a great-grandfather of mine—in Swedish, *farmors farfar*—was a chemist who discovered the element lithium just over 200 years ago. His name was Johan August Arfwedson (JAA), 1792–1841 (13) (**Figure 1*a***). He obtained his early university training at Uppsala University in mountain chemistry and was accepted as a graduate student and postdoctoral fellow by the famous chemist Jöns Jacob Berzelius. A thesis project of JAA was the detailed chemical analysis of an unusual mineral, petalite, that occurs as off-white streaks in iron-containing stones at Outer Islands, Utö, in a remote part of the Stockholm archipelago.

There were only preliminary data available at the time on the composition of petalite. JAA found mainly silicon and aluminum but surprisingly no potassium. The assumption was that approximately 4% of a component present in petalite might be sodium, but he could not account for this material as sodium in spite of repeated detailed analyses, checking for calculation errors, etc. Instead, he proposed that petalite also contained a previously unknown light element related to sodium and potassium, and he was able to isolate and identify this novel compound (13), which was given the name lithium. Berzelius, who had himself recently discovered two new elements, cerium and selenium, immediately realized the importance of the new work by JAA and went back to his laboratory to repeat, confirm, and extend JAA's results. When the work was subsequently published in Swedish in the Proceedings of the Royal Swedish Academy, 1818, Berzelius wrote a supportive appendix but generously declined to be a coauthor with JAA, apparently with the motivation that lithium had been discovered thanks to the very accurate experimental work performed by his junior coworker JAA. However, Berzelius had extensive correspondence with colleagues in France,

