Ultraviolet Radiation and the Skin

Overview

1. *Physics*
   - Electromagnetic Spectrum and Sources of EM Radiation
   - Cutaneous Optics
2. *UV Radiation and Skin Biology*
   - Acute and Chronic Effects of UV Radiation on Skin
   - Mechanism of Action of Effects
3. *Defenses against UV Radiation*
   - Endogenous
   - Exogenous

Physics

- 2 Types of Radiation
  - Ionizing (alpha, beta, gamma particles, X-ray)
  - Non- Ionizing (UV, Visible Light)
- Wave-Particle Theory of Light/Radiation states that Light has 2 properties:
  - Waves
  - Photons (packets of energy or quanta)

Physics

- The Energy of Electromagnetic Radiation:
  - $E=hc/\lambda$
  - $E=vh$
    - E=energy of photon; h=Planck's constant; c=speed of light; λ=wavelength; v=frequency
- **Take home points**:
  - As ***wavelength increases*** : ***energy decreases*** (**inverse**)
  - As ***frequency increases***: ***energy increases***

Physics
Electromagnetic Spectrum

- **Sun emits UV radiation as part of an electromagnetic spectrum.**
- **<10nm (Cosmic, Gamma & X-rays)**= *Ionizing Radiation*
  - Particles at this energy generally remove or ionize electrons
- **UVC (200-290nm)**
  - Filtered by the ozone
  - Well absorbed by DNA, RNA, and proteins
  - **Lethal** to viable cells in the epidermis
    - (AKA *Germicidal radiation*)
- **UVB (290-320nm)**
  - 1000X more erythemogenic than UVA
  - Window glass filters UV less than 320nm (Glass **B**locks UV**B**)

Physics
Electromagnetic Spectrum

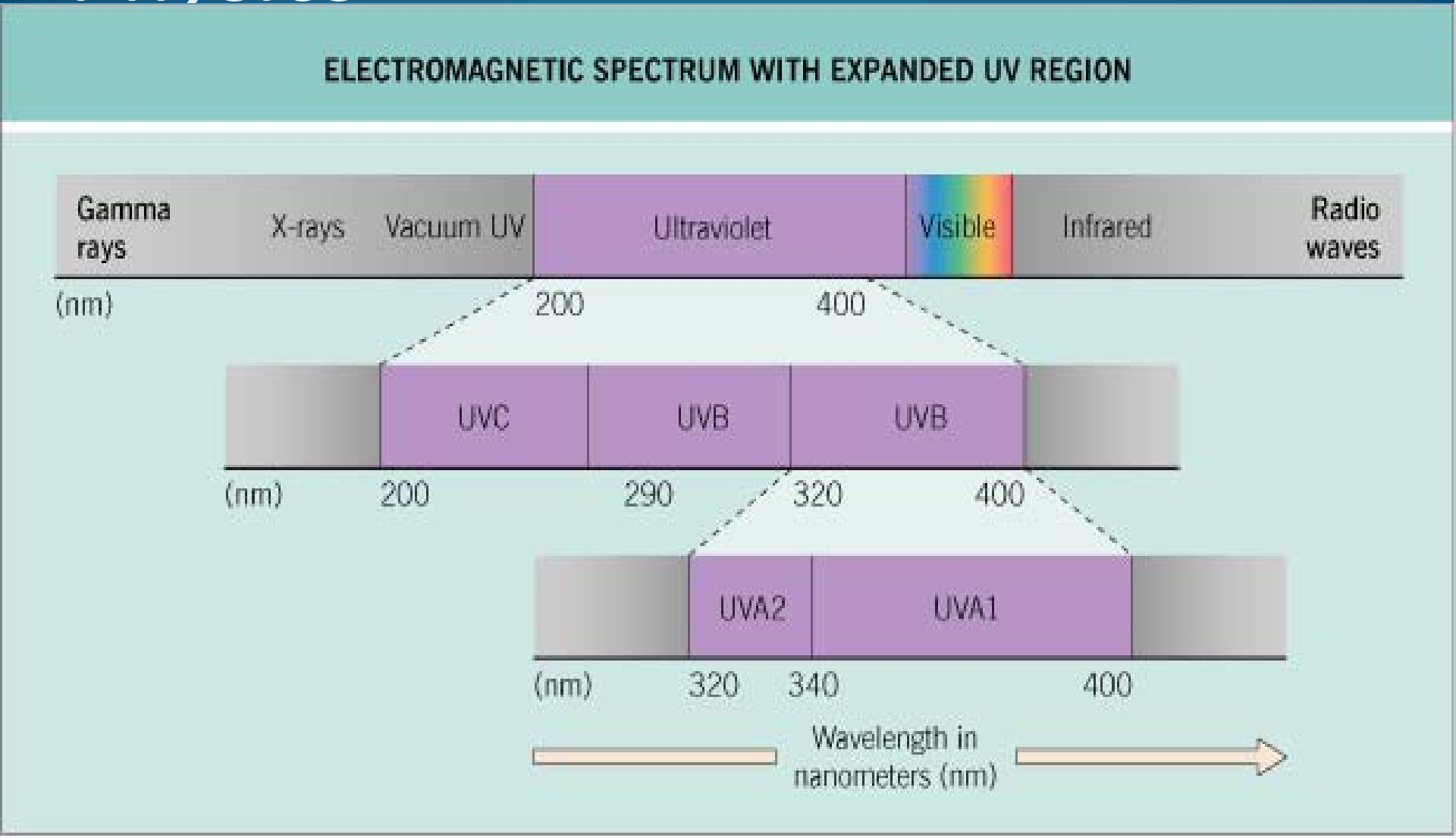
- **UVA (320-400 nm)**
  - **> 95% of sun's UV radiation reaching the earth's surface is UVA**
  - AKA ***Black Light*** because it is not visible to the human eye but causes certain substances to emit visible fluorescence
  - Woods lamp approx 365 nm (UVA1)
  - ***UVA2 (320-340)***
    - More erythemogenic wavelengths in UVA2
  - ***UVA1 (340-400)***

Physics

Electromagnetic Spectrum

- **VISIBLE LIGHT (400-760 nm)**
- **INFRARED & RADIO WAVES (>760 nm)**
- Remember that these are guidelines and that there is wide variation within the same spectrum
  - Example: UVB: 297nm is 100X more erythemogenic than 313nm
  - This is the principle used in Narrow-Band UVB therapy

Physics



Physics

SOURCES OF EM RADIATION

- UV Radiation comes from many sources
  - the sun is the most important
  - Incandescent and Fluorescent Lamps
  - Woods lamp (~320-420nm)
  - welder's arcs, etc.
- Luckily, the ozone filters out all EM energy <290nm since this is HIGHLY damaging to plants and animals
- Some scientists have calculated that a 1% decrease in the ozone level increases the risk of non-MM skin cancer by 2.7%

Physics

SOURCES OF EM RADIATION

- EM energy at the Earth's surface is also determined by the following:
  - Distance traveled through the atmosphere (Altitude and "Middle of Day")
  - *UVA actually changes little in intensity throughout the day*
  - Scattering by atmospheric molecules
  - Scattering by water droplets (clouds)
    - can decrease UV by 10-80%
  - Surface reflection (snow, water)

Physics

Cutaneous Optics

UV Radiation (Light)

1. Reflection
   - Due to different refractive index of air and skin
   - 5-10% of incident light is reflected by the outer surface of the Stratum Corneum.
2. Scattering
   - Dispersion of radiation
3. Transmission
4. Absorption- Energy is transferred to an atom or molecule (chromophore)
   - chromophore concentration
   - absorption coefficient (probability per unit path length that photon at given wavelength will be absorbed)

Physics
Cutaneous Optics

- When radiation strikes the skin the UVR is:
  - Remitted (reflected and scattered)
    - Very small fraction is re-emitted as fluorescence.
  - Absorbed
  - Transmitted inwards
- This is dependent on the angle of incidence.

