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INTERNATIONAL CENTRE FOR SCIENCE AND HIGH TECHNOLOGY

1/19 INTERNATIONAL CENTRE FOR THEORETICAL PHYSICS 34100 TRIESTE (ITALY) VIA GRIGNANO, 9 (ADRIATICO PALACE) P.O. BOX 586 TELEPHONE 040-234572 TELEFAX 040-234573 TELEX 40044 IAP I

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Medical Applications of Optical Radiation

R. PRATESI

*Università degli Studi di Firenze
Dipartimento di Fisica
&
Area della Ricerca CNR di Firenze
Firenze, Italy*

Medical Applications of Optical Radiation

Riccardo Pratesi

Dipartimento di Fisica

Università degli Studi di Firenze

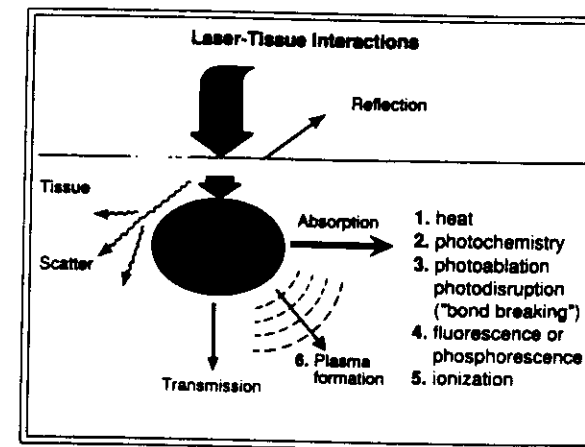
and

Area della Ricerca CNR di Firenze

- * **Basic physics of light interactions with biological matter**
- * **Optics of tissues**
- * **Therapeutic and diagnostic applications**

LASER-TISSUE INTERACTIONS

- * **Photothermal interactions**
- * **Photochemical interactions**
- * **Photomechanical interactions**



Thermal Interaction

Most of the surgical applications of optical radiation rely on the conversion of optical radiation energy into thermal energy.

Microscopic level

At the microscopic level, the photothermal process consists of a two-step reaction:

Absorption

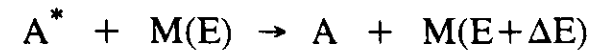
- * the excitation of the target molecule A:



the absorption of a photon of energy $h\nu$ promotes A to a rotational-vibrational excited state A^*

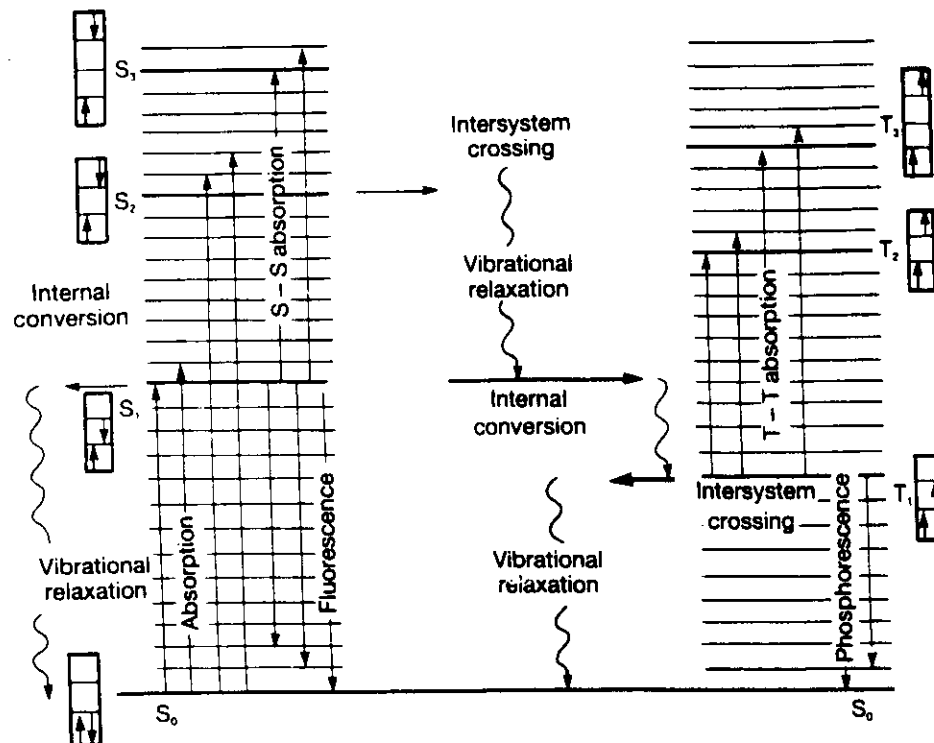
Non-radiative decay

- * the deactivation of A^* through inelastic scattering with a collisional partner M belonging to the surrounding medium, with an increase ΔE of kinetic energy of M:



The inelastic scattering occurs on a 1-100 ps time-scale.