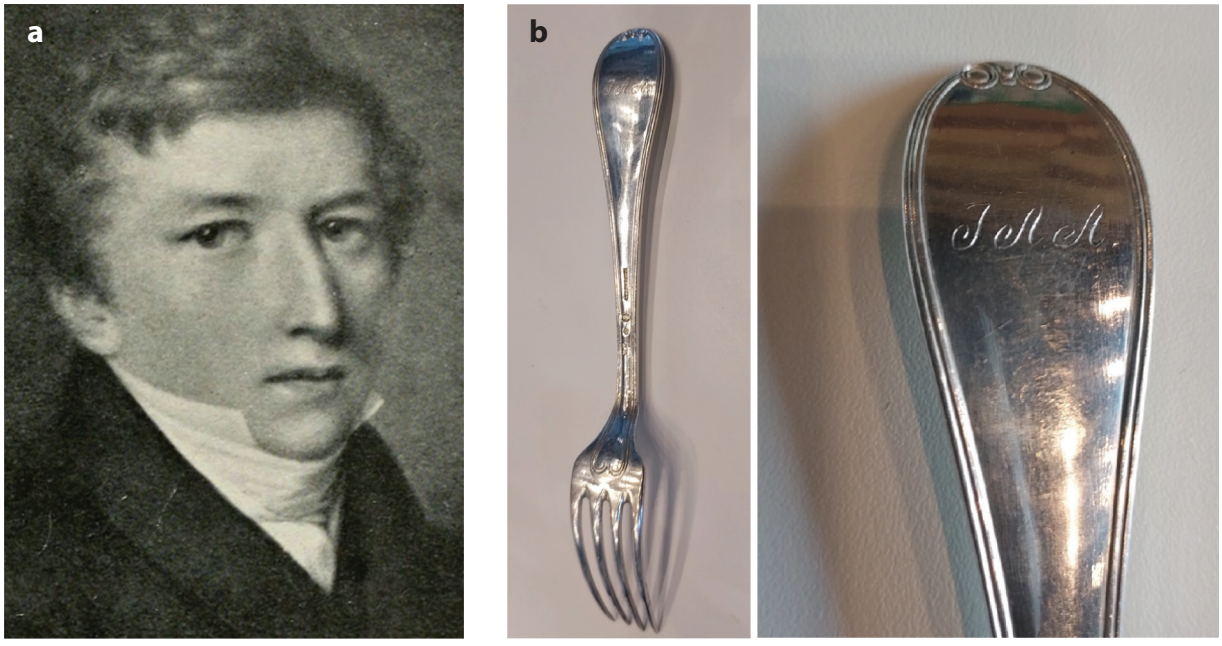

Figure 1

(*a*) The Swedish chemist, Johan August Arfwedson (JAA) who discovered the element lithium in 1817, great-grandfather of Tomas Lindahl. (*b*) A silver serving fork labeled JAA, inherited by the author from the estate of Johan August Arfwedson. Portrait in panel *a* by Johan Way (public domain). Photos in panel *b* courtesy of Tomas Lindahl.

Germany, and England and flagged up the new, exciting discovery by JAA, "un jeune chimiste de beaucoup de mérite."

In 1821, JAA was elected as a Fellow of the Swedish National Academy of Sciences and then as a corresponding member of the French Academy of Science. In a few years, he published novel work on previously unknown oxidized derivatives of manganese and different forms of uranium, in addition to the work on lithium. But then he inherited a large country estate, and its successful administration interfered greatly with his opportunities to perform experimental chemistry, although he built and financed a chemistry laboratory at home. Further, he married Sara Sophia von Ehrenheim and started a family. He continued to keep in close contact with Berzelius, including long travels abroad together with JAA as a junior scientific partner. A son of JAA, Robert Arfwedson-Ehrenheim, a distinguished lawyer who was elected twice to the Swedish Parliament, inherited his property and was the father of my grandmother, Calina Arfwedson-Ehrenheim. She did not inherit any real estate, which went to the sons of the family, but I still retain some family silver labeled A-E, and a large silver serving fork, engraved JAA, which provides a direct material link with the discoverer of lithium (**Figure 1*b***).

A brief account of my early career follows. I studied medicine at the Karolinska Institute in Stockholm, which had a strong reputation for excellence. But after concluding my basic courses and some of the more applied ones, I came to realize that I preferred to perform laboratory work in biochemistry and microbiology rather than practical medicine and surgery. So, I went back to the lab and never completed some of my medical courses. In consequence, I was ultimately awarded a doctoral degree but without a license to treat patients or write prescriptions. An inspiring influence on my decisions was the retired professor of Biochemistry, Einar Hammarsten, who

had a small emeritus laboratory in the microbiology department. Hammarsten had been studying DNA through most of his long career and had provided important evidence that DNA was a macromolecule rather than a simple tetranucleotide. Together with his outstanding junior collaborator and successor, Peter Reichard, he investigated the enzymatic reduction of ribose to the unusual sugar deoxyribose. Reichard brought these studies to a triumphant conclusion with the discovery and characterization of ribonucleotide reductase, which converts ribose to deoxyribose at the nucleoside diphosphate stage and is key to DNA synthesis. Reichard was very helpful to me in my early days as a researcher. I then spent a couple of years at Princeton University in the Department of Chemistry with Professor Jacques Fresco, investigating RNA folding. I found that a tRNA molecule could be trapped in two different conformations by manipulating magnesium concentrations during isolation, only one of which was biologically active in protein synthesis. After Princeton, and a shorter spell as a Helen Hay Whitney fellow at the Rockefeller Institute, New York, with the brilliant, but highly strung, Professor Gerald Edelman, I returned to a research position at the Karolinska Institute, funded by the Swedish Natural Science Research Council. Then I carried out my initial studies of DNA instability and built up a research group. After a few years, I was recruited by the friendly Chair of the medical chemistry department at Gothenburg University, Ulf Lagerkvist, to a Professor position there and then moved on a couple of years later to London, as a research group leader at Imperial Cancer Research Fund (ICRF) with the strong support of the ICRF Director of Research, Sir Walter Bodmer (**Figure 2**). I was soon promoted to a new post, Director of the newly established ICRF Clare Hall laboratories in the outskirts of North London, which gave me the opportunity to recruit outstanding independent scientists and Group Leaders such as Steve West, David and Birgit Lane, John Diffley, Tim Hunt, Jesper Svejstrup, Helle Ulrich, Simon Boulton, and Dale Wigley. Moreover, I continued my own work on the repair of endogenous DNA damage and related topics, greatly aided by an efficient research group (**Figure 3**).