Physics
Cutaneous Optics

- The real reason for our perception of skin color is actually the result of back-scattering from within the dermis
  - Caucasian skin remits 50% of visible light in this way
  - Melanin acts as a filter to *prevent dermal remittance*
  - Blood in the dermis absorbs blue and green wavelengths (but not red)

Physics
Cutaneous Optics

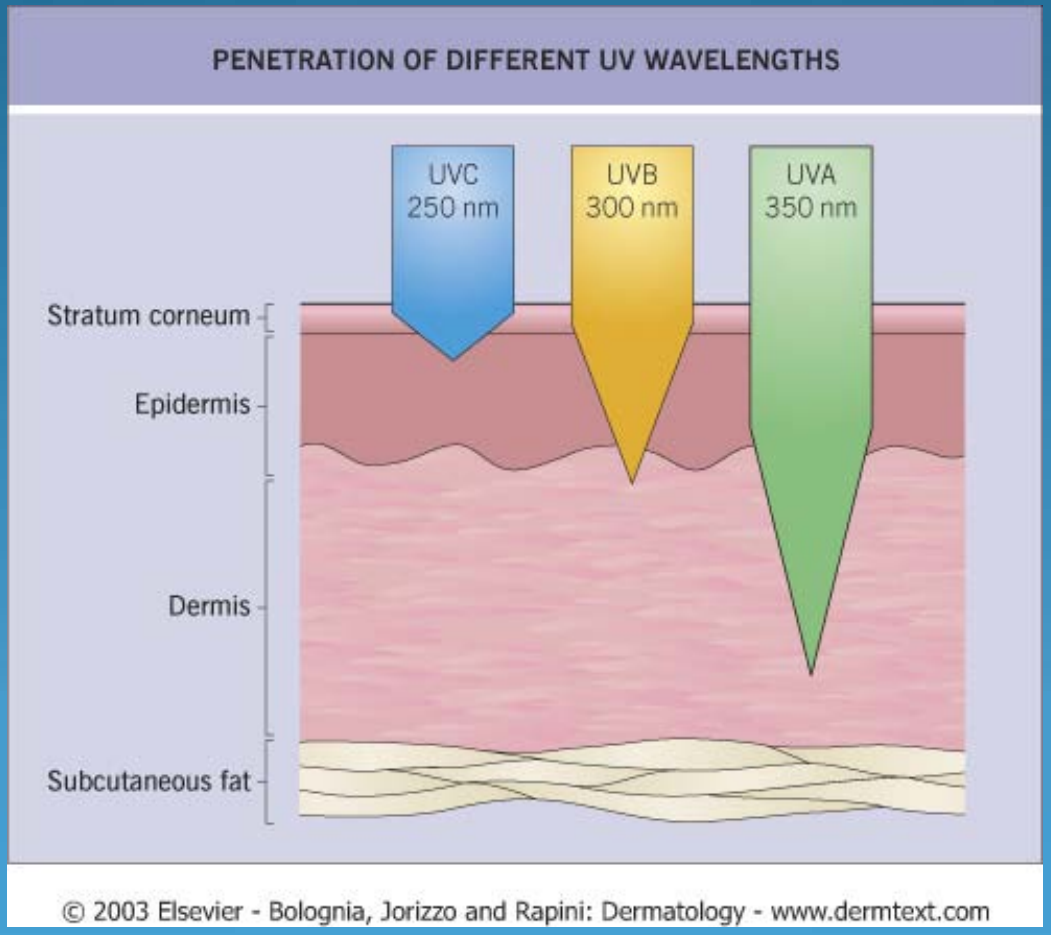
- White stratum corneum also transmits more radiance to the deeper layers.
- This increases the susceptibility to actinic damage.
- Things such as scale on the skin surface cause increased surface scattering of light.
  - Why patient's with psoriasis should apply a thin layer of Vaseline before PUVA treatments

Physics

Cutaneous Optics

- Depth of penetration of UV light is wavelength dependent.
  - Longer the wavelength = deeper penetration.
- **UVA** reaches the dermis (UVA goes all the way)
- **UVB** absorbed in epidermis and small part in upper dermis.
- **UVC** absorbed or reflected predominantly in the stratum corneum.
- Different wavelengths may have biological effects even in a layer that it does not reach secondary to secretion of an inflammatory mediator.

Physics
Cutaneous Optics



UV Radiation and Skin Biology
UVR Effects on Skin

- Molecular and Genetic
- Pigmentation
- Vascular alterations
- Immunosuppression
- Effects on Extracellular Matrix
- Effect on Retinoic Acids

UV Radiation and Skin Biology
UVR Effects on Skin

- UVR effects on Extracellular Matrix
  - Increased epidermal growth factor, IL-1, TNF-a receptors
    - ROS inhibit protein-tyrosine phosphatases which function to inhibit receptors therefore results in -increased receptors lead to signaling kinases
  - AP-1 is activated and results in increased metalloproteinase 1, MMP-3, MMP-9

UV Radiation and Skin Biology
UVR Effects on Skin

- UVR effects on Extracellular Matrix (cont)
  - MMP upregulation is dose dependent and occurs at suberythemogenic doses. = maintained at minimal exposures (5-15 minutes midday QOD)
  - Collagen production decreased
    - AP-1: **c-fos** (constitutive) and **c-jun** (UV inducible) decrease expression of collagen 1 in cultured fibroblasts.
    - Transforming Growth Factor -B (TGF-B) is a promoter of collagen that is decreased.
    - Damaged collagen may down-regulate new collagen synthesis
    - Similar to wound healing leading to solar scar- not a perfect process

UV Radiation and Skin Biology
UVR Effects on Skin

- Effects on Retinoic Acids
  - Retinoic Acid compounds negatively regulate AP-1
  - UVR decreases expression of RAR-y and RXR-a
  - Decreased expression may increase AP-1 to upregulate MMPs
  - UVR results in functional decrease in Vitamin A in the skin

UV Radiation and Skin Biology

- Phenotypes from UV Radiation Effects on Skin
  - Acute
    - Sunburn
    - Tanning
  - Chronic
    - Photoaging
    - Photocarcinogenesis

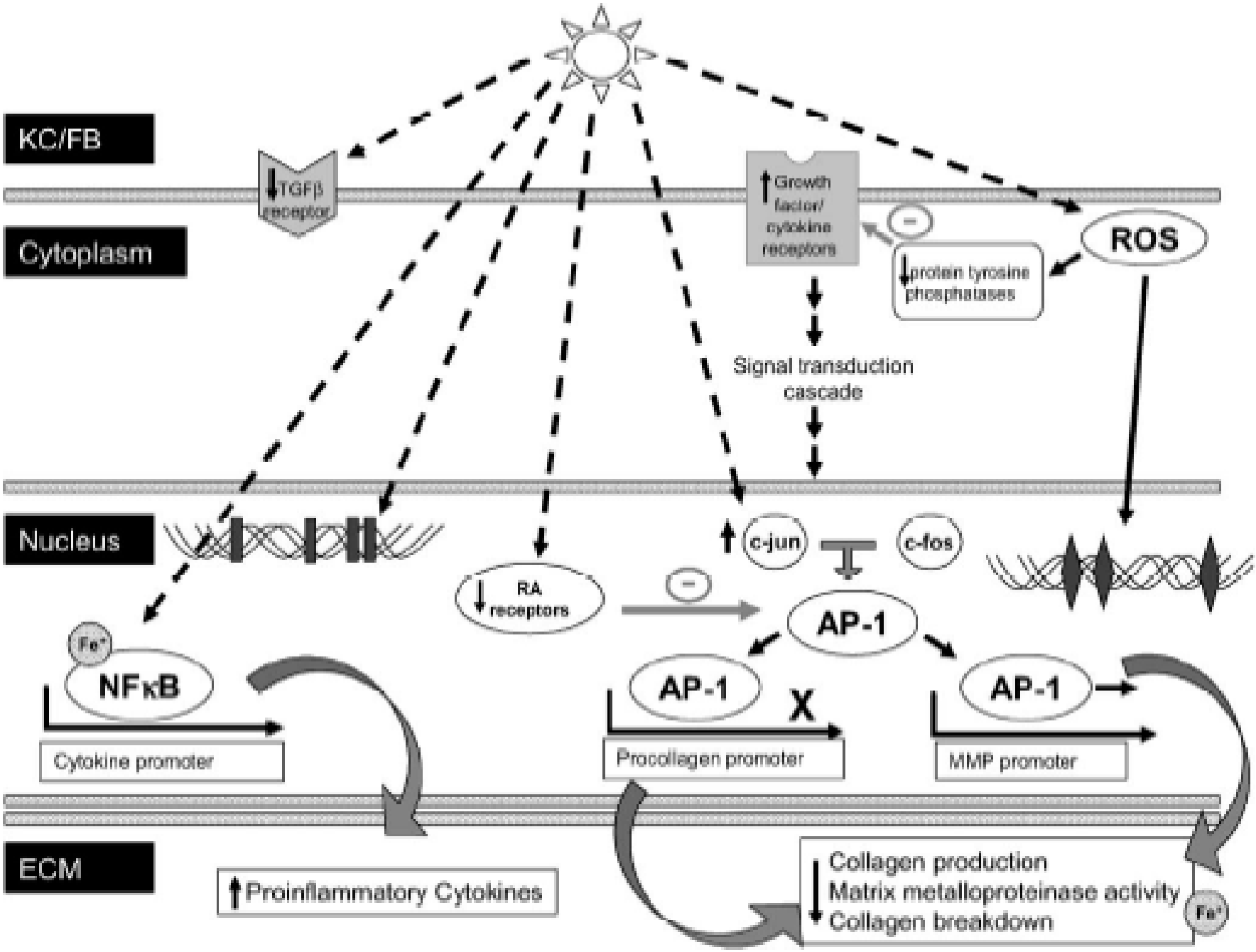
UV Radiation and Skin Biology

Acute - Sunburn

- The ability to induce sunburn rapidly declines with increasing wavelength.
- 360 nm is approximately 1000 fold less erythemogenic than light with a wavelength of 300 nm.
- UVB induced sunburn reaches its peak between 6 and 24 hours after exposure
- UVA an immediate erythema is observed followed by a distinct delayed erythema after 6 to 24 hours.
- SUNBURN CELLS = apoptotic keratinocytes

UV Radiation and Skin Biology
Acute - Sunburn

- Sunburn secondary to:
- Inflammation
  - UVR activates NF-kB which leads to increase in IL-1, IL-6, and TNF-a
- Vasodilation
  - Angiogenesis promoted:
    - Increased Vascular Endothelial Growth Factor
    - Decreased thrombospondin (angiogenesis inhibitor)


KC/FB
Cytoplasm
Nucleus
ECM
TGFβ receptor
Growth factor/ cytokine receptors
ROS
protein tyrosine phosphatases
Signal transduction cascade
c-jun
c-fos
RA receptors
AP-1
AP-1
AP-1
X
NFκB
Fe
Cytokine promoter
Procollagen promoter
MMP promoter
Proinflammatory Cytokines
Collagen production
Matrix metalloproteinase activity
Collagen breakdown
Fe

UV Radiation and Skin Biology
Acute - Tanning

- Dependent on:
  - 1. Biphasic 2. Wavelength 3. Phototype
- **Biphasic: *Immediate* and *Delayed***
- ***Immediate* pigment darkening**
  - During and immediately after exposure due to alteration and redistribution of existing melanin.
  - Most prominent with UVA.