The rapid thermalization through **nonradiative decay** produces an increase of local temperature.



Thermal processes in tissue

Simplified sequence of thermal processes and injuries in tissues.

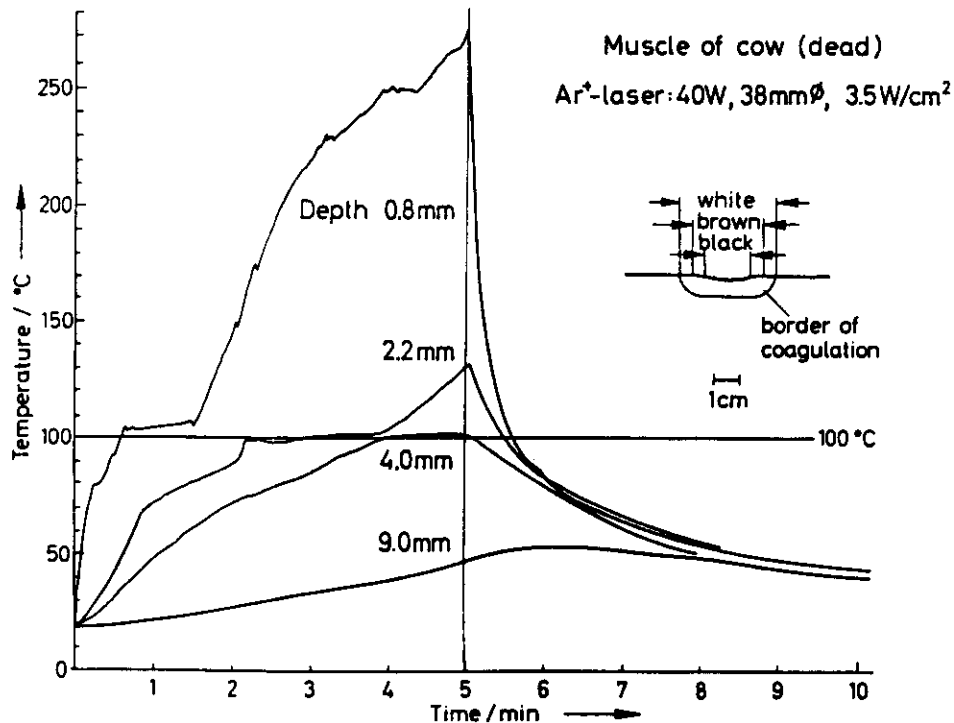
Table 1 Histological Changes in Photothermal Processes

Conversion of Electromagnetic Radiation into Heat	
Elevation of Tissue Temperature	
43°C → 45°C	Conformational changes Retraction Hyperthermia (cell mortality)
50°C	Reduction of enzyme activity
60°C	Protein denaturation Coagulation
80°C	Collagen denaturation Membrane permeabilization Carbonization
100°C	Vaporization and ablation

Thermal processes in tissue

Recent observations suggest that thermal biological effects can be separated into different thermodynamic processes:

- 1) lower temperature (~ 43 to $\sim 150^\circ\text{C}$) damage accumulation processes that can be described by **rate process kinetics**
- 2) higher temperature ($100^\circ\text{C}+$) effects dominated by **water vaporization** with confinement and release of heated water vapor from tissues
- 3) high temperature **ablation** ($\sim 300^\circ\text{C}$ into 1000's) by tissue vaporization, combustion, molecular dissociation and/or plasma formation.



Many of these changes can occur simultaneously at different sites within the irradiated volume.

Pathological photothermal effects

Table 1 Laser-tissue interactions: pathological photothermal effects

Photothermal interaction	Temperature at onset (°C)	Histopathologic effect
Low temperature damage accumulation processes	40-45	? Deactivation of enzymes: reversible cell injury
	43-45 +	Deactivation of enzymes: cell death
	?	Cell shrinkage and hyperchromasia
	43 +	Birefringence loss in frozen and thawed myocardium
	?	Thermal denaturation of structural proteins
	?	Membrane rupture
	58 +	Hyalinization of collagen
Water-dominated processes	69-72	Birefringence loss in fresh myocardium
	70-75	Birefringence changes in collagen
	140 +	Thermal denaturation of elastin
	100 +	Extracellular vacuole formation
High temperature ablation	over 100	Rupture of vacuoles: "popcorn" effect
	?	Tissue ablation by explosive fragmentation
	300-1000 +	Tissue ablation
	3550	Vaporization of carbon

* Low temperature thermal injury

Individual cells and various tissues heated to temperature ranging around 43-45°C can sustain reversible injury that becomes irreversible (death) after exposures ranging from 25 minutes to several hours depending on the type of tissue and experimental or therapeutic circumstances.

