LASERs in Medical Sciences

Lasers have many varied applications in

dentistry,

cardiovascular medicine,

dermatology,

gastroenterology,

gynaecology,

neurosurgery,

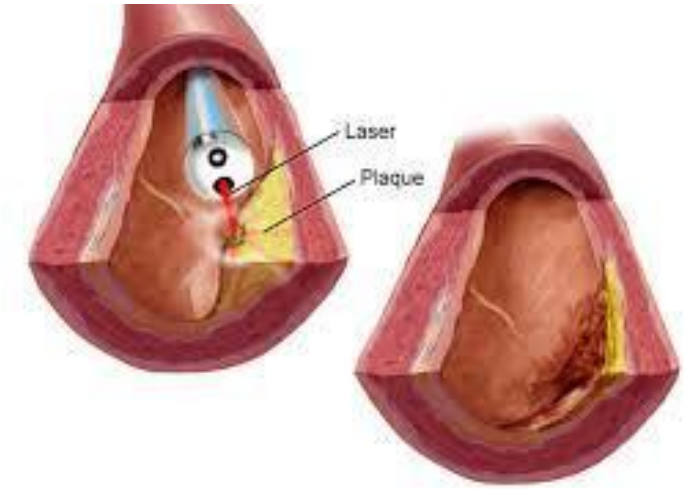
ophthalmology

otolaryngology.

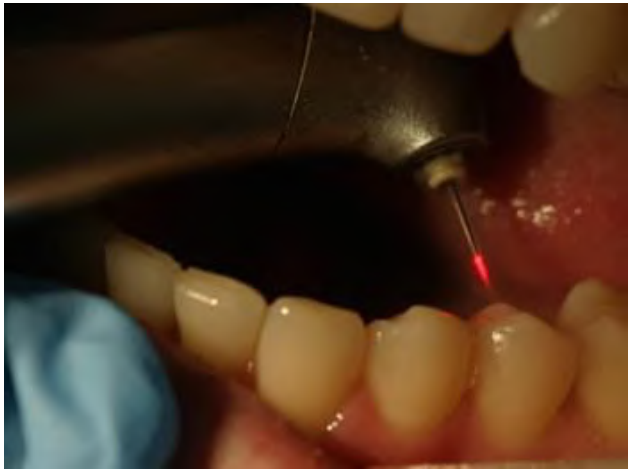
And ……

- In cardiovascular diseases, lasers are mainly used for laser angioplasty, laser thrombolysis, photo chemotherapy, laser treatment of arrhythmias and trans myocardial revascularization. The thermal interaction, photo ablation and photochemical interactions are used in these treatments.

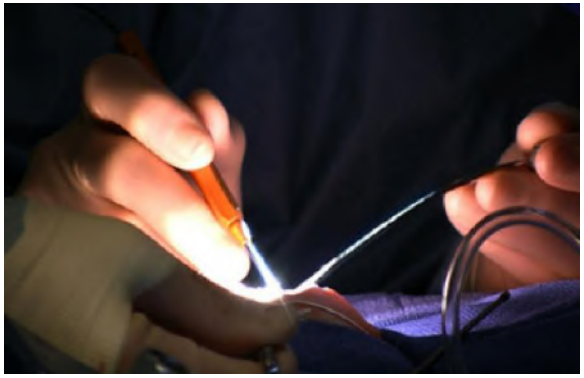
- For example, laser angioplasty uses thermal effects to vaporize the plaque material, in contrast to balloon angioplasty where the plaque material is fractured, compressed or displaced.



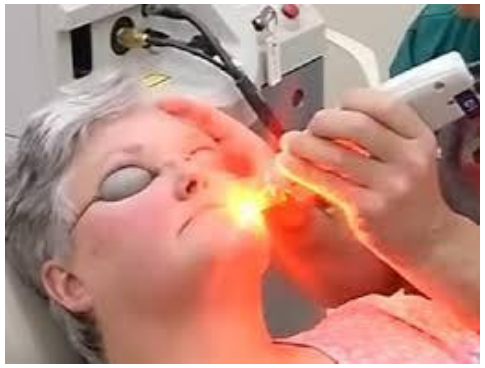
- One of the most obvious applications of lasers is removal of dental enamel, dentin, bone or cementum, instead of using an uncomfortable drill.