UV Radiation and Skin Biology
Acute - Tanning

- ***Delayed* Tanning** is result of UVB.
  - Peaks about 3 days after sun exposure.
    - ↑ number of melanocytes
    - ↑ melanin synthesis
    - ↑ transfer of melanosomes to keratinocytes.
- UVA induced tan provides 5-10 times less protection against sunburn secondary to less pronounced epidermal thickening and hyperkeratosis.

UV Radiation and Skin Biology

Acute - Tanning

Skin Phototypes

- An individual's tendency to develop sunburn and tanning after sun exposure has been used to categorize skin phototypes.
- These correlate well with susceptibility to long term effects of exposure.

Table 134.3 Skin phototypes. [a]Types I–IV are determined by history; types V and VI by physical examination (racial descent). [b]Patients with erythrodermic psoriasis are to be classified as skin phototype I for determination of UVA dosage. [c]Patients with this phototypes should be classified into a lower skin phototype category if the sunburning history so indicates.

SKIN PHOTOTYPES		
Skin phototype[a]	**Skin reaction**	**Recommended dose (J/cm^2)**
I[b]	Always burn, never tan	0.5
II	Always burn, but sometimes tan	1.0
III	Sometimes burn, but always tan	1.5
IV	Never burn, always tan	2.0
V[c]	Moderately pigmented skin	2.5
VI	Darkly pigmented skin	3.0

UV Radiation and Skin Biology Acute - Immunology

- UV Radiation has long been known to effect the immune system
- The effects are extremely complicated and highlight the complexity involved in mounting an immune response.

UV Radiation and Skin Biology Acute - Immunology

- There seems to be no single definitive primary action.
- Inhibition of immunosurveillance in carcinogenesis
- The effects of UV Radiation can be divided into
  - *Cellular Effects*
  - *Molecular Effects*

UV Radiation and Skin Biology
Acute - Immunology

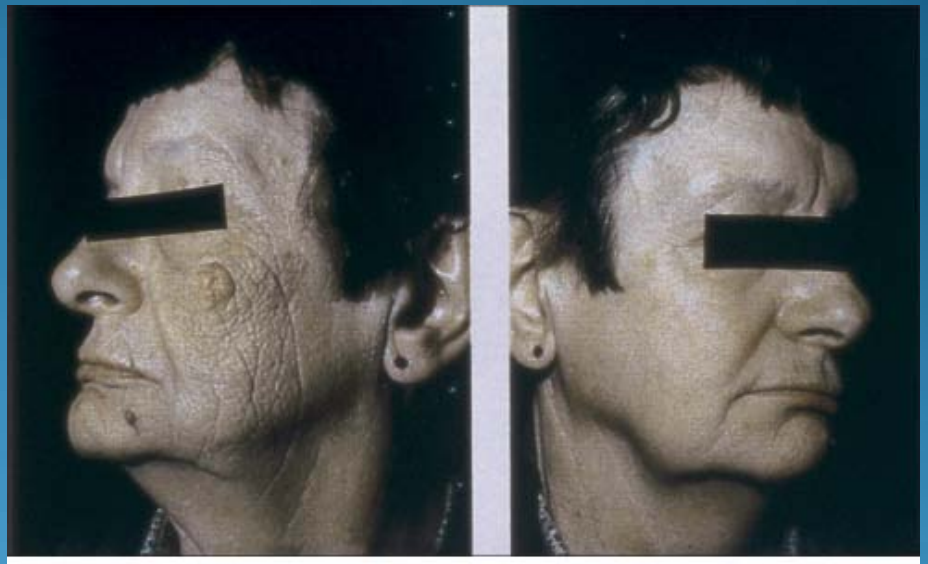
- ***Cellular Effects***:
  - UVR = Decrease in Langerhan's cell appearance, function, and absolute numbers.
  - UVR changes primary APC type to macrophages which are less efficient.
  - Darker skin suffers less Langerhan's cell depletion and returns to baseline more quickly than Caucasian skin.
  - All of the above lead to diminished delayed-type hypersensitivity reactions in UV exposed skin.

UV Radiation and Skin Biology
Acute - Immunology

- ***Cellular Effects***
  - UVR causes a *decrease* in *CD4 cells* and a slight i*ncrease* in *CD8 cells*.
    - This has not been absolutely proven and the significance is unknown
  - IL-10 production by melanocytes and activated macrophages on exposure to UVL may bias towards a Th2 type of local immune response.
- ***Molecular Effects***
  - Isomerization of ***trans*** to ***cis-Urocanic acid*** can suppress NK-cell activity in a dose-dependent manner.
  - DNA damage also plays a role in immunosuppression

UV Radiation and Skin Biology Chronic

- Photoaging
- Photocarcinogenesis
- UVA penetrates deeper in dermis thus probably more important role in photoaging.
- Only UVA penetrates glass not UVB.



UV Radiation and Skin Biology
Chronic - Photocarcinogenesis

- DNA Damage
- Mutation after DNA damage
- Malignant / monoclonal formation

UV Radiation and Skin Biology
DNA Damage

- For radiation to produce an effect it must first be absorbed by a *chromophore*.
- This absorption elicits *photochemical* and *photobiological* responses.
- Chromophores exist in their lowest energy state (Ground State).

UV Radiation and Skin Biology
DNA Damage

- The energy necessary to raise a certain molecule from its ground state to its excited state is precisely determined by its structure.
- There is a set energy (or range of energies in more complex systems) that a molecule will absorb.
- The wavelength of the photon corresponding to that energy determines the molecule's *absorption spectrum*.

UV Radiation and Skin Biology

- *Absorption Maxima*: Wavelengths that have the highest probability of absorption for a specific chromophore.
  - Examples:
    - DNA 260nm (thus UVC most effective)
    - DNA in basal layer 300 nm
    - Urocanic acid 280nm
    - Aromatic amino acids 280-290nm
    - Hemoglobin 410nm
    - Porphyrins 400-420nm
    - Beta-Carotene 460nm
    - ***Melanin absorbs throughout the UV and visible spectrum and does NOT have a distinct Absorption maxima*

UV Radiation and Skin Biology
DNA Damage

- DNA is a Chromophore
  - upon absorption of the radiation's energy, the chromophore is elevated to an unstable excited state.
- The molecule must return to its ground state by releasing absorbed energy. This can be accomplished by:
  - FLUORESCENCE (Emission of light)
  - GENERATION OF HEAT
  - CONVERSION TO CHEMICAL ENERGY (***PHOTOCHEMICAL REACTION***)

UV Radiation and Skin Biology

- These reactions require energies found only at <750nm.
- Ensuing ***photochemical reactions*** may either lead to *photoproducts* via
  1. Changing the chromophore directly *or*
  2. Energy transfer indirectly change a molecule other than the chromophore.