* Molecular denaturation

The first mechanism by which tissue is thermally affected is **molecular denaturation** (proteins, collagen, lipids, hemoglobin).

In the neighborhood of $T \sim 45^\circ\text{C}$ (*hyperthermic range*) one observes

- * macromolecular conformational changes
- * bond destructions and
- * membrane alterations.

The range of protein denaturation is between 50°C and 60°C.

*** Coagulation photothermal effects**

Thermal **coagulation** of tissues is defined as the thermally induced, irreversible alterations of proteins and other biological molecules, organelles, membranes, cells and extracellular components that are observable with the naked eye and/or microscopic techniques.

Most of these alterations are due to thermal denaturation of structural proteins although membrane rupture may result from alterations in lipids.

Cell shrinkage

Coagulated cells shrink because of thermal denaturization and contraction of intracellular proteins and probable collapse of the cytoskeleton.

Membrane rupture

Extensive rupture of cellular membranes becomes more prominent in more severely damaged cells of all types.

Birifrangence changes in muscle and collagen

The regular, crystalline-like array of actin and myosin molecules within the sarcomere of striated muscle and the longitudinal fascicles of the same contractile proteins in the cytoplasm of smooth muscle cells are responsible for their birifrangence properties.

Recent observations suggest that the loss of birifrangence in striated muscle is due to the destruction of the regular relationship of the contractile proteins of the sarcomere by thermal denaturization of the contractile proteins.

STRUCTURE OF THE SARCOMERE

The sarcomere is the fundamental unit of contraction.

Thick and thin filaments are constructed principally of the **proteins myosin and actin**, respectively.

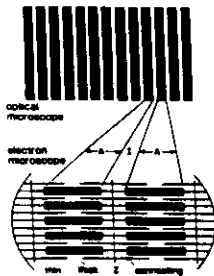


Fig. 1. A- and I-bands, as seen in the optical microscope, shown diagrammatically. Protein filaments corresponding to these bands are diagrammed below.

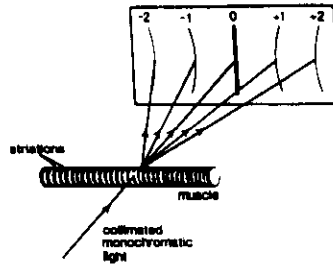


Fig. 2. Optical diffraction pattern obtained from striated muscle, shown diagrammatically. As the sarcomere shortens, the bands move apart.

The striation pattern closely resembles a diffraction grating.

* Water dominated photothermal effects

Most soft tissues are composed of about 80% water, thus water is a major optical and thermal influence in laser-tissue interactions.

As tissue temperature approach the threshold temperature of vaporization of water, the photothermal effects of laser-tissue interactions come under the influence of

- 1) the energy requirements of phase changes of water
- 2) tissue desiccation
- 3) formation of steam vacuoles within the tissue, and
- 4) the mechanical effects of rapidly expanding steam vacuoles trapped in the tissue.

Computer models supported by experimental results indicate that **subsurface temperatures** of tissues irradiated in air are greater than those on the surface due to **back scatter** of light and **surface water evaporation**.

Increased subsurface heating produces hot pockets of superheated steam and tissue constituents that influence the progression and distribution of thermal injury.

Grossly apparent bubbles form in the hotter tissues below the surface of the irradiated tissue.

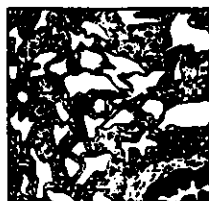
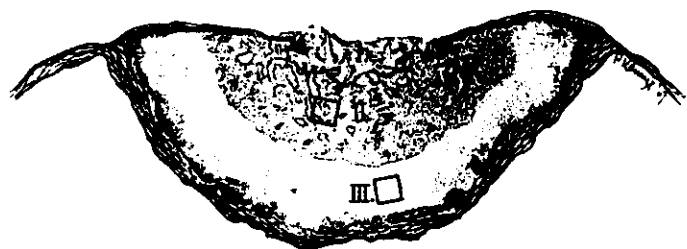
As the irradiation continues, the bubbles enlarge and eventually rupture explosively, a series of events called the "**popcorn effect**".

Microscopically, the bubbles are seen to be extracellular vacuoles forming between layers of coagulated, shrunken, desiccated tissues beneath the surface. As critical pressures are reached, the thin walls of the vacuoles rupture and coalesce to form larger holes.

Vacuoles that rupture on the surface allow water vapor to escape, thus momentarily cooling the surface as the hot gas dissipates.