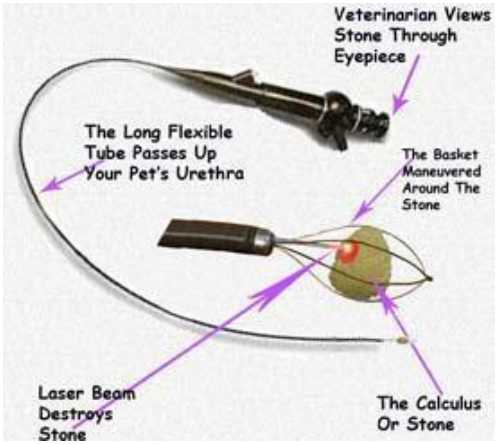
- A CO_2 laser is commonly used to ablate or vaporize superficially thin layers of soft tissue or to perform excisional surgery.



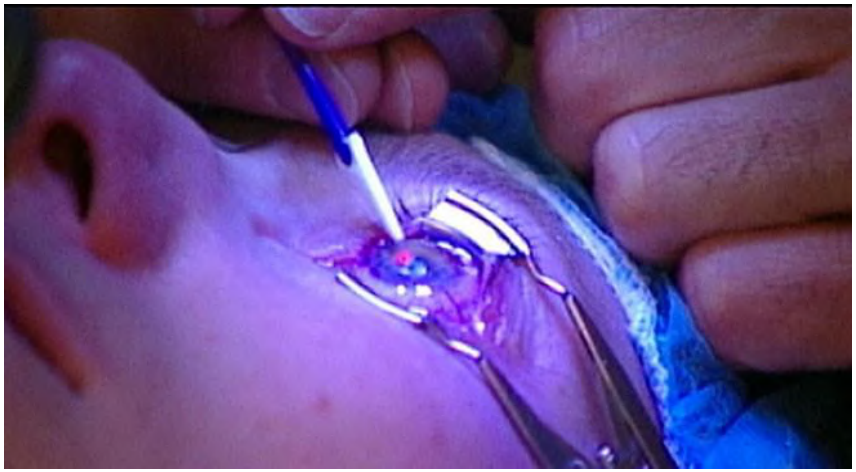
- The most common imperfections of the skin, such as pigmented lesions (port wine stains, haemangioma, lentigines) and tattoos, are usually treated with visible lasers including dye, argon, diode and ruby lasers.



- Laser are applied in gastroenterology to treat gastrointestinal haemorrhage from peptic ulcers (Nd:YAG) lithotripsy to fragment common duct stones in humans (tuneable dye, Q-switched Nd:NAG, pulsed Nd:YAG) and many other applications.



LASIK (laser-assisted in situ keratomileusis)



- LASIK surgery involves a suction ring that holds the eye steady while the platform for the microkeratome, a cutting instrument, is put in place.

- The microkeratome glides across the surface of the cornea, cutting through the outer layers. The instrument leaves an uncut part of the outer layer of the cornea to act as a hinge.

- The microkeratome is removed, the attached corneal flap is lifted out of the way, exposing the underlying layers of cornea to the laser beam, which corrects the curvature of the surface by ablation.