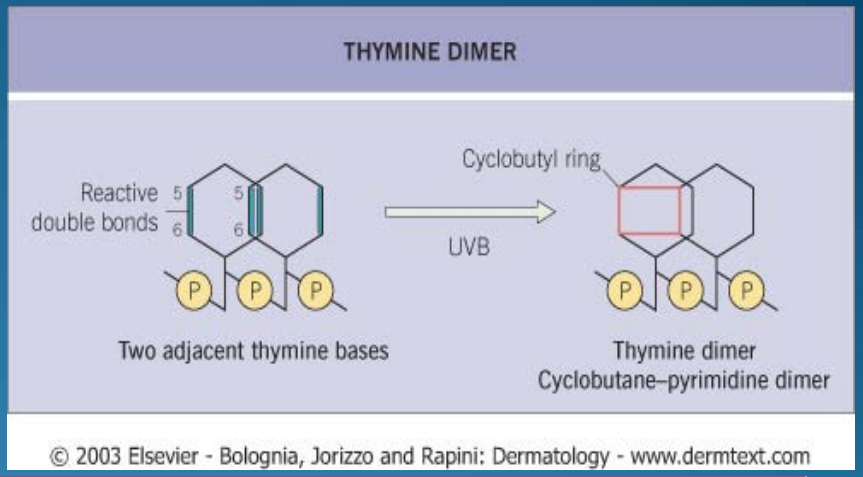
UV Radiation and Skin Biology
DNA Damage

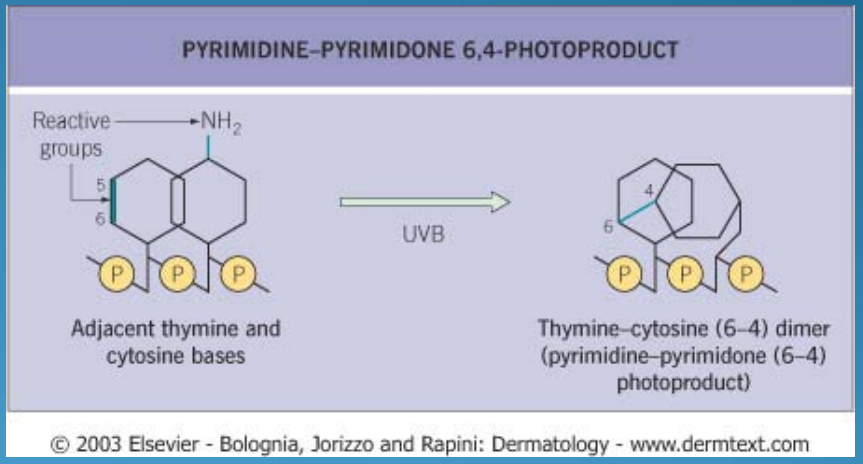
- Direct DNA Damage results in Photoproducts.
- Photoproducts lead in a stepwise fashion to
  - Biochemical reactions
  - Cellular changes
  - Observable organ (skin) responses

DNA Damage Photoproducts

Photoproducts:

1. Pyrimidine dimers (T-C, T-T, C-C)
    1. ***Cyclobutane Dimer is most common***
        1. T-T is the most common
        2. Followed by C-T and T-C
        3. Then C-C
    2. ***6-4 Pyrimidine-Pyrimidone* 2nd most common**
        1. T-C is the most common
        2. C-C and T-T are also observed
2. Free radicals
3. Oxidized lipids
4. Pre-Vitamin D3





What is the Soret band?

SORET Band

Peak absorption of porphyrins at 400-410 nm region

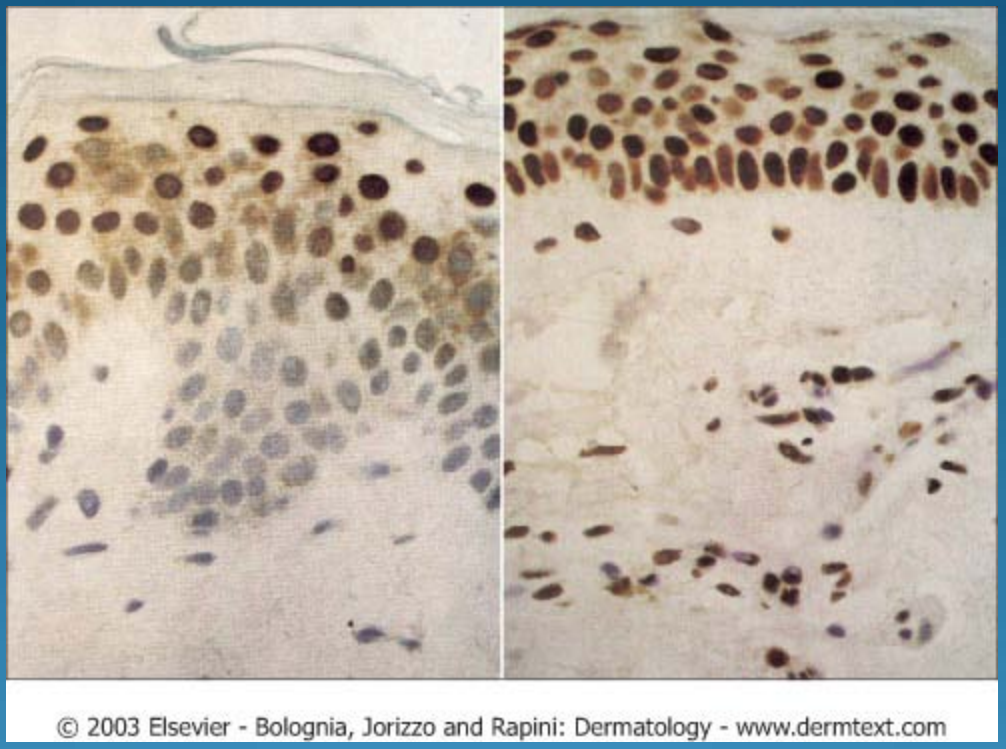


Fig. 86.8 A wavelength of 300 nm is more effective than one of 290 nm in inducing thymine dimers in the basal layer of the human epidermis. After irradiation of human skin with monochromatic 290 nm UVB (2 MED) and staining with anti-thymine dimer antibodies, most cells in the basal layer show only blue counterstaining, while suprabasal layers demonstrate pronounced reactivity. In contrast, with 2 MED of monochromatic 300 nm UVB, a pronounced immunostaining is also evident in the basal layer of the epidermis. (Reproduced with permission from Young AR, Chadwick CA, Harrison GI, et al. The similarity of action spectra for thymine dimers in human epidermis and erythema suggests that DNA is the chromophore for erythema. J Invest Dermatol. 1998;111:982–8.)

UV Radiation and Skin Biology
Molecular & Genetic Effects

- Different wavelengths of UV light induce different types of DNA damage.
- UVC and UVB are capable of exciting the DNA molecule *directly*.
  - DNA is regarded as the chromophore for most of the biological effects of UVB and UVC
    - These include erythema, tanning, immunosuppression, mutagenesis, and carcinogenesis.

UV Radiation and Skin Biology
Photosensitivity

- Photoproducts can also be from ***exogenous*** chromophores that can lead to photosensitizing reactions (T**oxic** and A**llergic**)
  - This is done indirectly by transfer of energy to
    - DNA (Type I photosensitized reaction) or
    - To molecular oxygen, with reactive oxygen species in turn being able to damage DNA (Type II photosensitized reaction).
  - This indirect generation of DNA damage is relevant to UVA.
  - UVA is barely able to excite the DNA molecule directly thus rarely produces pyrimidine dimers.
  - Many of the biological properties of UVA is strictly dependent upon oxygen.
  - UVA has been shown to be responsible for almost all guanine oxidation products in DNA.
    - We take advantage of this every day with PUVA treatments.

UV Radiation and Skin Biology
Indirect Damage

- UV induced reactive oxygen species (ROS)
  - 1. singlet oxygen
  - 2. hydrogen peroxide
  - 3. superoxide radical.
- UVA still produces few pyrimidine dimers.
- Raises a question of debate—are the mutagenic properties of UVA (particularly UVA1) really mediated by oxidative DNA damage or by the weak ability to form a few pyrimidine dimers?

UV Radiation and Skin Biology
Indirect Damage

- Recently, researchers exposed samples of whole skin to either UVB or UVA radiation and examined the samples by a new, sensitive technique.
- Predominant DNA damage in the UVB-irradiated skin was the Cyclubutane Pyrimidine Dimer (CPD).
- UVA-radiated skin showed DNA damage induced by reactive oxygen intermediates.