Histological observations of the *popcorn* **craters** indicate that the craters are not formed due to tissue mass loss but are a result of the merger, expansion and rupture of **cluster of vacuoles**.

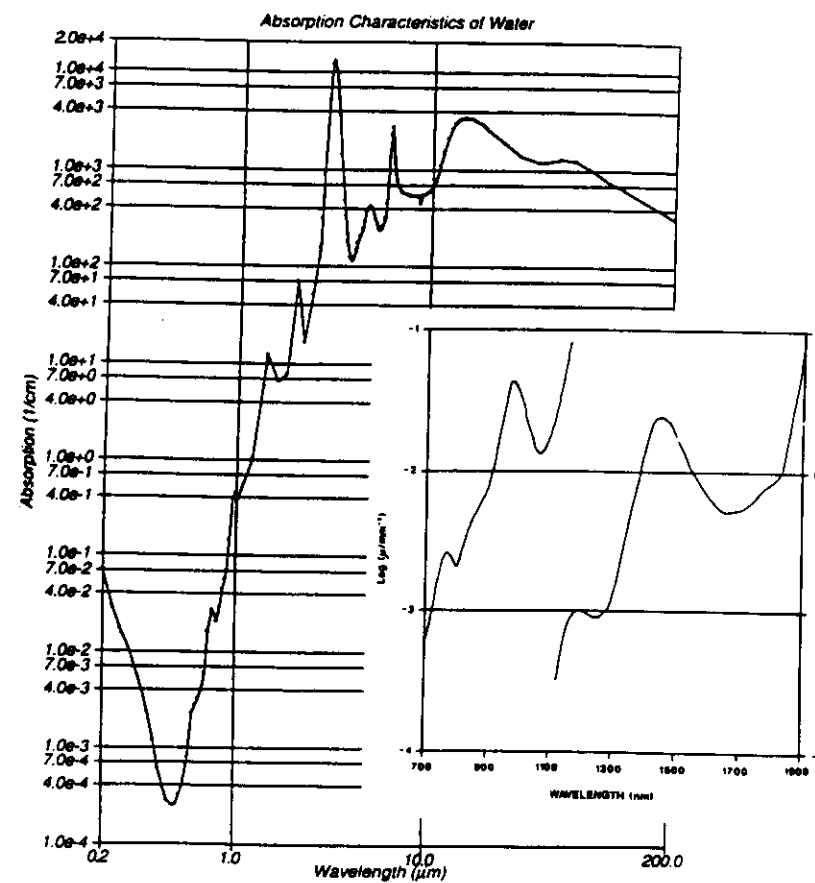
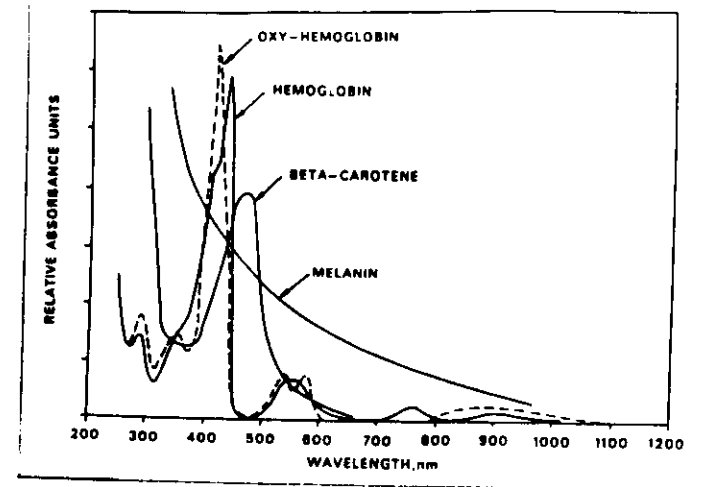
More rapid heating associated with pulsed laser irradiation results in explosive rupture of the vacuoles with expulsion of fragments of tissue.