NEW DEPARTURES IN DNA REPAIR AND PRELIMINARY STUDIES ON THE ORIGINS OF LIFE

Much of my own DNA repair research has focused on the correction of endogenous lesions by the BER pathway (2–12) (**Figure 4**). In my early work, I investigated the biochemical properties of previously unrecognized DNA exonucleases and DNA ligases from mammalian cells. Together with Richard (Rick) Wood and Peter Robins, a human cell-free system for nucleotide excision repair was also established (14), in parallel with similar work by Aziz Sancar. I later shared the Nobel Prize in Chemistry with Aziz Sancar, along with the outstanding expert on DNA mismatch repair, Paul Modrich. Rick and I published a list of known DNA repair enzymes and related factors (15), and Rick continues to update this useful resource (16). Another interesting early DNA repair discovery was made in collaboration with Monica Olsson, who was a star in the technical section of the medical chemistry department at the University of Gothenburg when I was there for a few years. This department has remained one of the leading Swedish biochemistry research departments for the last fifty years, and I am pleased to see that two of the outstanding researchers there have contributed invited articles to this 2023 volume of the *Annual Review of Biochemistry*, in addition to my autobiographical article. Monica and I showed that there is a unique DNA repair strategy for correcting the mutagenic DNA lesion O^6-methylguanine by direct damage reversal, with transfer of the offending methyl group from DNA to a cysteine residue in the repair protein itself, which was then consumed in the reaction rather than regenerated, because of the great chemical stability of methylcysteine (17, 18).

In subsequent years, Monica (**Figure 5**) and I kept in research contact, even after I had left Gothenburg, and when we reached retirement age, with the kind support of our Gothenburg

Figure 2

The Imperial Cancer Research Fund (ICRF) Clare Hall Laboratories were officially opened in 1986 by Sir Andrew Huxley, President of the Royal Society 1980–1985 (third on the left), together with Sir Walter Bodmer, Director of Research, ICRF, and Tomas Lindahl, Director of Clare Hall Laboratories. Honourable Sir Angus Ogilvy, President of the ICRF, is on the right.

department, we carried out a few speculative and potentially interesting experiments. In a situation where we could only try to produce some exciting work with very limited research facilities, we attempted a high risk project, that is, investigating alternative possibilities to the origin of life on Earth. The chances of success were of course low and would not have impressed a grants committee. Nevertheless, we went ahead and took a gamble.

There have been many expensive and unsuccessful attempts to find life in the hostile climates of Mars, Venus, and our Moon. Surprisingly, fewer efforts have been made to detect simple alternative life forms in liquids on Earth. This is largely because our present aqueous DNA/RNA form of life is so abundant and versatile, thermophiles and halophiles leave practically no vacant niches, even at high temperatures or high salt concentrations. In environments with high concentrations of organic solvents together with some water and salts, the situation seems more intriguing. Double-stranded DNA retains its macromolecular structure in solution at room temperature in 99.9% glycol with salts and also at high concentrations of glycerol or formamide (19), but no life forms have been detected in such solutions. We have made several unsuccessful attempts, but this is a field where negative results are inconclusive. In addition to several different types of salts, an energy source such as ATP would be required and perhaps an inoculum from great ocean or soil depth or some unusual volcanic area. If alternative life forms remain on Earth, they are presumably

Figure 3

The Tomas Lindahl research group at the ICRF Clare Hall laboratories in 1999, including, in the front row, Peter Robins (first on the left) and, in the back row, Dr. Deborah Barnes (first on the left), Dr. Barbara Sedgwick (third from the left), Tomas Lindahl (fourth from the right), Brenda Marriott (Clare Hall administrator; third from the right), Frank Fitzjohn (Clare Hall manager; second from the right).

