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DNA Repair: Its Importance and How to Improve it

An Interview with Dr. Noah Scheinfeld

BY RICHARD A. PASSWATER, PH.D.

The key to maintaining good health is to maintain our DNA. One of the major emphases of my antioxidant research has been to protect DNA. Complete protection is not possible, so we must rely on protecting DNA as well as we can and then relying on our body's ability to repair much of the damage that occurs to DNA. Fortunately, we are learning how to improve our body's DNA repair mechanisms. I have had the privilege to join with Dr. Noah Scheinfeld, M.D., J.D., in a series of educational talks about DNA repair and I would like to share some of Dr. Scheinfeld's teaching with you.

Dr. Scheinfeld is an assistant clinical professor at Columbia University, and a leading expert in DNA repair. He recently co-authored a state-of-the-art review of DNA repair with Dr. Patrick Emanuel of Mount Sinai Medical in the *Dermatology Online Journal* [13 (3): 10]. The review is entitled, "A Review of DNA Repair and Possible DNA-Repair Adjuvants and Selected Natural Anti-Oxidants," and is available free at *http://dermatology.cdlib.org/133/reviews/DNA/scheinfeld.html.*

Passwater: Dr. Scheinfeld, please review for our readers what is DNA. How important is DNA to us?

Scheinfeld: Deoxyribonucleic acid (DNA) is a nucleic acid that contains the genetic instructions used in the development and functioning of all known living organisms. A

main role of DNA molecules is the storage of information. Chemically, DNA is a long polymer of simple units called nucleotides with a backbone made of sugars and phosphate groups joined by ester bonds. Attache d to each sugar is one of four types of molecules called bases. It is the sequence of these four bases along the backbone of DNA that encodes information. Three nucleotides (nucleic acids) in DNA encode for three nucleotides in ribonucleic acid (RNA), which encode one protein molecule when the DNA is read (translated) from RNA to protein in the ribosome.

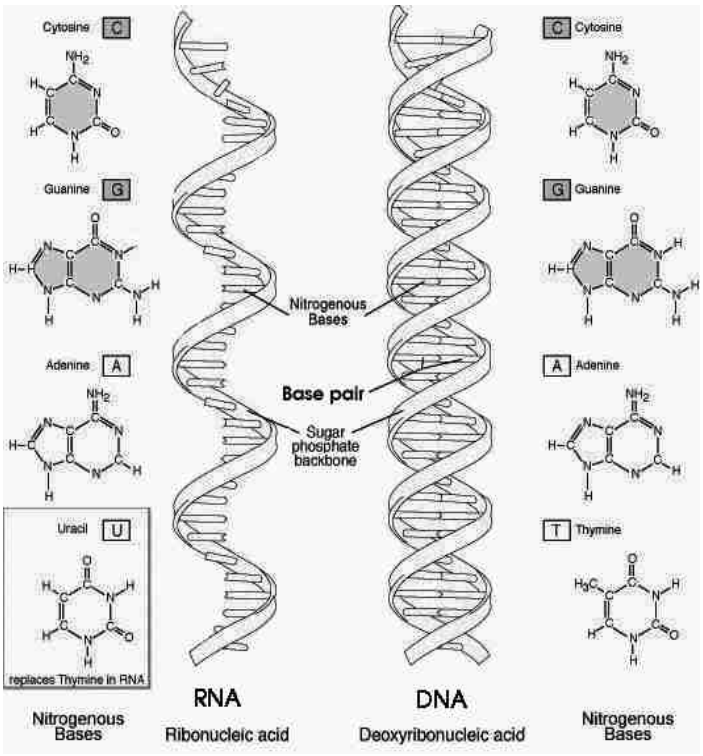
Passwater: Basically, what is it about the chemical structure of DNA that allows it to make us and make us be us?

Scheinfeld: DNA furnishes a template or blueprint for the production of RNA that is translated into proteins. DNA is often compared with a set of blueprints, since it contains the instructions needed to construct other components of cells such as proteins and RNA molecules. The DNA segments that carry this genetic information are called genes, but other DNA sequences have structural purposes or are involved in regulating the use of this genetic information.