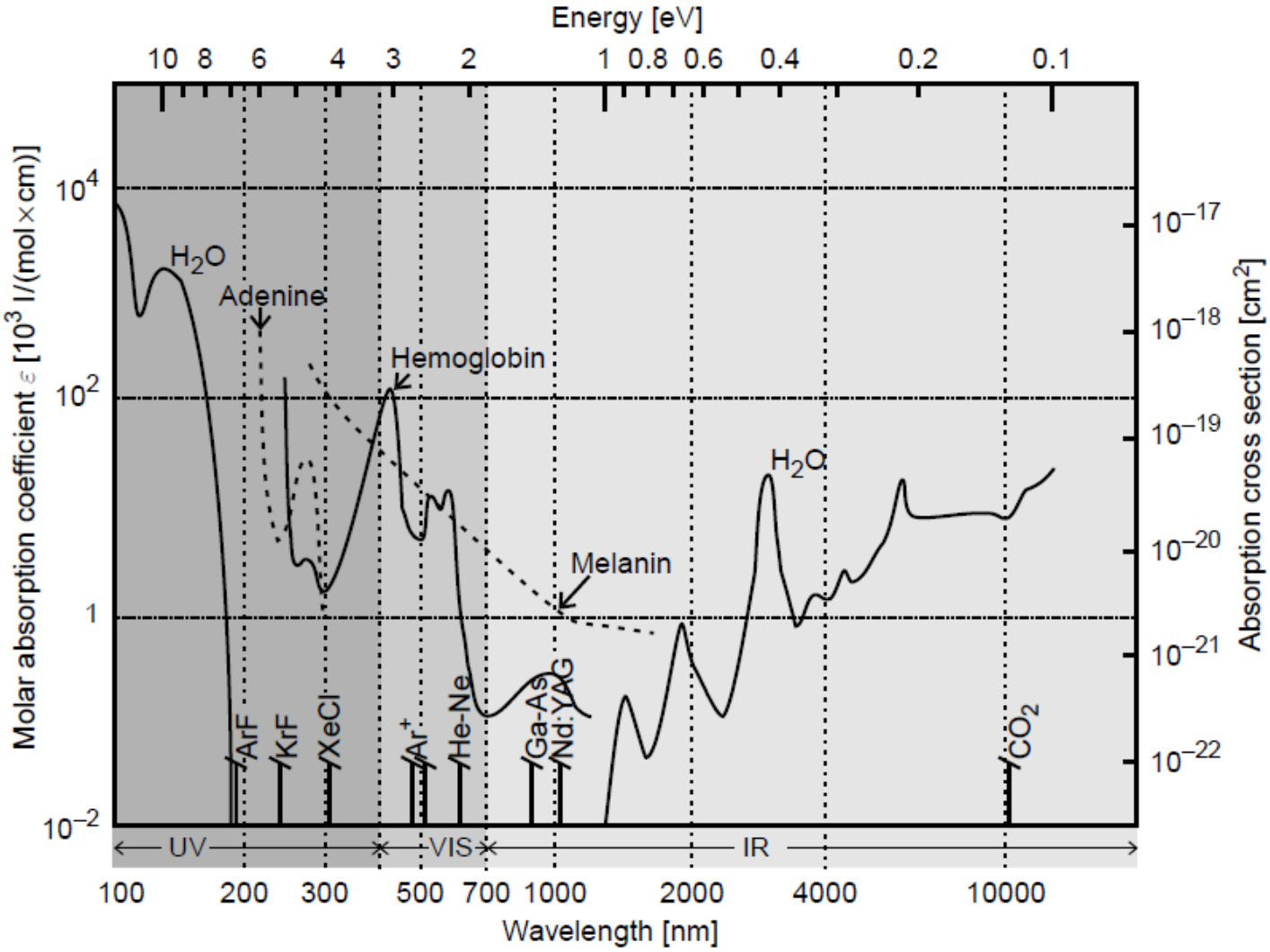
A few important points

- In surgery, femtosecond pulses allow for much more precise cutting than do nanosecond lasers.

- The biggest advantage of ultrashort pulsed lasers in surgical applications is limiting biological tissue damage. The pulse interacts with the tissue faster than thermal energy can diffuse to surrounding tissues. It simply means less, if any, burning and destruction of neighbouring tissue.

- The radiation–biological tissue interaction is determined mainly by the laser irradiance [W/cm^2], which depends on the pulse energy, pulse duration, and the spectral range of the laser light. The interaction depends also on thermal properties of tissue – such as heat conduction, heat capacity and the coefficients of reflection, scattering and absorption.

- The main components of biological tissue that contribute to the absorption are melanin, haemoglobin, water and proteins.



Absorption spectra of main absorbers in biological tissue..

- The absorption properties of the main biological absorbers determine the depth of penetration of a laser beam.

Comparison of penetration depths in biological tissue for different types of lasers