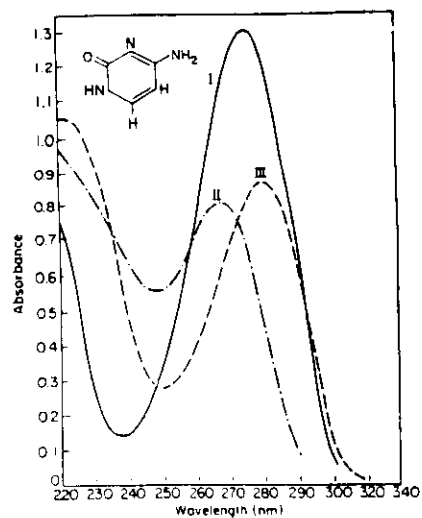


Zone II-260X

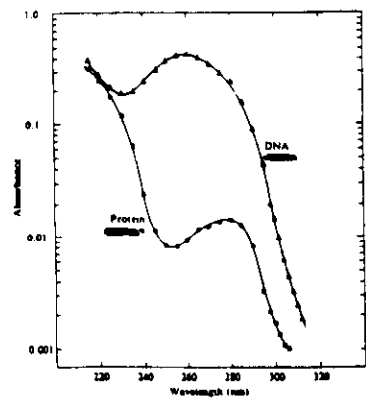
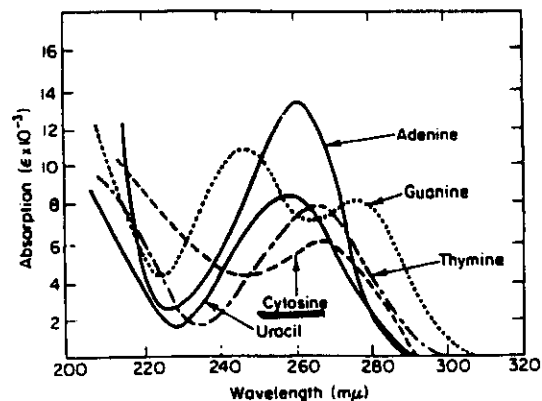


Zone III-260X





a



c

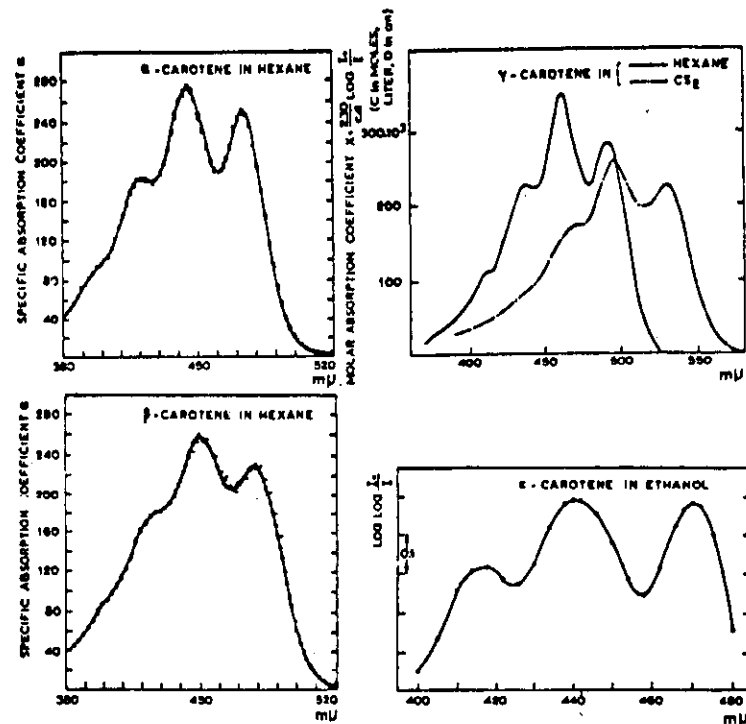
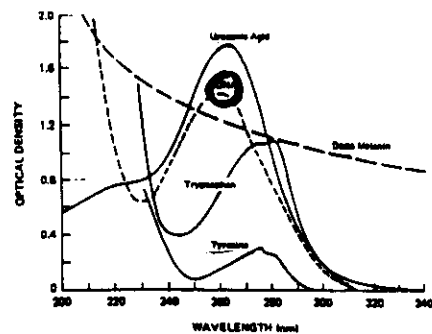
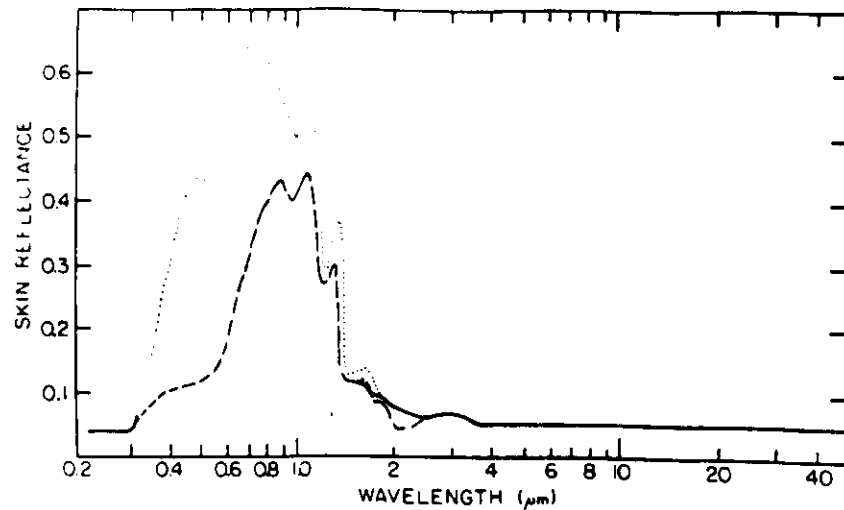
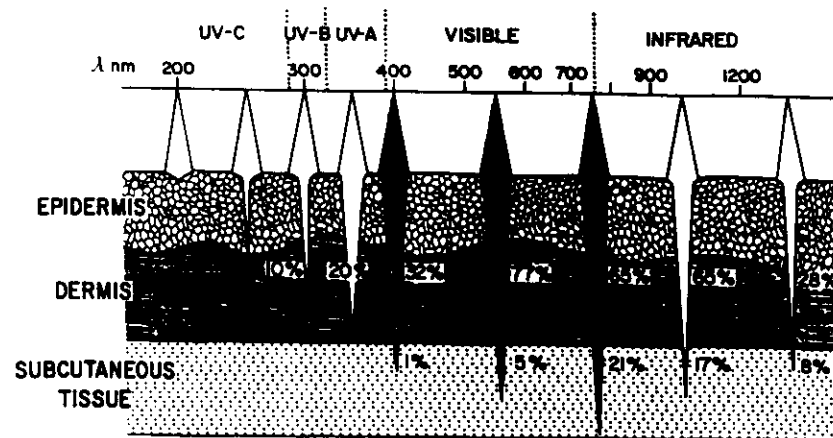