The information contained in DNA is read using the genetic code, which specifies the sequence of the amino acids within proteins. The code is read by copying stretches of DNA into the related nucleic acid RNA in a process called transcription. Most of these RNA molecules are used to synthesize proteins, but others are used directly in struc tures such as ribosomes and spliceosomes.

There are two kinds of nucleic acids: DNA and RNA. DNA is found in the chromosomes of a cell's nucleus and it carries hereditary information. RNA is located in the cell, but not in the nucleus. Just as proteins con sist of long chains of amino acids, DNA and RNA consist of nucleic acid chains called nucleotides.

Nucleotides are composed of three units: base, sugar (monosaccharide) and phosphate. Bases are found in both DNA and RNA. As seen below they are adenine, cyt osine, guanine, thymine and uracil. They are abbreviated (A, C, G, T, U). Three of the bases (A, G, C) are found in both DNA and RNA. However, uracil (U) is found only in RNA and thymine (T) is found only in DNA.



Within cells, DNA is organized into structures called chromosomes. These chromosomes are duplicated before cells divide in a process called DNA replication. Eukaryotic organisms such as animals, plants and fungi store their DNA inside the cell nucleus, while it is found in the cell's cytoplasm in prokaryotes such as bacteria. Within the chromosomes, chromatin proteins such as histones compact and organize DNA, which helps control its interactions with other proteins and thereby control which genes are transcribed.

Passwater: It certainly is obvious why it is important to protect our DNA. What can happen to unprotected DNA?

Scheinfeld: If DNA repair does not take plac e, defective DNA is present in the cell and this leads to defective RNA and the translation of defective RNA into non -functional or defective proteins in the ribosome.

A variety of rare diseases are related to a total lack of any of a host of DNA repair enzymes. These include:

* Ataxia Telangiectasia

* Ataxia Telangiectasia-like

* Ataxia with neuropathy

* Cockayne Syndrome A

* Cockayne Syndrome B

* Xeroderma Pigmentosum

Types of defects:

* base modifications: methylation, oxidation

* mispairs: mistakes in DNA synthesis

* cross-linked nucleotides: intrastrand, interstrand covalent links

* double-stranded DNA breaks.

Passwater: How extensive is DNA damage and what does this mean in regards to our health?

Scheinfeld: DNA repair refers to a collection of p rocesses by which a cell identifies and corrects damage to the DNA molecules that encode its genome. In human cells, both normal metabolic activities and environmental factors such as ultraviolet (UV) light can cause DNA damage, resulting in *as many as one million individual molecular lesions per cell per day.* Many of these lesions cause structural damage to the DNA molecule and can alter or eliminate the cell's ability to transcribe the gene that the affected DNA encodes. Other lesions induce potentially harmful mutations in the cell's genome, which affect the survival of its daughter cells after it undergoes mitosis. Consequently, the DNA repair process must be constantly active so it can respond rapidly to any damage in the DNA structure.

Passwater: Can our bodies do anything about damaged DNA?

Scheinfeld: DNA repair mechanisms exist in the cell. Single-strand and double-strand DNA damage are forms of DNA damage. Cells cannot function if DNA damage corrupts

the integrity and accessibility of essential information in the genome (but cells remain superficially functional when so-called "non-essential" genes are missing or damaged). Depending on the type of damage inflicted on the DNA's double -helical structure, a variety of repair strategies have evolved to restore lost information. If possible, cells use the unmodified complementary strand of the DNA or the sister chromatid as a template to recover the original information without any loss of information. Without access to a template, cells use an error -prone recovery mechanism known as translesion synthesis as a last resort.

Passwater: Do these repair mechanisms involve enzymes?

Scheinfeld: Yes, they do. These enzymes include:

* Human AP Endonuclease (APE/Ref -1)

* Human DNA Polymerase ß

* Human Fen-1

* Human DNA Ligase IV/XRCC4 Tetramer

Additional mechanisms that underlie DNA repair have been extensively explicated in recent years. A few recent discoveries in the field DNA repair enzymes follow.

Modrich found that a protein called PCNA is clamped onto the DNA at the strand break. This PCNA, together with the protein that clamps PCNA onto the DNA double helix, regulates the enzyme whose job it is to snip out the segment containing the mismatch by "aiming" the enzyme—known as *exonuclease I*—in the right direction to work itself along the strand, and remove the mismatch. A notable aspect of this PCNA repair system is that it can evaluate the placement of the strand signal to one side or the other of the mismatch and work from there. Placement of the str and break that directs repair to one side or the other of the mismatch might be the result of a mechanism by which DNA is copied by the replication machinery.