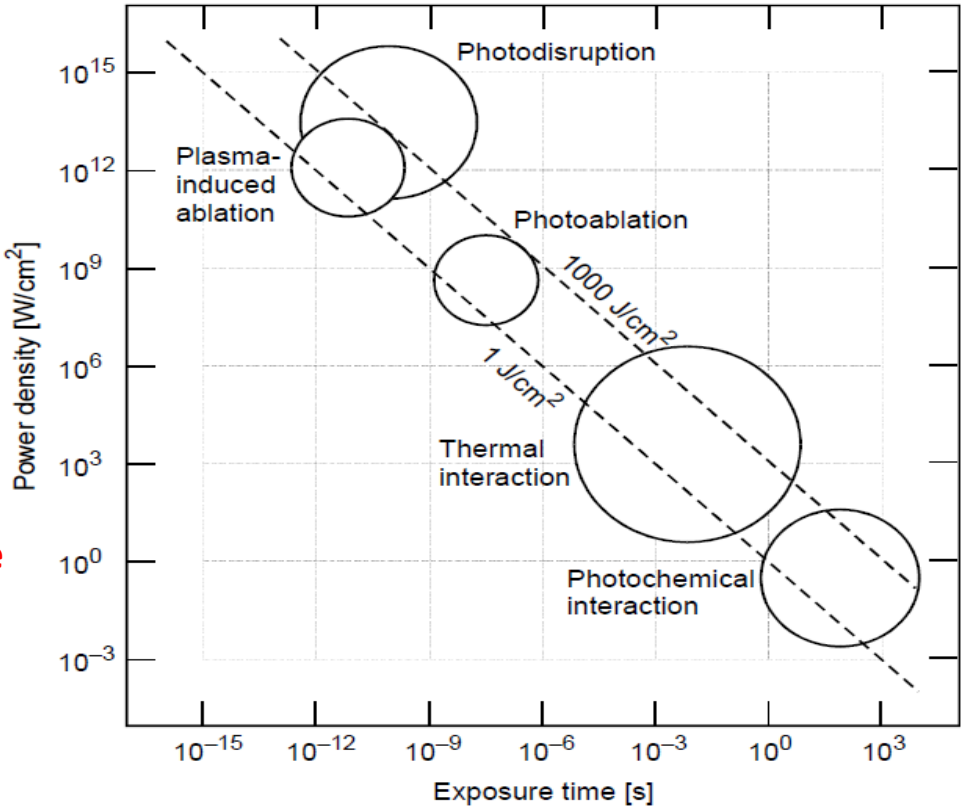
Laser type	Wavelength [μm]	Penetration depth [mm]
CO_2	10.60	0.10
Nd:YAG	1.064	6.00
Ar^+	0.4880, 0.5145	2.00
Excimer	0.193–0.351	0.01

- For example, the Nd:YAG laser can penetrate deeper and a cut made with the Nd:YAG laser will not bleed due to tissue coagulation, in contrast to the CO_2 laser which is a better ‘‘scalpel’’ for precise thermal cutting of tissue due to vaporization by focusing on the tissue along a short optical path.

Categories of Interactions

There are five main categories of interaction:

- Photochemical interactions
- Thermal interactions,
- Photoablation,
- Plasma-induced ablation,
- Photodisruption.



Double logarithmic plot of the power density as a function of exposure time. The circles show the laser parameters required from a given type of interaction with biological tissue.

- With cw lasers or exposure time >1 s, only photochemical interaction can be induced. Powers of only a few mW can be used for these purposes.

- For thermal interactions shorter exposure times (1 min–1 μs) and higher energies must be used. Thermal effects can be induced both by cw or pulsed lasers of 15–25 W power.

- Photoablation occurs at exposure time between 1 μs and 1 ns. In practice, nanosecond pulses of 10^6–10^9 W/cm^2 irradiance should be employed.

- Plasma-induced ablation and photodisruption occur for pulses shorter than nanoseconds. In practice, pico- and femtosecond lasers with an irradiance of 10^{12} W/cm^2 should be used.

- Both phenomena occur at a similar time exposure and irradiance, they differ according to the energy densities that are significantly lower for plasma-induced ablation.

PHOTOCHEMICAL INTERACTIONS

- Photochemical interactions do not need a high power density. Lasers of 1 W/cm^2 power density and long exposure times ranging from seconds to cw light are sufficient.

- For this category of interactions, a laser induces chemical effects by initiating chemical reactions in tissue. For example, vision processes in rhodopsin or proton pumping in bacteriorhodopsin are initiated by a laser beam from the visible range.