UV Radiation and Skin Biology

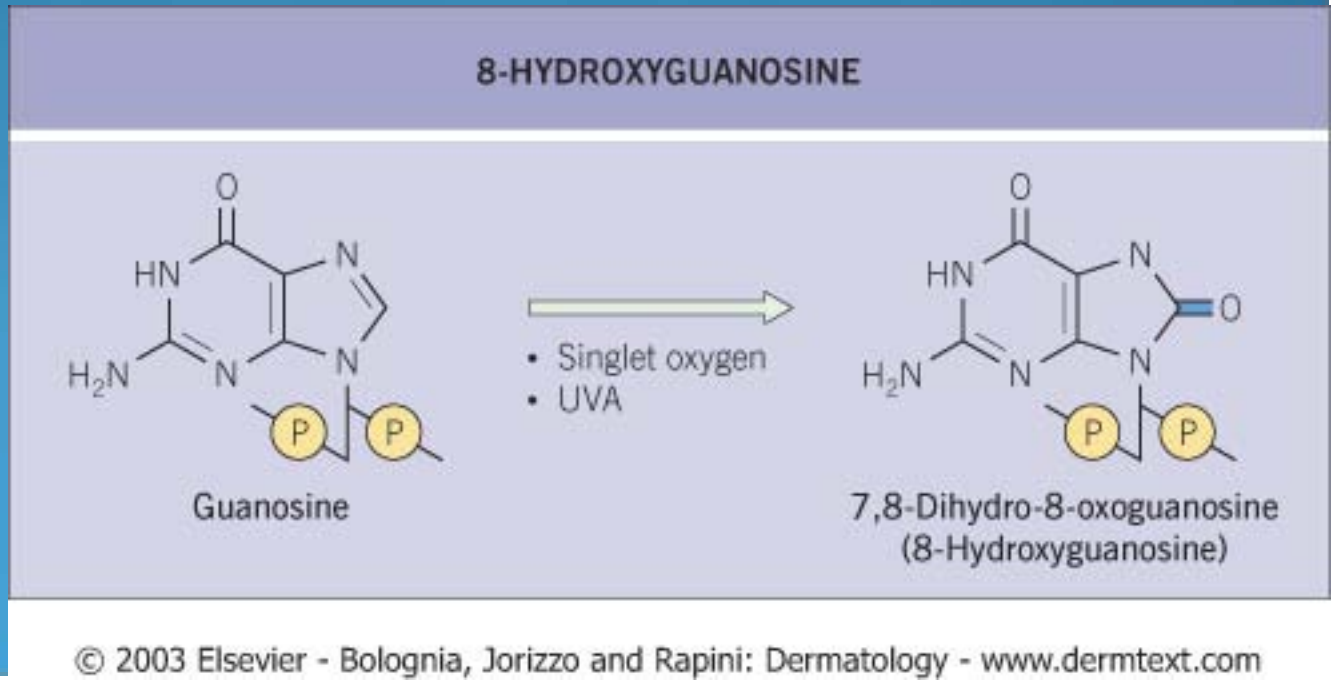
Indirect Damage

- BUT, numerous CPDs were found in the UVA samples as well.
- There were more CPDs than reactive-oxygen-intermediate–induced DNA lesions in the UVA-exposed skin.
- UVA-induced CPDs persisted longer in the skin, suggesting that the DNA-repair processes were less effective in removing UVA-induced CPDs than UVB-induced lesions.

- Mouret S et al. Cyclobutane pyrimidine dimers are predominant DNA lesions in whole human skin exposed to UVA radiation. *Proc Natl Acad Sci U S A* 2006 Sep 12; 103:13765-70.

UV Radiation and Skin Biology
Indirect Damage

- *Singlet oxygen* reacts predominantly with *guanine* and *generates 8-Hydroxyguanosine*.



Defenses against UV Radiation

- ***Endogenous***
  - *UV radiation protection*
    1. Epidermal Thickness
    2. Pigment
    3. Repair Mechanisms – NER and BER
    4. Tissue inhibitors of MMPs
       1. Decreased TIMP-1 and TIMP-2 in fibroblast culture exposed to UVR
    5. Antioxidants
       1. Endogenous: Vitamin E, Coenzyme-Q10, ascorbate, carotenoids
       2. Enzymatic: superoxide dismutase, catalase, glutathione peroxidase

Defenses against UV Radiation

- Exogenous
  - Avoidance
  - Sunscreens

Defenses against UV Radiation
Endogenous –UV Protection

- Epidermis
  1. Stratum corneum with its melanin content plays a major factor in skin protection.
  2. Thicker areas (palms/soles) rarely burn
     - also difficult areas to treat with light therapy.
  3. Amelanotic skin thickens in response to UVB radiation.

Defenses against UV Radiation Endogenous –UV Protection

- Melanin
  - Protects by absorbing energy (chromophore) and by acting as a free radical scavenger
    - Eumelanin (brown/black) more effective scavenger than Pheomelanin (red/yellow)
  - *Melanin actually exists in human skin as a stable free radical*
- Constitutive
  - Baseline color
  - More protective than Facultative

Defenses against UV Radiation Endogenous – UV Protection

- Facultative
  - Ability to tan in response to UV exposure (adaptive)
- Beta-Carotene
  - Believed to work as free-radical scavenger
  - NO photoprotective role in UVB spectrum (doesn't work as sunscreen)
  - Used in treatment of EPP

Defenses against UV Radiation
Endogenous – Repair Mechanisms

- UV induced DNA damage requires excision and replacement of damaged nucleotides by DNA repair pathways.
- DNA photoproducts are *mutagenic*.
- They can be repaired by nucleotide excision repair (NER) pathway.

Defenses against UV Radiation
Endogenous – Repair Mechanisms

- A defect in this pathway (XP) increases UV sensitivity and cancers.
- XP includes seven genetic complementation groups (XPA-XPG).
- These represent different proteins in the NER pathway.
- There is no backup pathway for NER.

Table 86.1 Deficient DNA repair genes. Deficient DNA repair genes in xeroderma pigmentosum (XP) complementation groups XPA to XPG, trichothiodystrophy (TDD), Cockayne syndrome (CS), and xeroderma pigmentosum variant (ERCC1, excision repair cross complementing gene 1; NER, nucleotide excision repair; TFIIH, transcription factor IIH).

DEFICIENT DNA REPAIR GENES		
Complementation group or inherited disorder	**Function of affected gene product in DNA repair**	**Also associated with**
Nucleotide excision repair		
XPA	High affinity for injured DNA (single strands) Has many interactions with other NER proteins Might have a role in assembling the DNA repair machinery around the DNA lesion	–
XPB	Subunit of the transcription factor TFIIH Unwinds the DNA helix around the DNA lesion with its 3′→5′ helicase function	XP/CS[a], TTD
XPC	DNA damage recognition Only required for global genome repair, not for transcription-coupled repair	–
XPD	Subunit of the transcription factor TFIIH like XPB Unwinds the DNA helix around the DNA lesion with its 5′→3′ helicase function	XP/CS[a], TTD
XPE	Affinity for UV-damaged DNA Might have an auxiliary role in DNA damage recognition	–
XPF	5′-repair endonuclease The ERCC1/XPF complex cuts at the single-strand to double-strand transition 5′ of the DNA lesion	–
XPG	3′-repair endonuclease Cuts at the single-strand to double-strand transition 3′ of the DNA lesion	XP/CS[a]
TTD	Possibly another subunit of TFIIH See XPB and XPD	–
CSA	Only required for transcription-coupled repair Might be necessary for dissociation of RNA polymerase upon stalling at DNA lesion	–
CSB	Only required for transcription-coupled repair Might be necessary for dissociation of RNA polymerase upon stalling at DNA lesion	–
Translesional DNA synthesis		
XP variant	DNA polymerase-η Bypasses T–T dimers with correct insertion of two A residues	–

[a] *Xeroderma pigmentosum/Cockayne syndrome overlap syndrome.*

Defenses against UV Radiation Endogenous – Repair Mechanisms

Nucleotide Excision Repair (NER) involves

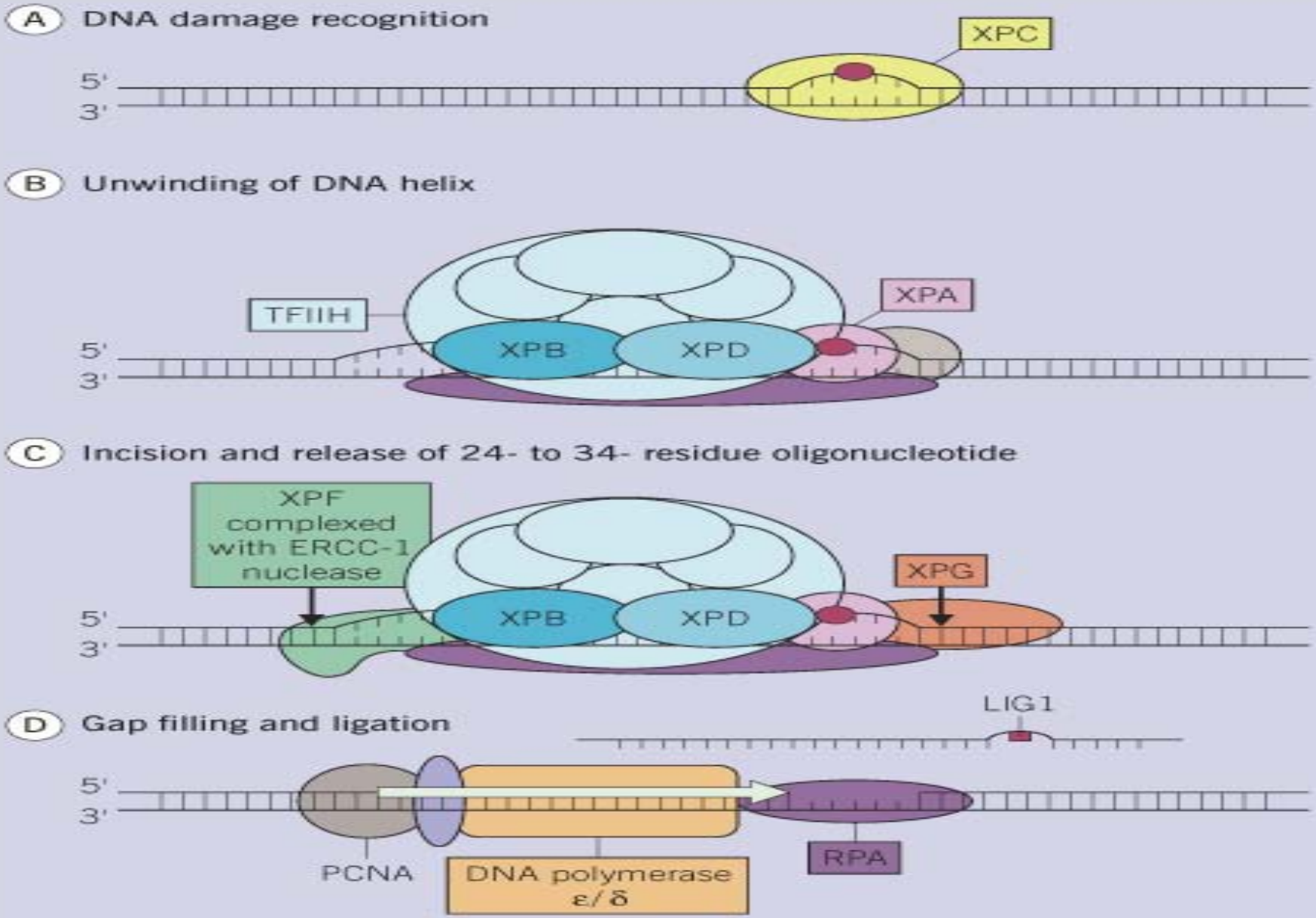
1. Recognition of DNA damage
2. Unwinding of DNA helix
3. Incision of the DNA strand containing a lesion
4. DNA synthesis and ligation to replace an excised oligonucleotide