Ronai found that the protein ATF2 (Activating Transcription Factor -2) is activated by a protein kinase called ATM (Ataxia-Telangiectasia Mutated), which stimulates DNA repair. ATF2's role in regulating the expression of proteins that control cell cycle and programmed cell death is well established. Ronai demonstrated ATF2's role in DNA repair, an intracellular process that prevents the formation of genetic mutations, including those that lead to cancer. This ATF2 is regulated by ATM and this regulation is central to the cell's ability to initiate DNA repair processes following ionizing irradiation or o ther

exposures that cause breaks in DNA. ATF2 likely works by halting the cell's cycle to allow repair of damaged DNA before such damage becomes permanent.

Powell discovered that MDC1, a protein previously recognized only for its function in sensing DNA damage and signaling its presence, also transports DNA -repair proteins to the site of DNA strand breaks. Without MDC1 to pave the way, repair happens slowly because the fix-it proteins have a hard time reaching damaged areas, which are buried in the tightly packed chromosomal material of the cell's nucleus. The MDC1 can bind to chromatin, the complex mixture of DNA and proteins that holds the genetic material. Because of chromatin's properties, getting into it to reach the DNA strand requires the right "passwords." The MDC1 provides the DNA -repair proteins with this privileged access and efficiently transports them to the site of damage so they can affect repair.

Although the relationship between sun exposure, DNA damage and the development of malignant melanoma remains controversial, a growing body of evidence supports a role for MSI and defective MMR protein expression in melanoma tumorigenesis. Absent hMLH1 and hMSH2 expression has been demonstrated in melanomas and correlates with tumor progression.

What is clear from our current understanding of DNA repair is that rather than being a process in which a few protein complexes detect and repair damaged DNA, the mechanisms of DNA repair are complex, intricate and involve a number of dynamic systems. Our understanding of genetic diseases in DNA repair and the profound clinical manifestations (*e.g.,* XP) has shown that a clearer understanding of DNA mechanisms is likely to pave the way for understanding of carcinogenesis.

Passwater: What can these repair mechanisms do?

Scheinfeld: Damage to DNA alters the spatial configuration of the helix and such alterations can be detected by the cell. Once damage is localized, specific DNA repair molecules are summoned to, and bind at or near the site of damage, inducing other molecules to bind and form a complex that enables the actual repair to take place. The types of molecules involved and the mechanism of repair that is mobilized depend on the type of damage that has occurred and the phase of the cell cycle that the cell is in.

Direct Reversal. Cells are known to eliminate three types of damage to their DNA by chemically reversing it. These mechanisms do not require a template, since the types of damage they counteract can only occur in one of the four bases. Such direct -reversal mechanisms are specific to the type of damage incurred and do not involve breakage of the phosphodiester backbone. The formation of thymine dimers (a common type of cyclobutyl dimer) upon irradiation with UV light results in an abnormal covalent bond between adjacent thymidine bases. The photoreactivation process directly reverses this

damage by the action of the enzyme photolyase, whose activation is obligatorily dependent on energy absorbed from blue/UV light (300 –500 nm wavelength) to promote catalysis. Another type of damage, methylation of guanine bases, is directly reversed by the protein methyl guanine methyl transferase (MGMT), the bacterial equivalent of which is called as ogt. This is an expensive process because each MGMT molecule can on ly be used once; that is, the reaction is stoichiometric rather than catalytic. A generalized response to methylating agents in bacteria is known as the adaptive response and confers a level of resistance to alkylating agents upon sustained exposure by upr egulation of alkylation repair enzymes. The third type of DNA damage reversed by cells is certain methylation of the bases cytosine and adenine.

Single-Strand Damage. When only one of the two strands of a double helix has a defect, the other strand can be used as a template to guide the correction of the damaged strand. To repair damage to one of the two paired molecules of DNA, several excision repair mechanisms can remove the damaged nucleotide and replace it with an undamaged nucleotide complementary to that found in the undamaged DNA strand.