- Photochemical interactions are used in photodynamic therapy (PDT)

Photodynamic Therapy

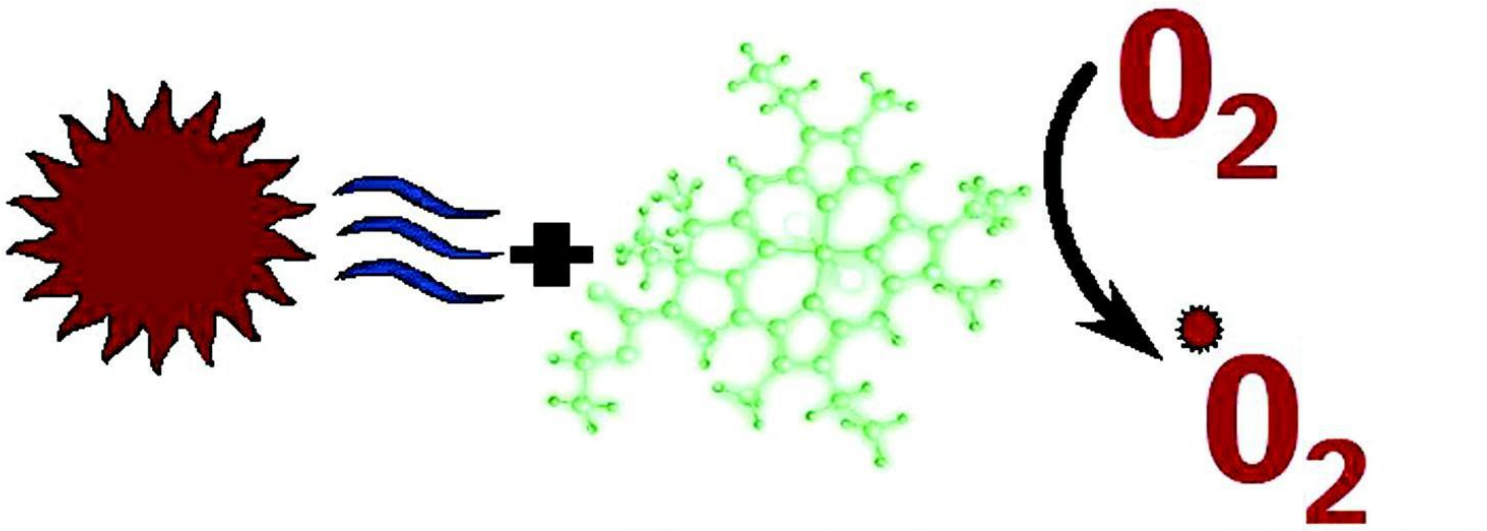
- Photodynamic therapy utilizes the laser light effect on various chemical substances (e.g., some porphyrins) in an oxygen-rich environment. Light induces a sequence of reactions that produce toxic substances such as singlet oxygen or free radicals. These substances are very reactive and can damage proteins, lipids, nucleic acids as well as other cell components.

- In the PDT method, a chemical substance known as a sensitizer is injected intravenously. During the next several hours the sensitizer is distributed to all of the organism's soft tissues, both healthy and diseased.

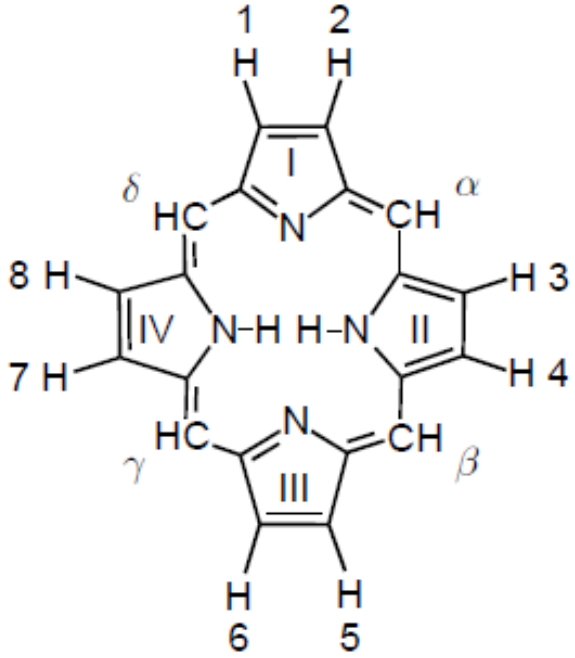
- At first, the substance concentration is the same in healthy and diseased cells, but after about 48–72 hours the sensitizer leaves the healthy cells in contrast to cancer cells, where it remains accumulated for 7–10 days.