Figura 2.3

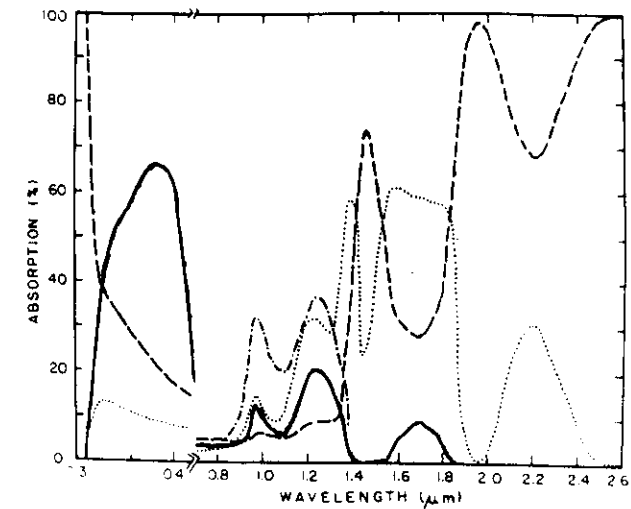
- Spettro di assorbimento della citosina a vari valori di pH (I: 1.2; II: 6.0; III: 12.7);
- Spettri di assorbimento di varie basi puriniche e pirimidiniche a pH 7.
- Spettri di assorbimento di DNA ed albumina (BSA) a uguali concentrazioni (~20 μg/ml). L'assorbimento del DNA è dovuto alle basi puriniche e pirimidiniche; l'assorbimento delle proteine è dovuto principalmente agli aminoacidi aromatici.
- Spettri di assorbimento dei principali cromofori con assorbimento UV presenti nell'epidermide.



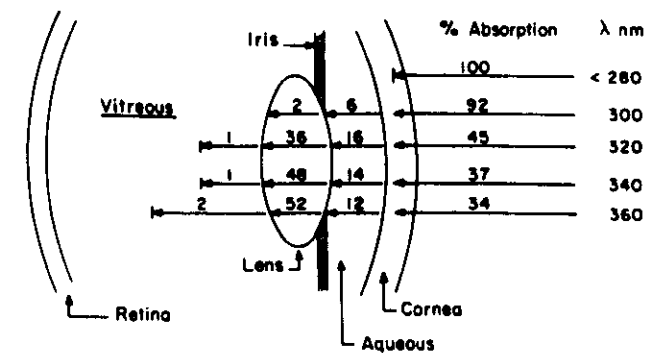
Spettro di riflettanza della cute umana. La curva punteggiata si riferisce a un soggetto con pelle molto chiara.



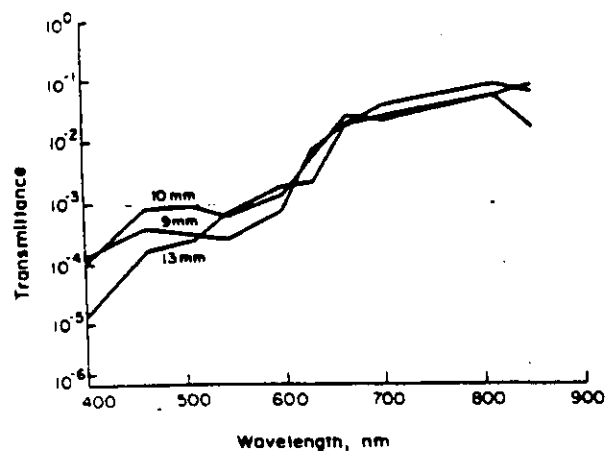
Indicazione schematica delle profondità di penetrazione cutanea della radiazione ottica.