Base excision repair (BER) fixes damage to a single nucleotide caused by oxidation, alkylation, hydrolysis or deamination. The base is removed with glycosylase and ultimately replaced by repair synthesis with DNA ligase.

Nucleotide excision repair (NER), mends damage affecting longer strands of 2 –30 bases. This process recognizes bulky, helix-distorting changes such as thymine dimers as well as single-strand breaks (repaired with enzymes such UvrABC endonuclease). A specialized form of NER known as transcription-coupled repair (TCR) deploys high-priority NER repair enzymes to genes that are being actively transcribed.

Mismatch repair (MMR) corrects errors of DNA replication and recombination that result in mispaired (but normal, that is non-damaged) nucleotides following DNA replication.

Double-Strand Breaks. Double-strand breaks (DSBs), in which both strands in the double helix are severed, are particularly hazardous to the cell because they can lead to genome rearrangements. Two mechanisms exist to repair DSBs: non-homologous end joining (NHEJ) and recombinational repair (also known as template-assisted repair or homologous recombination repair).

DNA ligase is an enzyme that joins broken nucleotides together by cat alyzing the formation of an internucleotide ester bond between the phosphate backbone and the deoxyribose nucleotides. In NHEJ, DNA Ligase IV, a specialized DNA Ligase that forms a complex with the cofactor XRCC4, directly joins the two ends. To guide accu rate repair, NHEJ relies on short homologous sequences called microhomologies present on the single-stranded tails of the DNA ends to be joined. If these overhangs are compatible, repair is usually accurate. NHEJ can also introduce mutations during repair. Loss of damaged nucleotides at the break site can lead to deletions, and joining of nonmatching termini forms translocations. NHEJ is especially important before the cell has replicated

its DNA, since there is no template available for repair by homologou s recombination. There are "backup" NHEJ pathways in higher eukaryotes. Besides its role as a genome caretaker, NHEJ is required for joining hairpin-capped double-strand breaks induced during V(D)J recombination, the process that generates diversity in B -cell and T-cell receptors in the vertebrate immune system.

Recombinational repair requires the presence of an identical or nearly identical sequence to be used as a template for repair of the break. The enzymatic machinery responsible for this repair proces s is nearly identical to the machinery responsible for chromosomal crossover during meiosis. This pathway allows a damaged chromosome to be repaired using a sister chromatid (available in G2 after DNA replication) or a homologous chromosome as a template. DSBs caused by the replication machinery attempting to synthesize across a single -strand break or unrepaired lesion cause collapse of the replication fork and are typically repaired by recombination.

Topoisomerases introduce both single - and double-strand breaks in the course of changing the DNA's state of supercoiling, which is especially common in regions near an open replication fork. Such breaks are not considered DNA damage because they are a natural intermediate in the topoisomerase biochemical mechan ism and are immediately repaired by the enzymes that created them.

Translesion Synthesis. Translesion synthesis allows the DNA replication machinery to replicate past damaged DNA. This involves the use of specialized translesion DNA polymerases that can insert bases at the site of damage. Some mechanisms of translesion synthesis introduce mutations, but others do not. For example, Pol η mediates error -free bypass of lesions induced by UV irradiation, whereas Pol ζ introduces mutations at these sites. From the cell's perspective, the potential for introducing mutations during translesion synthesis is less dangerous than continuing the cell cycle with an incompletely replicated chromosome.

Passwater: Can we help these repair enzymes somehow?

Scheinfeld: A number of substances seem to have the ability to enhance DNA repair DNA repair adjuvants (from nature, enzymes and cytokines) and selected natural antioxidants discussed here include the following: selenium, *Urcaria tomentosa (AC-11)*, T4 endonuclease V, u biquitin and interleukin-12. Polypodium leucotomos will be discussed as well because it has been included in discussions of the aforementioned substances although it is primarily an antioxidant.

Table I: DNA-Repair Adjuvants and Selected Natural

Category	Adjuvants	Trade name	Route	Mechanism	Antioxidant	DNA Repair
Minerals	Selenium, selenomethionine		Oral	Unclear NER	Conflicting reports.	Unknown
Carboxyl alkyl ester	Uncaria tomentosa (aqueous extract)	AC-11 (formerly C-MED-100)	Topical, oral	NER	Yes	Yes
DNA repair enzyme	T4 endonuclease V	Dimericine	Topical	NER	No	Yes
Heat shock protein	Ubiquitin		Experimental	NER, Double strand breaks.	No	yes
Cytokine	Interleukin-12		Experimental	NER	No	Yes
Fern	Polypodium leucotomos	Heliocare	Oral	Reduced UV induced damage to DNA repair mechanism	Yes	Unknown

NER-nucleotide excision repair

Passwater: Do any studies demonstrate that this approach works?