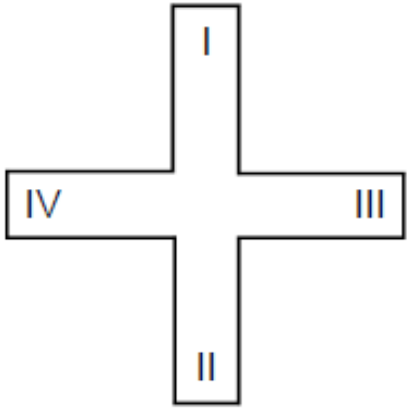
- After about 3 days post injection, the concentration of the sensitizers is about 30 times higher in diseased cells than in healthy ones.
- About 3 days after the sensitizer injection, a patient is irradiated by a laser light. The laser light induces a sequence of reactions with the excited singlet state of oxygen $^1O_2$* as a final product.
- The singlet oxygen $^1O_2$* is very reactive, which makes it extremely toxic as it reacts with components of biological cells and destroys them.
- To protect healthy cells carotene is injected. Carotene reacts with $^1O_2$* causing oxygen transfer to the harmless triplet oxygen state $^3O_2$.
- The advantage of photodynamic therapy in cancer treatment over commonly used radio– and chemotherapy is selective destruction of diseased cells while saving healthy cells to a large extent.
- In most clinical applications haematoporphyrin derivatives (HPD) as well as dihaematoporphyrinethers (DHE) are used. The commercial name for DHE is sodium porfimer.

Mechanism of Photodynamic Therapy



- Reactive oxygen species / free radicals
- PDT initiates cellular apoptosis



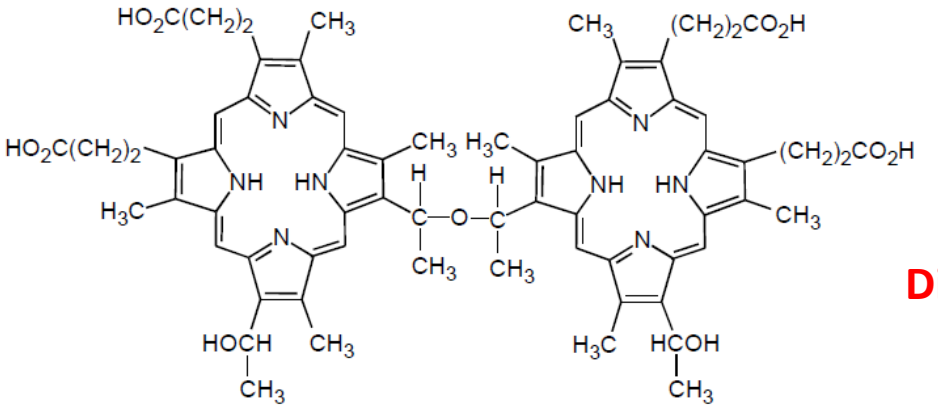


- The names of porphyrins contain also a number, e.g., uroporphyrin I. The number I defines a regular substituent repetition, e.g., AP AP AP AP, beginning with the pyrrole ring I. For porphyrins numbered with III, the order in ring IV is reversed: AP AP AP PA, where,
  - A acetic acid ($-CH_2COOH$)
  - P propionic acid ($-CH_2CH_2COOH$)
  - M methyl group ($-CH_3$)
  - V vinyl group ($-CH=CH_2$)

- Some porphyrins such as dihematoporphyrin have already found application in photodynamic therapy or they have reached the III phase of clinical tests. HPD and DHE belong to the first generation of sensitizers. Their main side effect is skin photosensitivity.

- To reduce the side effects and increase efficacy, investigations have been made to synthesize second- and third generation sensitizers, which absorb at longer wavelengths (>650 nm). Examples- porphyrin, purpurin, benzoporphyrin, phthalocyanine, and naphthalocyanine derivatives.

  - For phthalocyanine or naphthalocyanine, which absorb at 670 nm and 770 nm, the photosensitivity side effect disappears.



Dihematoporphyrin

Photochemistry of Sensitizers

- There are two main mechanisms of photochemical reactions in sensitizers- I and II type photooxidation.

- In type I photooxidation, the sensitizer reacts directly with another chemical entity by hydrogen or electron transfer to yield transient radicals, which react further with oxygen.

- In type II photooxidation, the sensitizer triplet interacts with oxygen, most commonly by energy transfer, to produce an electronically excited singlet state of oxygen, which can react further with a chemical entity susceptible to oxidation.