The spectral absorption of the Ocular Media for the Human Eye. Each portion of the ocular media, the cornea (---), the aqueous humor (···), the lens (—), and the vitreous humor (- · - ·), absorb different portions of the incident optical radiation at different wavelengths. Very little is absorbed in the visible region, hence the break in the curves. Note the strong absorption of the lens in the near-ultraviolet region and the absorption of the vitreous in the 0.86-1.35 μm infrared region.



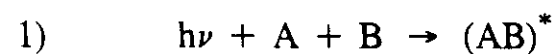
Schematic of absorption of ultraviolet radiation in the ocular media. Values represent the percent of ultraviolet radiation incident upon the corneal surface that are absorbed by various layers, redrawn from a figure by Matelaky, 1969. Based on data by Boettner and Wolter, 1962.



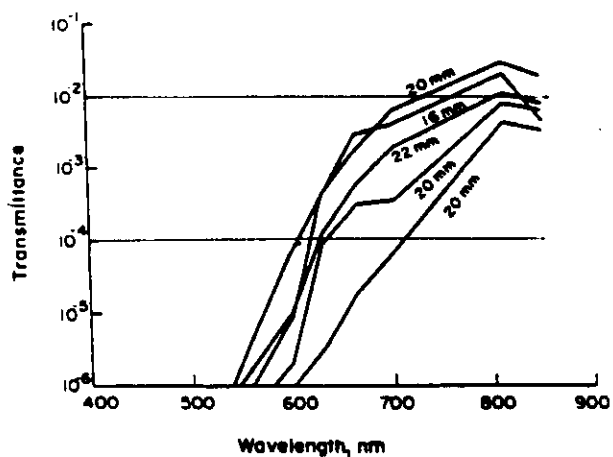
Photochemical Interaction

Photons can act as *reactants* in a photochemical reaction:

Microscopic level



The reaction 1) represents the photoinduced **formation** of the molecule AB following the absorption of the photon $h\nu$ by either molecule A or B.



Photoinduced addition

Photoaddition reaction between a furocoumarin molecule and a thymine component in a DNA molecule:

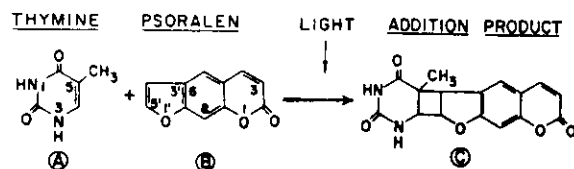
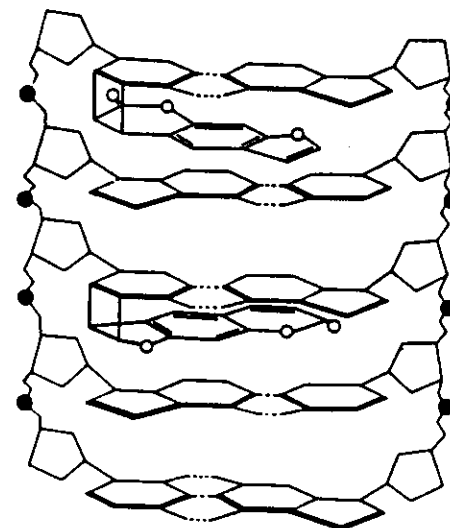


Photo-induced addition product (C) between a thymine molecule (A) and a furocoumarin, psoralen (B). Similar addition products are formed between a furocoumarin molecule and a thymine component in a DNA molecule.

[Psoralens is the popular name of furocoumarins, three-ringed organic compounds found in a variety of plants].

Monofunctional adducts

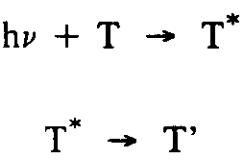
Absorption of photons by psoralens leads to covalent binding of the psoralens to DNA or RNA, with the formation of monofunctional adducts of psoralens with pyrimidine bases (thymine, cytosine).



A drawing of a segment of DNA illustrating the covalent linking of psoralen to thymine (a single-strand linkage). Two types of monofunctional adducts are shown. The 5,6 double bond of thymine photoreacts with psoralen at either its 3,4 double bond or the 4', 5' double bond to produce the C₄-cycloadduct.