Scheinfeld: Yes. Please allow me to detail the studies.

Selenium. Clark supervised a randomized trial of 1,312 patients for the prevention of skin cancers supplementing diets with baker's yeast rich in selenium and found that the selenium-rich yeast reduced the overall risk of developing cancer by 40% and reduced their risk of dying from cancer by nearly half, compared with the placebo group. Selenium intake did not protect against the malignant degeneration of skin cell into basal or squamous cell carcinomas of the skin. This report of Clark, carried forward a study that Clark had published in 1991 showing that selenium supplementation had cancer chemopreventive effects in humans.

Studies have confirmed the cancer chemopreventive activity of selenium and have suggested that this effect may be related to selenium -induced apoptosis of cancer cells. Seo and co lleagues found that cells whose DNA was damaged by UV radiation, when treated with selenomethionine, elicit activation of Ref-1—a protein which is able to switch on p53 activity and double the rate of DNA repair. The presence of selenomethionine allows cells to tolerate greater levels of ultraviolet radiation, because of the higher level of competent p53.

Rafferty concluded that selenite and selenomethionine protect keratinocytes from UVR-induced oxidative damage, but not through creation or formation of UV R-induced excision repair sites. So although selenium might prevent cancer, it might not be acting to do this by promoting DNA repair.

More recently, however, Fischer and coauthors have shown that selenomethionine preferentially induced the DNA repair branch of the p53 pathway. Accordingly, pretreatment with selenomethionine protected normal fibroblasts from subsequent DNA damage. Interestingly, Brca1 (breast carcinoma gene 1) was required for SeMet -mediated DNA damage protection, as brca1 -/- mouse fibroblasts were not protected from UV - radiation by SeMet treatment. This indicates that besides p53 and Ref1, Brca1 is required for selenium protection from DNA damage. The controversy surrounding the use of selenium as an antineoplastic agent can partially be explained by its dose related effects: mutagenic, carcinogenic and probably teratogenic effects have been reported following administration of toxic doses.

The mechanism for the toxic effects of Selenium, has been suggested to result from its high affinity for non-specific substitution for sulfur in SH-containing DNA repair proteins. Although the recommended daily allowance (RDA) of Se by the U.S. Food and Drug Administration is 50 µg/day, cancer preventive use of Se is typically 200 µg daily intake, exceeding the RDA by four-fold with no harmful effects. Human dietary intakes of Se vary according to ecological abundance, being as low as 20 µg/day in parts of New Zealand and as high as 5000 µg /day in parts of China.

Aqueous Extract of *Uncaria tomentosa* (*i.e.,* AC-11 or C-Med-100). The aqueous extract of *Uncaria tomentosa* (previously named *C-Med-100* and now renamed *AC-11*), an extract of cat's claw, appears to enhance the normal repair of cyclobutyl pyrimidine dimers following UVB exposure. The observed reducti on in oxidative DNA damage (8-hydroxyguanine and strand breaks) is possibly the result of enhanced base excision repair or an inherent antioxidant effect, or both.

Reduced non-melanoma skin cancer following topical application of AC-11 in hairless mice (an unpublished study) is likely from a reduced dimer burden and leads to: decreased dimers, - decreased p53 mutations, - decreased actinic ketatosis, - and decreased malignancies.

The DNA data in humans have been supplemented with two animal studies in whic h the effects of known DNA damaging agents were compared in AC -11-treated and control animals.

In the first study of AC -11, eight daily doses of 40 mg/kg or 80 mg/kg of AC -11 were administered to 20 rats (an additional 10 rats served as controls) by gavage for eight weeks. Half the animals from each group were exposed to 12 Gy whole body radiation (137Cs source) and allowed three hours to repair *in vivo* before DNA damage was assessed. AC -11-treated animals almost completely repaired single -strand DNA breaks ($p < 0.05$) for both AC -11 doses compared with untreated animals. Double -strand DNA breaks were substantially fewer in animals treated with 40 mg/kg/day of AC -11 and significantly ($p < 0.05$) fewer in animals treated with 80 mg/kg/day of AC -11 compared with untreated animals.