Type I Photooxidation

- The sensitizer in a singlet state, ^1S, absorbs a photon of energy hv and is promoted to the singlet excited state, $^1S^*$.
- The excited singlet state $^1S^*$ emits the energy as fluorescence or in a radiationless way, returning to the ^1S state or crossing to the excited triplet state $^3S^*$ as a result of intersystem crossing (ISC) with breaking of the selection rule (spin change). The return from the triplet state to the ground singlet state ^1S may occur via emission of phosphorescence
- The triplet state $^3S^*$ can also vanish as a result of proton transfer or electron transfer between the sensitizer and another chemical entity (RH) (for example substances that are the components of a human cell)

$$^3S^* + RH \longrightarrow SH^{\bullet} + R^{\bullet} \quad (1)$$

$$^3S^* + RH \longrightarrow S^{-\bullet} + RH^{\bullet +} \quad (2)$$

- The reactions (1) or (2) induce further reactions with the oxygen triplet state $^3O_2$ contained in a cell environment

$$SH^{\bullet} + {}^3O_2 \longrightarrow {}^1S + HO_2^{\bullet}$$

$$S^{\bullet -} + {}^3O_2 \longrightarrow {}^1S + O_2^{\bullet -}$$

Type II Photooxidation

- In type II photooxidation the triplet state of a sensitizer $^3S^*$ interacts directly with the oxygen triplet state $^3O_2$, leading to generation of the singlet excited oxygen state $^1O_2^*$.
- Oxygen in the singlet excited state is very reactive. This leads to oxidation of cell components such as proteins, lipids, and nucleic acids and eventually to necrosis of the cell.

$$^3S^* + {}^3O_2 \longrightarrow {}^1S\,H + {}^1O_2{}^*$$

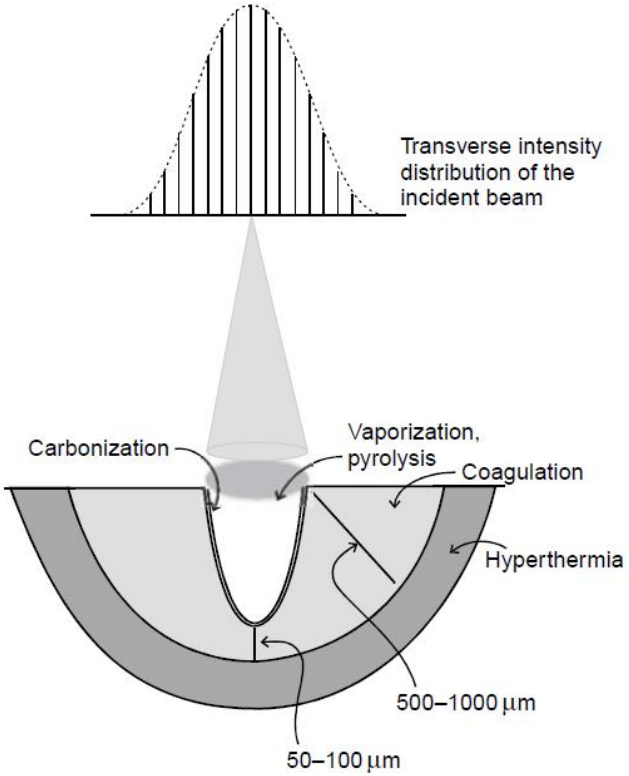
Thermal Interaction

- Thermal interactions are induced in a tissue by the increase in local temperature caused by a laser beam.
- In contrast to photochemical interactions, thermal interaction may occur without only specific reaction path and is highly non-selective and non-specific.

Depending on the temperature achieved, the thermal effect on the tissue can be classified as:

- Reversible hyperthermia ($T > 31^0$ C) – some functions of the tissue can be perturbed but the effect is reversible.
- Irreversible hyperthermia ($T > 42^0$ C) – some fundamental functions of the tissue can be destroyed irreversibly
- Coagulation ($T > 60^0$ C) – the tissue becomes necrotic,
- Vaporization ($T \geq 100^0$ C),
- Carbonization ($T > 150^0$ C),
- Pyrolysis ($T > 300^0$ C).

- In some cases all of these thermal effects can be observed as a result of interaction with the laser.
- In most applications one effect usually dominates, depending on the goal of the surgery. For example, an Nd:YAG laser beam traveling long path in the tissue is used for coagulation, whereas CO_2 lasers are more suitable for vaporization.