simple, slowly proliferating anaerobic microorganisms, perhaps similar to our present form of life in their basic strategy but still distinct and different. Experimental searches for remnants from an early world based on RNA or a similar nucleic acid rather than DNA can be performed in the presence of hydroxyurea, which is a specific inhibitor of ribonucleotide reductase. We have been encouraged in this project by the discovery of coelacanths at two different ocean sites at 50–100 meters depth (**Figure 6**). These evolutionary links between modern fishes and reptiles were believed to have gone extinct hundreds of millions years ago, until an enthusiastic young scientist discovered them to be alive, and they are named after her as Latimeria. Perhaps there are informative unusual anaerobic microorganisms 20–40 times older than Latimeria waiting to be revealed that have retained features of early alternative life.

MUTAGENESIS

Large-scale DNA sequencing over the last few years has shown that cancer cells regularly contain mutations in so called oncogenes or tumor suppressor genes. These exciting results strengthen the link between mutations and the origins of cancer. Moreover, DNA-repair defects resulting in mutations can contribute to human cellular aging (20–24).

The understanding of the causes of these critical mutations remains incomplete and is an important future research field. However, there has been considerable progress with regard to certain forms of cancer. Skin cancer is often caused by exposure to ultraviolet light from the sun, which induces the formation of miscoding pyrimidine dimers in the DNA of irradiated cells. Individuals with the inherited cancer-prone disease xeroderma pigmentosum usually have defects in the DNA incision components of nucleotide excision repair (25). Chain smokers of cigarettes are susceptible to the smoke mutagens such as benzopyrene that generate bulky adducts in the DNA of lung cells.

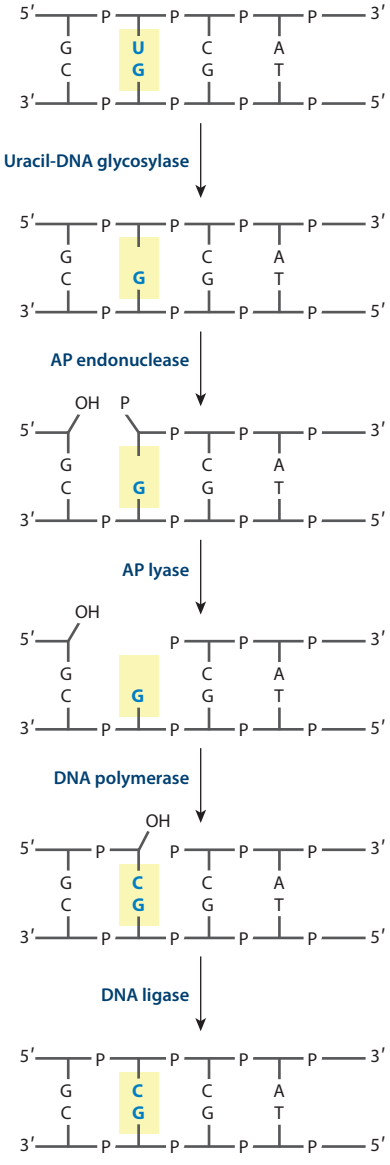

Figure 4

The DNA base excision repair (BER) pathway. A damaged base in DNA may be removed by one of several DNA glycosylases, as shown for a cytosine residue hydrolytically deaminated to uracil. Abasic sites are also generated at relevant rates in vivo by spontaneous hydrolytic cleavage of base–sugar bonds. Following enzymatic single-strand chain cleavage at the abasic site by an AP endonuclease, the removal of the base-free deoxyribose-phosphate residues is catalyzed by the AP lyase function of DNA polymerase β in mammalian cells. This polymerase, and perhaps also the error-prone DNA polymerase θ, fills in the resulting one-nucleotide gap in DNA (41). DNA ligase 1, or DNA ligase 3 together with the scaffolding protein XRCC1, then completes the repair reaction. The reaction intermediates with a single-strand DNA interruption are also protected by poly ADP-ribose formation (42), and the efficiency of BER may be perturbed by interactions with certain other cellular proteins and small molecules. Abbreviation: AP, apurinic/apyrimidinic.