In the second study, nine daily doses of 40 mg/kg or 80 mg/kg of AC -11 were administered orally to eight rats (four at each dose) 24 hours after the last of three 2 - mg/kg intraperitoneal doses of doxorubicin. Four animals received doxor ubicin only. Animals treated with 80 mg/kg of AC -11 had significantly ($p < 0.05$) reduced DNA damage in the form of single -strand DNA breaks.

More recently, Pero reported on the combination of a cat's claw water extract (AC -11, carboxy alkyl esters) plus medicinal mushroom extracts (*Cordyceps sinensis, Grifola blazei, Grifolafrondosa, Trametes versicolor* and *Ganoderma lucidum*, polysaccharides) and nicotinamide plus zinc into a formulation designed to optimize different modes of immunostimulatory action in 14 subjects treated for four weeks and found patient experienced reduced pain, reduced fatigue, weight loss and a reduced presence of DNA damage in peripheral blood assessed by (8 -OH) guanine DNA adducts and elevation in serum protein thiols.

The mechanism for AC-11 activity has yet to be fully defined; however, research in humans and in human living skin equivalents shows that AC-11 reduces erythema and blistering after ultraviolet exposure. AC -11 significantly enhanced the repair, but not the formation, of cyclobutyl pyrimidine dimers (TT-dimers) in human living skin equivalents exposed to UV -B light.

In a study of five healthy volunteers (aged 35 to 55 -years-old) taking 350 mg/day of AC-11 orally for four weeks, 8 -hydroxyguanine levels were significantly ($p < 0.05$) decreased. The beneficial effect was noted to persist two weeks after therapy was discontinued.

Another study reported a significant ($p < 0.05$) decrease in DNA single -strand breaks following peroxide -induced DNA damage in monocytes of healthy vol unteers who received eight weeks of AC -11 at 350 mg/day.

Pero and colleagues assessed oxidative DNA damage in 14 volunteers, most of whom (more than 75%) had chronic diseases, and reported that nine of the 14 volunteers had

decreased 8-hydroxyguanine DNA adducts after 400 mg of AC-11 per day for four weeks. Finally, in a in a single-blind, right side-left side, beach sun exposure pilot study that included 42 healthy volunteers there were dramatic and significant ($p < 0.0001$) reductions in erythema and blistering in volunteers who applied 0.5% topical AC-11 with an SPF-15 sunscreen when compared with the group who just applied an SPF-15 sunscreen.

In 2001, Sheung did a study involving 12 men and women. He divided them into three groups (one placebo, one 250 mg of AC-11 daily and one of AC-11 350 mg daily) for eight consecutive weeks. DNA damage was induced by a standard dose of H_2O_2 was measured three times before supplementation and three times after the supplementation during the last three weeks of the eight-week supplement period. Supplement groups (250 and 350 mg/day) experienced statistically significant decreases of DNA damage and simultaneous increases of DNA repair versus men and women taking placebo.

In 2006, Mammone treated skin cultures with 5 mg/mL C-Med-100 or without 5 mg/mL C-Med-100. The cultures where then irradiated with 0–100 mJ/cm2 UVB, and microscopically analyzed for necrosis and the level of pyrimidine dimers using immunofluorescent TT-dimer antibody staining. It was found that co-incubation of keratinocytes with C-Med-100 reduced skin cell death from UV exposure likely related to an increase of DNA repair.

T4 endonuclease V. T4 endonuclease V (Dimericine) is a DNA repair enzyme produced in bacteria that is delivered in liposomes in the form of a topical cream. The liposome utilized in T4 endonuclease V is a microsphere called a T4N5 liposome made from lipid lecithin, from the egg. It is thought to act via two mechanisms. Immediately, T4 endonuclease V removes DNA dimers, primarily cyclobutane pyrimidine type. In the long term, it may restore p53 gene function and exert a lasting chemopreventative effect. T4 endonuclease V has been studied as a topical cream to decrease the development of skin cancer in patients with xeroderma pigmentosum and renal transplant patients on immunosuppressive therapy. T4 endonuclease V received orphan drug designation for this indication in 1989.