Defenses against UV Radiation Endogenous – Repair Mechanisms

NER Process

1. DNA damage recognition requires that the DNA photoproduct **distort the DNA helix**.
2. A key intermediate is an **open, unwound structure** formed around a DNA lesion in a reaction that uses the helicase activities of XPB and XPD
3. This creates sites for cutting by the endonucleases XPG on the 3' side and the XPF-ERCC1 complex on the 5' side
4. The **oligonucleotide** is released.
5. The gap is filled by **DNA polymerase** delta or sigma.
6. It is sealed by **DNA ligase 1**.

NUCLEOTIDE EXCISION REPAIR IN NON-TRANSCRIBED REGIONS



What other 2 diseases are defects in NER found?

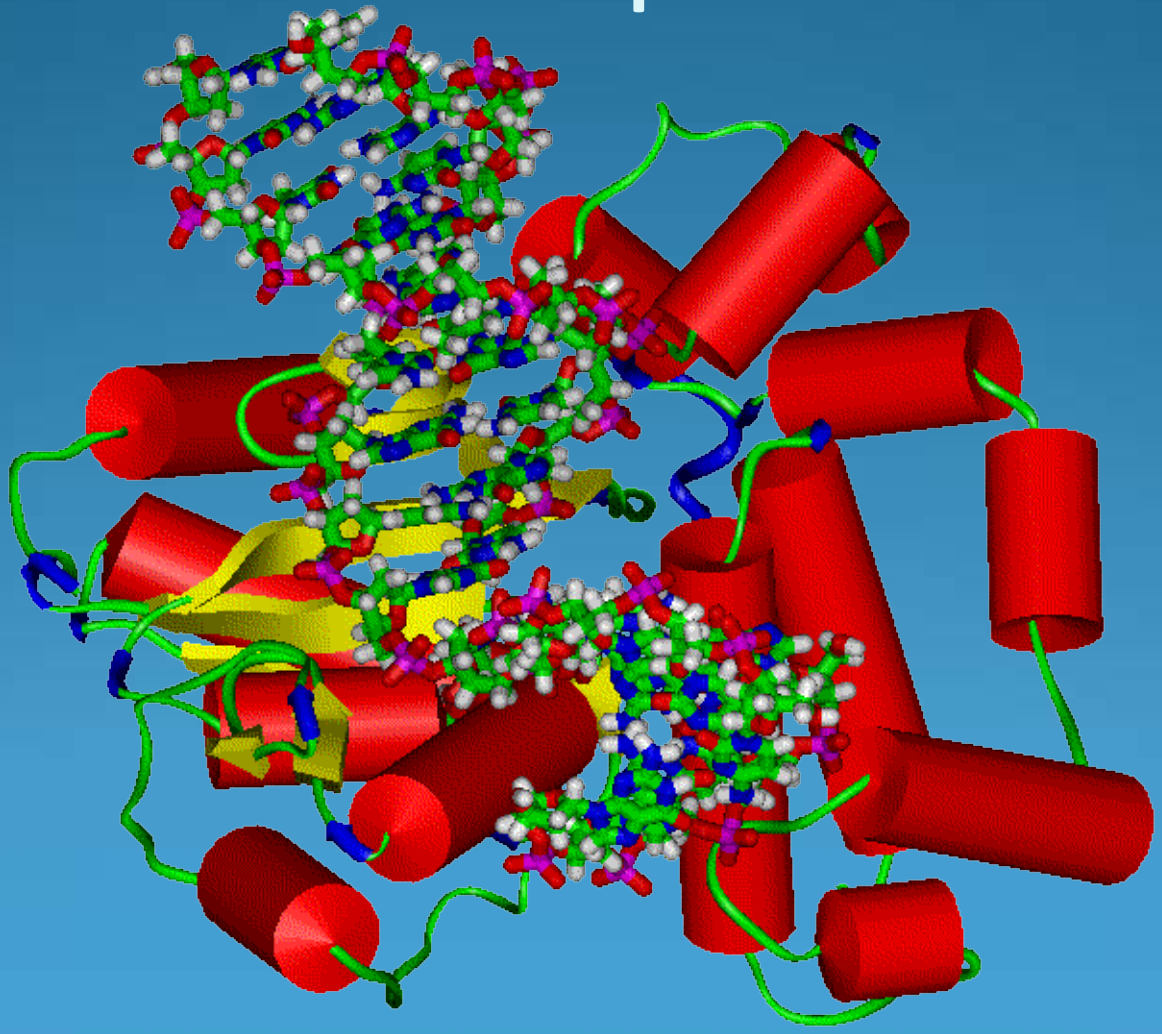
1. Cockayne Syndrome
2. Photosensitive form of brittle hair syndrome trichothiodystrophy

Defenses against UV Radiation Endogenous – Repair Mechanisms

Base Excision Repair (BER) (Think UVA)

1. Repairs O***xidative DNA base*** modifications.
2. Initial step is removal of a base rather than a nucleotide.
3. This step is carried out by a ***DNA glycosylase***.
4. ***Human DNA glycosylase 8-oxoG DNA glycosylase 1 (hOGG-1)*** repairs 8-Hydroxyguanosine.
5. Loss of this enzyme leads to cellular hypersensitivity to UVA, not UVB.
6. The backup for BER is *DNA Glycosylase MYH*.
7. This enzyme removes misincorporated A residues opposite 8-hydroxyguanosine.

Base Excision Repair



Defenses against UV Radiation
Exogenous - Sunscreens

- Sunscreens are especially important for Fitzpatrick Skin Types I, II, and III
- Two Types are available
  - *Chemical or Organic*
    - Absorb UV Radiation
  - *Physical or Inorganic*
    - Reflect & Scatter UV Radiation
- *Products may also have mixtures of these two types*

Defenses against UV Radiation
Exogenous - Sunscreens

- SPF
  - SPF = MED Sunscreen Protected / MED Unprotected
  - *UVB protection ONLY*

- Many recommend using SPF 30 since almost no one applies the correct amount of sunscreen.

- SPF determined using 2 mg/cm^2.

- Most apply less than ½ this amount.

Defenses against UV Radiation Exogenous - Sunscreens

- NO standard or agreement on UVA protection measure – *Mexoryl SX and XL*
- Suggested UVA Protection Factor include
  - measuring IPD (Immediate pigment darkening)
  - PPD (Persistent pigment darkening)
  - PFA (Protection Factor A which measures MED much like SPF)

Defenses against UV Radiation
Exogenous - Sunscreens

- **Ecamsule** (**Mexoryl® SX**, Terephthalylidene Dicamphor Sulfonic Acid) is a chemical which is added to many sunscreens to filter out UVA rays.
  - benzylidene camphor derivative = excellent photostability.
- ***Mexoryl SX*** (water soluble) and ***Mexoryl XL*** (INCI Drometrizole Trisiloxane, oil soluble).
  - Together they show a synergistic effect in protection.
- Exclusive to L'Oréal and its brands.

Defenses against UV Radiation
Exogenous - Sunscreens

Mexoryl

- **Mode of action**
- Exposed to UV, ecamsule undergoes reversible photoisomerization and then photoexcitation. The absorbed UV is released as thermal energy, without penetrating the skin.
- Ecamsule protects against 290–400 nm range, peak protection at 345 nm.
- In contrast to the widely used UVA absorber avobenzone that is not intrinsically photostable and requires photostabilizers to prevent significant degradation in light.
- **Efficacy**
- A 5% ecamsule containing sunscreen can prevent early changes leading to photoaging in humans. A broad spectrum sunscreen with ecamsule, avobenzone and octocrylene significantly reduces the skin damage associated with UV exposure in human subjects.[8]

Defenses against UV Radiation
Exogenous - Sunscreens

Mexoryl

- **Safety**
- Ecamsule has little percutaneous absorption and little systemic effects, therefore it is considered relatively safe. A mouse study shows that it does not increase the probability of promoting skin cancer. Studies done in vitro show that it is not photomutagenic.
- Ecamsule is an acid so needs to be neutralized in order to be used without offsetting the final pH of the sunscreen too much.
  - triethanolamine.