Figure 5

Monica Olsson, Department of Medical Chemistry, University of Gothenburg Medical School.

But most forms of human cancer do not have such credible identifiable causes. One well known risk factor for cancer is obesity, but this effect is more likely due to altered metabolism than any specific noxious mutagenic compound in our food. Mutagens in foods, such as aflatoxins in moldy nuts, are readily identified and avoided by appropriate legal measures. Air pollution is a relevant but relatively minor risk factor for DNA damage, along with the associated problems of cancer and aging. Ionizing radiation is a risk factor for cancer, but thanks to our Earth's magnetic field and atmosphere, we are well protected against cosmic radiation damage which consequently accounts for at most only 1–2% of human cancers. Carcinogenic radiation-induced DNA lesions will be a much bigger problem if extended travels to locations such as Mars are attempted. In conclusion, most cancer-causing mutations remain of unknown origin. Serious candidates include different forms of endogenous DNA damage, in addition to the various forms of exogenous DNA damage mentioned above, combined with less-than-perfect DNA repair.

The most common form of endogenous DNA damage is due to hydrolytic loss of the purine bases guanine and adenine from DNA. Such events are immediately corrected by BER (**Figure 4**) in more than 99.9% of cases, but even a small remaining proportion of damage not corrected before replication can explain most or all of the spontaneous DNA damage in tumor suppressor genes. More unusual types of endogenous damage, such as deamination of 5-methylcytosine residues in DNA, which are repaired more slowly, also contribute in a relevant fashion. In consequence, similar mutation rates are observed in dividing and nondividing human cells (23).

Water and active oxygen are two of the most investigated causes of endogenous DNA damage. But there are additional factors to be considered. I have been particularly interested in the spontaneous alkylation of DNA by methylating agents. The most important of those is S-adenosylmethionine, which in addition to its role in several aspects of metabolism is an alkylating

Figure 6

Latimeria menadoensis (coelocanth). This species is probably approximately 100 million years old. Photo reproduced from **https://commons.wikimedia.org/wiki/File:Latimeria_menadoensis.jpg** (CC BY-SA 2.5).

agent under the solvent conditions present in vivo (26). This may explain the occurrence of multiple forms of DNA repair directed against deleterious DNA lesions such as 3-methyladenine, 3-methylguanine, 1-methyladenine, and O^6-methylguanine (27). Other small reactive endogenous molecules that generate repairable DNA damage include the DNA crosslinking agents formaldehyde and acetaldehyde, which recently have been investigated in detail by KJ Patel (28, 29). There are many other small reactive molecules present in cells in addition to *S*-adenosylmethionine and formaldehyde. It seems plausible that several such molecules are able to damage DNA at relevant rates, and this is a promising future field of DNA repair research. There may be several additional DNA repair strategies that remain to be clarified because the relevant DNA lesions have not yet been biochemically defined. In addition, overproduction of certain proteins involved in oxygen metabolism may cause endogenous DNA damage (30).

Interestingly, there are forms of DNA damage that are not corrected by BER but through different biochemical mechanisms present in both bacteria and human cells. The methylation lesions 3-methylcytosine and 1-methyladenine are generated in single-stranded regions of DNA and are potentially lethal because they block DNA synthesis. The repair occurs via direct demethylation by DNA dioxygenases of the AlkB family, with the restoration of the original undamaged base. In addition, our experiments showed that the repair reaction has the unusual cofactor requirements

of ferrous ions and alpha-ketoglutarate (31). Similar work was also performed by Erling Seeberg in Oslo (32). In my collaboration with the group of Chuan He, in the Department of Chemistry, University of Chicago, one member of the AlkB family, FTO (fat mass and obesity associated protein) was shown to act on N^6-methyladenosine residues in nuclear RNA (33). Recently, Chuan He has spectacularly extended these studies to plant biology and shown that FTO regulates growth under starvation conditions, facilitating increased plant yield by gene manipulation.