One study found the T4 endonuclease V lotion reduced the incidence of basal cell carcinomas by 30% and actinic keratoses by 68%. Furthermore, the effects on actinic keratoses were observed within the first three months of treatment, so the improved repair of DNA damage seems to affect tumor promotion or progression. In the same study, no adverse effects were observed among the patients during treatment, and no antibodies against the enzyme were detected in the patients' serum. This absence of toxicity confirms early safety studies and may be explained by immunohistological observations that T4 endonuclease V delivered by liposomes is localized in the epidermis and does not readily penetrate into dermis.

In another study, *in vivo* testing involving T4N5 liposome lotion has yielded intriguing results. In a test conducted with 12 xeroderma pigmentosum (XP) patients and 15 patients without this condition who had a history of skin cancer, researchers applied the cream at

various intervals after controlled UV exposure. Biopsies conducted six hours after UV exposure revealed that patients with XP had achieved approximately 15% fewer CPDs (improved DNA repair) while patients with a history of skin cancer achieved less than 10% fewer CPDs. The results of this study demonstrate that liposomal delivery represents an effective way of introducing proteins into the cells of human skin, including keratinocytes and Langerhans cells. The results showed that a DNA repair enzyme delivered in this manner can reverse some of the deleterious effects of UV irradiation that seem to be caused by DNA damage such as the upregulation of the immunosuppressive cytokines, IL-10 and TNF-α. Topical DNA repair enzyme application therefore may be a clinically useful approach of photo-protection in humans. In contrast to conventional sunscreens, which are effective owing to their content of chemical or physical UV filters, liposomes containing DNA repair enzymes may be able to protect against UV-induced damage to the skin, even when they are applied after UV exposure and initiation of the sunburn reaction. Thus, the immunoprotective effects of topical DNA repair enzyme application may open new avenues for photoprotection, particularly by protecting efficiently against the effects of UV radiation on the immune system, which are not always prevented by sunscreening agents.

T4N5 liposomes overcome the drug block in DNA repair seen in immunosupression in organ transplant patients. This indicates that the inhibition is an early incision step of DNA repair.

Phases I and II trials of T4 endonuclease V for prevention of skin cancer in xeroderma pigmentosum patients were completed. T4 endonuclease V, however, is not commercially available. The company states, "The XP trial was registered with the FDA as a Phase III trial because it had a clinical endpoint: reduction of actinic keratoses and skin cancer and that its application is open. The FDA has undergone reorganization twice in the last 3 years and our application has been moved. We are discussing the number of XP patients required for market approval."

New studies of T4 endonuclease V are ongoing. Craig A. Elmets, M.D., chair of the University of Alabama at Birmingham's Department of Dermatology and senior scientist at the UAB Comprehensive Cancer Center is leading a three-year, multicenter, Phase II, randomized, double-blind controlled study of T4N5 liposome lotion to determine its success in preventing recurrence of non-melanoma skin cancer in 100 renal transplant patients. Enrollment is ongoing.

It would seem that the most useful role for T4 endonuclease V would be its inclusion in sunblock. With no reported side effects, T4 endonuclease V is promising. Whether it will change clinical outcomes will become clearer as Phase III trials are completed.

Passwater: Interesting that you list selenium and AC-11 as top supplements for DNA repair. We certainly discuss selenium often in this column and we had the opportunity to chat with Dr. Ronald Pero about carboxyl alkyl esters (CAE) and AC-11 when it was still

called C-Med-100. Readers may wish to review the December 1999 column entitled, "Immune Enhancement and Health: An interview with Dr. Ronald Pero" (please see *www.drpasswater.com/nutrition_library/pero.htm*). I remind readers that they can find more details about DNA repair in on-line Dr. Scheinfeld's detailed peer reviewed PubMed indexed open access article (*http://dermatology.cdlib.org/133/reviews/DNA/scheinfeld.html*).

What will you look at next concerning DNA repair?

Scheinfeld: I want to see an impact of these substances on outcomes, that is, I want to see data that DNA repairs substances help people to l ive longer and better.

Passwater: Thank you, Dr. Scheinfeld. **WF**