Defenses against UV Radiation Exogenous - Sunscreens

- New AAD Labeling:
  - **SPF 30**
  - May use 30+ if over 30
  - Extended wear claims or use of terms such as “All Day Protection” not permitted
  - AAD “Seal of Approval”

Defenses against UV Radiation
Exogenous - Sunscreens

- **Water Resistant**
  - Maintains SPF after **40** minutes in water immersion
- **Very Water Resistant**
  - Maintains SPF after **80** minutes in water immersion
- These new regulations also include very specific standards for SPF determination.
- Sunscreen in Children <6 months old
  - Current recommendations discourage use in this age group but there is no evidence supporting this.
  - Common sense argues that children should be protected with clothing and sun avoidance.

SUNSCREEN	SPECTRAL RANGE
PABA	UVB
Octyl dimethyl PABA	UVB
Octyl salicylate/ salicylates	UVB
Homomenthyl salicylate	UVB
Ethyl hexyl p-methoxyl cinnamate/cinnamates	UVB
Methyl anthranilate	UVA
Dioxybenzone	UVA
Sulisobenzone	UVA
Oxybenzone	UVA
Butylmethoxydibenzoyl methane (avobenzone or Parsol 1789)	UVA
ZnO, TiO_2 (absorption, reflection, and scatter of UVA and UVB)	UVA, UVB
Camphor derivatives	UVB
Red veterinary petrolatum	UVA

Defenses against UV Radiation Exogenous – Quick Tanners

- Quick Tanners:
  - *Dihydroxyacetone and Lawsone*
    - Auto-oxidizers that bind the Stratum corneum
  - *Tyrosine rich compounds*:
    - Diffuse into the skin and increase the *in vivo* rate of melanization via tyrosinase.
  - These have little photoprotective value.

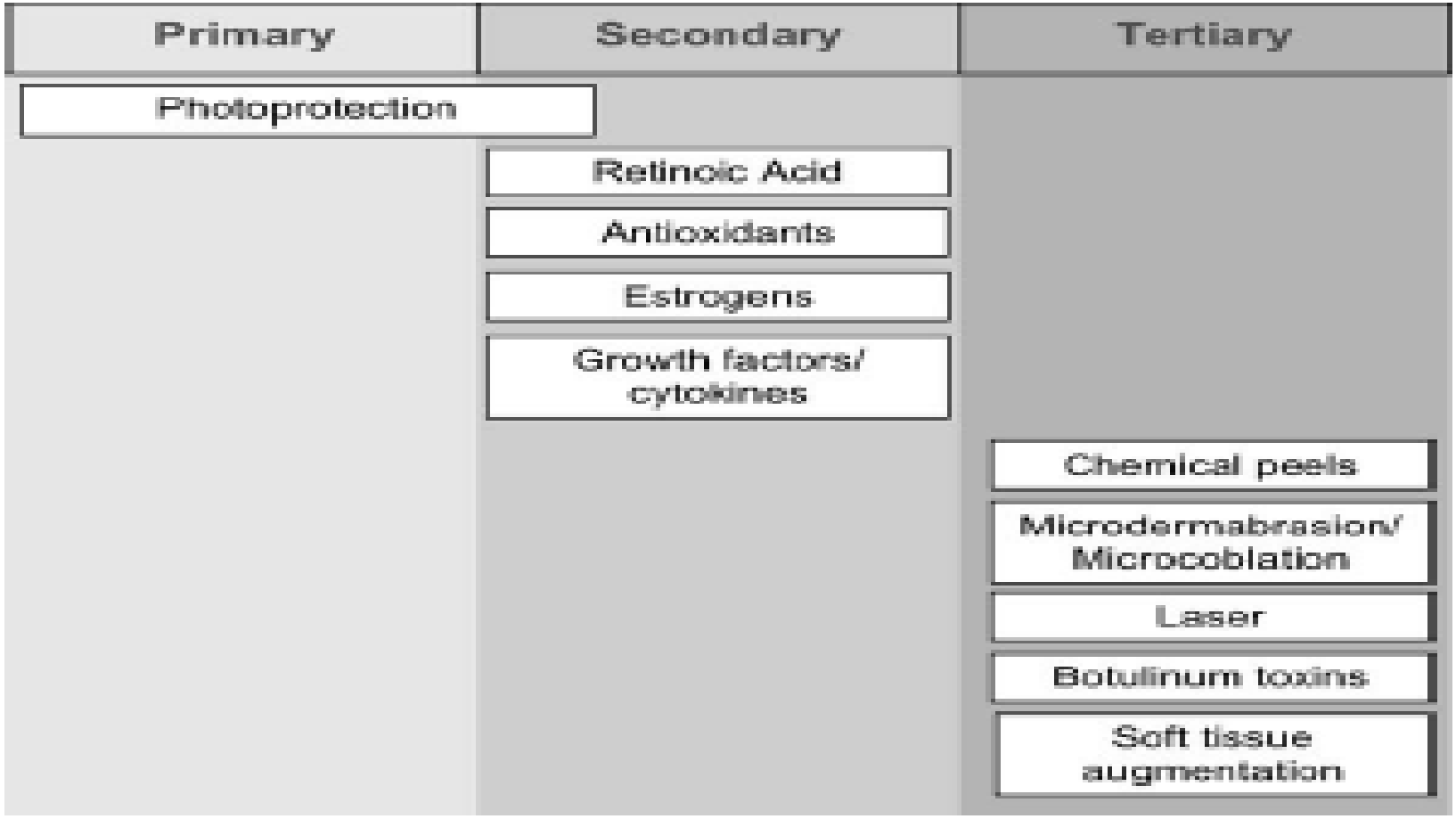


Fig 3. Photoaging treatments categorized by prevention strategy. Primary prevention reduces risk factors before disease occurs. Secondary prevention postpones or attenuates the condition. Tertiary prevention treats an existing symptomatic disease process to ameliorate its affects or delay its progress.[128]

PHOTOMEDICINE

- Until the 1970's UV treatment (only broadband UVB) was mainly confined to the management of psoriasis and acne
- Now many treatment modalities are available for the treatment of over 40 skin diseases
- *Broadband UVB Therapy*:
  - Energy usually from "sunlamp" fluorescent bulbs that emit a significant amount of
    - UVC
    - all wavelengths of UVB
    - large amount of UVA
    - visible light

UVB

- Broadband UVB Therapy
  - Fairly safe and simple if used properly.
  - Psoriasis is main indication with ~70% of patients cleared within 30 treatments.
  - Particularly good for guttate type.
  - Also used for mild-moderate atopic eczema (works poorly in severe disease).
  - The only quantitative study in acne actually showed no benefit!
  - Limited by poor penetration; therefore ineffective for thick plaques or palms/soles.
  - Frequently used in combination with tar (Goeckerman Method).
  - Dose calculated by determining MED (Europe).
  - Skin type (American) and then increasing in conservative increments.

UVB

- Broad Band UVB
  - Usually 3-5 treatments per week to equal 25-30 total.
  - Always apply emollient for optical effects.
  - Most patients need at least weekly maintenance treatments.
  - Avoid topical steroids
    - these actually reduce the duration of remission
  - Review
  - UVB is absorbed by endogenous chromophores.
  - Photochemical reactions mediate a variety of biological effects.
  - This leads to therapeutic effects.

UVB

- The most important chromophore is DNA.
- This causes the formation of pyrimidine dimers.
- UVB exposure reduces DNA synthesis.
- This suppresses the accelerated DNA synthesis found in psoriatic epidermal cells.
- It also induces p53 leading to cell cycle arrest or apoptosis of keratinocytes (sunburn cells) if DNA damage is too severe.
- P53 thus prevents photocarcinogenesis by this mechanism.
- UVB induces the release of prostaglandins and cytokines.
- IL 10 is important in immune suppression.
- Langerhan's cells decreased.
- Adverse effects
  - Erythema
  - long-term photodamage

Table 134.4 Differences between the US and European protocols.