It also needs to be mentioned that valuable active somatic hypermutation in antibody genes is dependent on the targeted interaction with DNA repair processes (34), and temporary inhibition of DNA repair maybe an important tool to supplement anticancer drugs (35).

EPSTEIN–BARR VIRUS

At the Karolinska Institute in Stockholm, I had the privilege to collaborate with the tumor virologist George Klein, who was a world leading expert on the human Epstein–Barr virus (EBV). In a fruitful project, my biochemical DNA expertise could complement his work. Besides helping the Klein group, I made one pleasing contribution to the EBV field. It was assumed that EBV-transformed lymphocytes carried the viral information as EBV DNA integrated at specific sites, the model being the extensively studied bacteriophage lambda integrated into the host *Escherichia coli* genome, and there was a search for these hypothetical viral integration sites. But *E. coli* also provided a different, less investigated model with its large bacteriophage P1. This phage is carried as nonintegrated plasmids in lysogenic bacteria, replicating in synchrony with its host. I was interested in the possibility that EBV DNA in transformed cells might also be carried as plasmids and searched for DNA circles the size of the viral genome in EBV-transformed cells. We were able to isolate such large EBV DNA circles, first from human lymphocyte lines and then from human tumor biopsies of Burkitt lymphoma origin (36, 37). There now seems to be a real possibility that, using appropriate vaccines, EBV could be eliminated from the human population, perhaps resulting in a decreased frequency of the human diseases known to be associated with EBV such as infectious mononucleosis, Burkitt lymphoma in African children, and multiple sclerosis (38). But it should also be remembered that approximately 90% of adult humans are already carriers of EBV DNA, in the very great majority of cases, without any detectable health risks. Suitably weakened derivatives of EBV might be useful vectors of foreign DNA in human cells when there is hesitancy about the introduction of permanent gene therapy in humans because of the irreversibility of the process.

I have worked on a number of additional projects and enzymes, such as the intriguing exonuclease DNase III/TREX 1 in mammalian cells, which I discovered over fifty years ago. DNase III is important for reducing autoimmunity (39, 40) and may serve to remove fragments of damaged DNA from cell nuclei by a strategy similar to the removal of damaged proteins by the proteasome.

Perhaps I have sometimes been pursuing too many projects, but such challenges make research activities consistently exciting and sometimes very productive. In relatively recent years, I have also had stimulating interactions with many outstanding scientists including Marco Foiani, Errol Friedberg, Michael Neuberger, Svante Pääbo, Hans Krokan, Jean-Marc Egly, Steve West (**Figure 7**), Rick Wood, Yun-Gui Yang, Chuan He, Ningning Li, KJ Patel, and my brother Gunnar Lindahl.

I have been pleased and honored by a number of recognitions and awards over the years, including memberships in the Royal Society, UK (FRS 1988); the Swedish Academy of Sciences (1989); the Norwegian Academy of Science and Letters (1999); the US National Academy of Sciences (2018); and EMBO (1976) and receiving the Svedberg Prize (1977); the Prix Étranger d'INSERM, France (2008); the Royal Medal (2007) and the Copley Medal (2010) from the Royal Society; a shared Nobel Prize in Chemistry (2015); and six honorary Doctorate degrees. Furthermore, an already productive research unit named after me was opened in Shenzhen, China, in 2019.

Figure 7

(*Left to right*) Tomas Lindahl, Steve West, and Richard Treisman (current Director of Research at the Francis Crick Institute) in 2007.

It has been a privilege and pleasure to contribute to a research field that has revolutionized our view on genetic stability and variability.

DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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