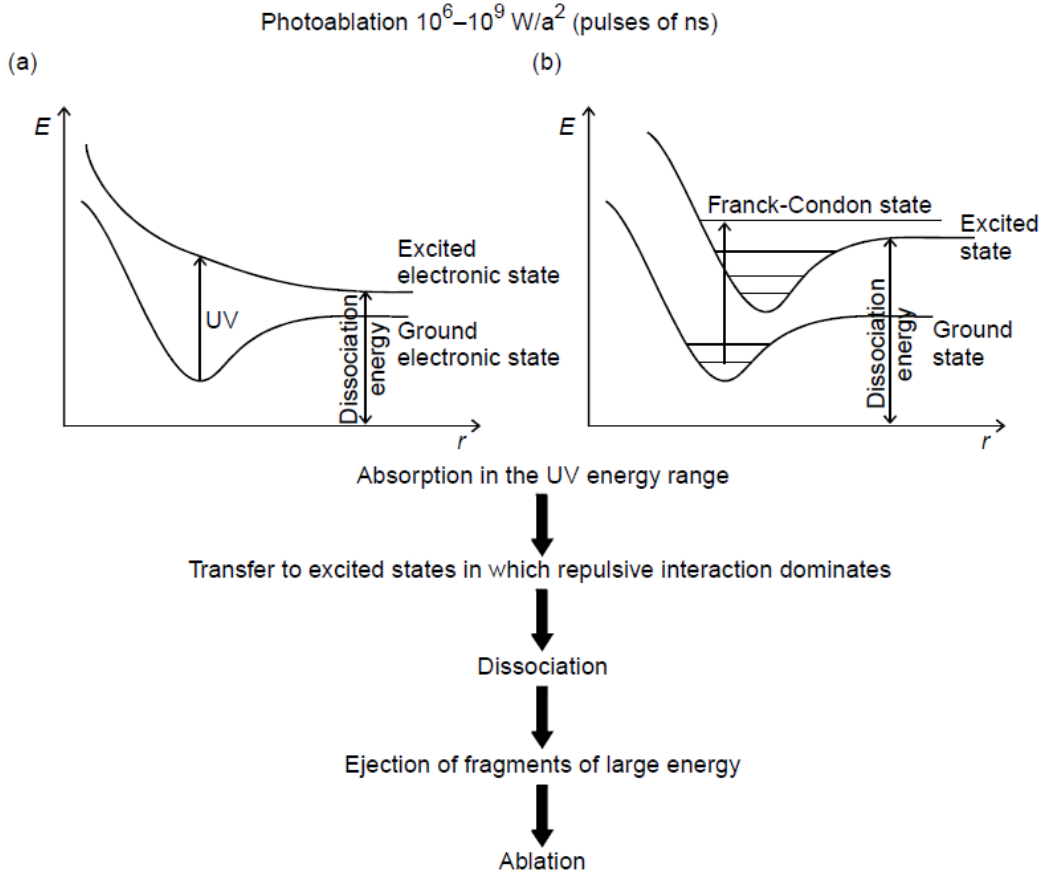
The thermal effects on tissue.

PHOTOABLATION

- A molecule is promoted to the repulsive excited state (or to the Franck-Condon vibrationally hot state) followed by dissociation.

- The chemical bond is broken, leading to the destruction of biological tissue.

- As electronic transitions occur usually in the UV range, the photoablation process is usually limited to UV lasers. Therefore, excimer lasers (ArF, KrF, XeCl, XeF) are mainly employed but higher harmonics of other lasers can also be applied.



Mechanism of photoablation (a) the excited state is repulsive, (b) the excited state is a Franck-Condon state.

PLASMA-INDUCED ABLATION

- Typical lasers used for plasma-induced ablation are Nd:YAG, Nd:YLF, Ti:sapphire with pico- or femtosecond pulses generating irradiance at about 10^{12} W/cm^2.

- Therefore, the Q-switched or modelocked lasers can ionize molecules in biological tissue.

- An ultrashort pulse from a Q-switched or mode-locked laser ionizes biological tissue and generates a very large density of free electrons in a very short period of time with typical values of 10^{18} cm^{-3} due to an avalanche effect.

- Free electrons from ionization accelerate to high energies and collide with molecules, leading to further ionization.

- Light electrons and heavy ions move at different velocities, leading to the effect similar to that in the acoustic wave with areas of compression and dilation.

Plasma-induced ablation 10^{12} W/cm^2 (pulses of ps, fs)
Typical lasers: Ti:sapphire, Nd:YAG, Nd:YLF