DIFFERENCES BETWEEN THE US AND EUROPEAN PROTOCOLS		
	US	Europe
UVA dosimetry	Predetermined dose according to skin phototype	Individualized dose according to MPD determination
Frequency of treatment	Two to three times/week	Four times/week
Dose increments	Predetermined	Individualized
Principle of approach	Regimented, cautious	Flexible, aggressive
Goal	To clear without ponderous testing and acute side effects	To clear rapidly before maximum pigmentation develops

UVB

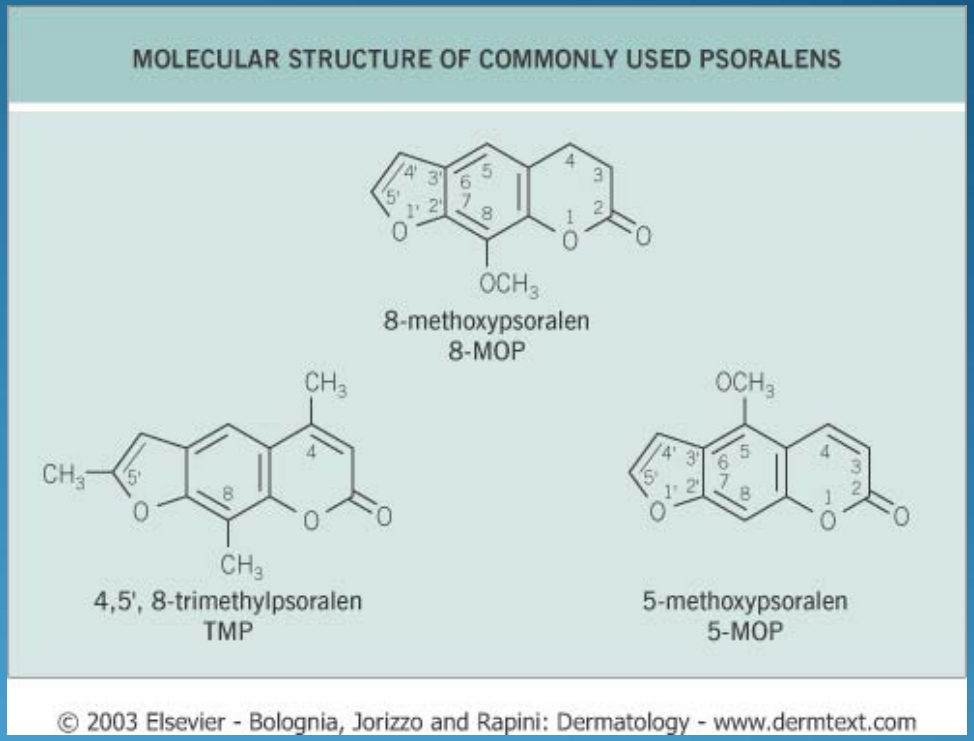
- •*Narrowband UVB (313nm)*
  - Newer treatment that takes advantage of the more therapeutic and less erythemogenic wavelengths of UVB spectrum.
  - Unfortunately the bulb (Philips TL01) is an inch longer than standard UVB, so a dedicated unit is needed.
  - Definitely superior to standard UVB.
  - Better clearance and fewer treatments required.
  - One study showed NB-UVB to be equivalent to PUVA.
  - Also better for severe atopic eczema.

UVB

- Narrow Band UVB
  - Penetration is still an issue with NB-UVB.
  - Technique essentially same for standard UVB.
  - Adverse effects also similar.
  - NB-UVB has been shown to be more carcinogenic in mice, but this risk may be offset by its greater efficacy.

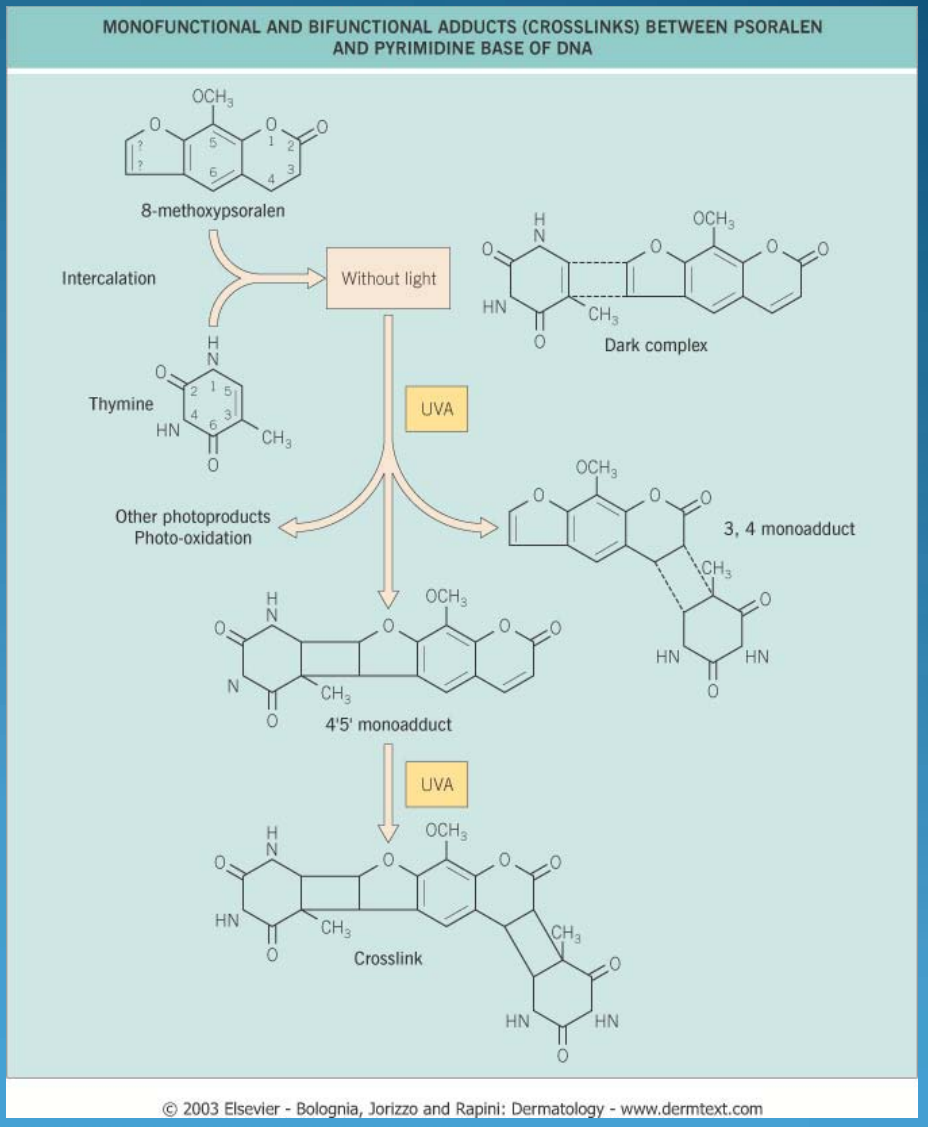
PUVA

- •*PUVA (Psoralens & UVA)*
  - Available in both oral and topical forms.
  - Psoralens are naturally occurring linear furocoumarins.
  - 8-methoxypsoralen is used primarily.
  - Get GI intolerance
  - 5-MOP is less erythemogenic and not associated with GI intolerance.
  - TMP is less phototoxic than 8-MOP



PUVA

- Psoralens react with DNA in three steps
  - Psoralen intercalates into the DNA double strand.
  - UVA results in formation of 3,4 or 4',5' cyclobutane monoadduct with pyrimidine bases of native DNA.
  - This monoadduct can absorb second photon.
  - This leads to formation of interstrand cross link of the double helix.



PUVA

- Excited psoralens can also react with molecular oxygen.
- This causes cell membrane damage by lipid peroxidation.
- These reactions inhibit DNA replication and cause cell cycle arrest.
- PUVA is far more potent in inducing apoptosis in lymphocytes than in keratinocytes.
- This may explain efficacy in CTCL.
- “Gold Standard” for moderate to severe psoriasis.
- Produces more than 90% clearing within 30 treatments.
- Also induces longer remissions and requires fewer and less frequent maintenance treatments

PUVA

- PUVA
  - Adverse effects
    - Erythema
    - Photoaging (Lentigines)
    - Carcinogenicity
      - SCC highest risk
      - Melanoma
      - BCC
    - Ocular damage (?cataracts) are the main concerns
  - RePUVA
    - Combination of UVA and oral Retinoids
    - Benefit of quicker response and fewer total treatments required.

Table 134.2 PUVA-responsive diseases. †Experience is limited to a small number of patients. *May flare.

PUVA-RESPONSIVE DISEASES	
Therapy of disease	Prevention of disease
Psoriasis	Polymorphous light eruption
Palmoplantar pustulosis	Solar urticaria
Atopic dermatitis	Chronic actinic dermatitis†
Mycosis fungoides (stages IA, IB, IIA)	Hydroa vacciniforme†
Vitiligo	Erythropoietic protoporphyria†
Generalized lichen planus	
Urticaria pigmentosa	
Cutaneous graft-versus-host disease	
Generalized granuloma annulare	
Prurigo nodularis	
Pityriasis lichenoides (acute and chronic)†	
Lymphomatoid papulosis†	
Pityriasis rubra pilaris†,*	
Purpura pigmentosa chronica†	
Langerhans cell histiocytosis†	
Dermatitis herpetiformis†	
Localized scleroderma†	

UVA1

- *UVA1 (320-400nm)*:
  - Takes advantage of less erythemogenic UVA spectrum.
  - Available in high and low dose protocols.
  - No reported adverse effects.
  - Carcinogenicity is still a concern.
  - Not yet available in the US.