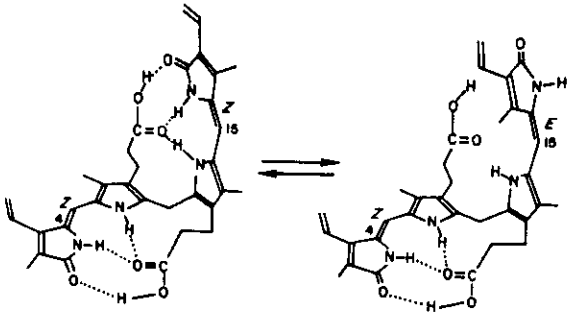
Reactions in which the chromophore molecules are **modified** and **converted** into *photoproducts*:

Photoconversion

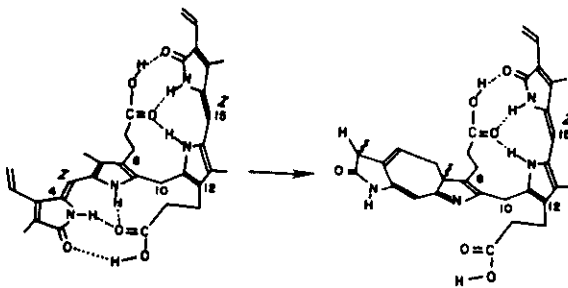


Example: Photoisomerization of bilirubin

Configurational isomerization
(cis-trans reactions)



Structural isomerization
Photocyclization



Photodissociation



The reaction 2) represents the **photodissociation** process which follows the promotion of the molecule AB by photon absorption to a repulsive state.

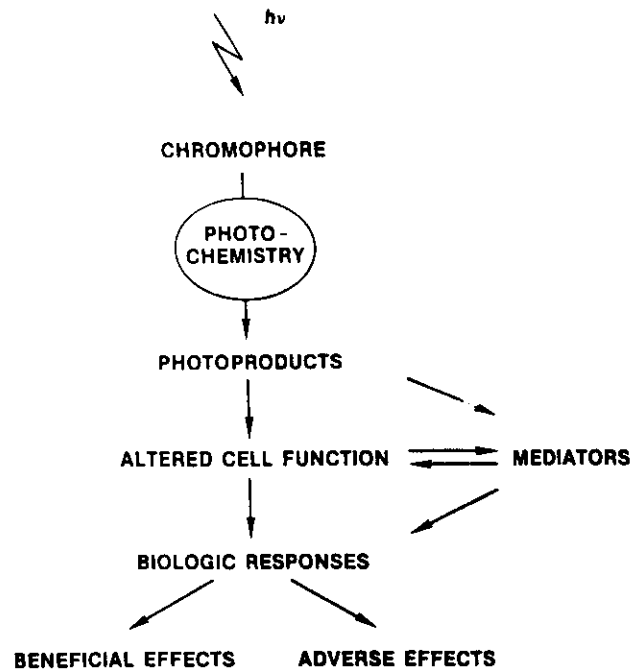
Chromophore-mediated reaction

In this case the photon energy is used to excite a particular **chromophore** that in turn initiates a complex biological process whose final products have a **therapeutical** relevance.

In these reactions the molecules is involved as *energy carriers* or as *catalytic regulators* after experiencing a photoexcitation.

A chromophore compound capable of causing light-induced reactions in molecules that do not absorb light in the same wavelength range is called a **photosensitizers**.

Possible sequence of photochemical and biological events



Possible sequence of events following exposure of skin to nonionizing radiation ($h\nu$) leading to beneficial and/or adverse effects.

The sequence of molecular reactions undergone by a given photosensitizer can be separated into several stages:

- * resonant excitation
- * decay
- * substrate reaction, or
- * reactant formation and
 - * oxidation.

These kinetics can be further separated schematically into two types of *mechanisms*, depending on the substrate involved in the crucial stage of reactant formation.

These different pathways are encountered in the therapeutic treatment of tumors based on selective photo-sensitized oxidation [called **photodynamic therapy (PDT)**], and are summarized in the Table.

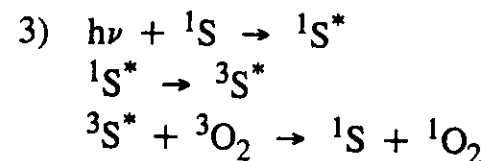
Table 4 Photosensitization Kinetics in Type I and Type II Mechanisms and Possible Carotenoid Protection

Resonant excitation	
1. Singlet state absorption	$^1S + h\nu \rightarrow ^1S^*$
Decays	
2. Radioactive decay (fluorescence)	$^1S^* \rightarrow ^1S + h\nu'$
3. Nonradioactive singlet decay	$^1S^* \rightarrow ^1S$
4. Intersystem crossing	$^1S^* \rightarrow ^3S^*$
5. Triplet state decay	$^3S^* \rightarrow ^3S$
6. Triplet phosphorescence decay	$^3S^* \rightarrow ^3S + h\nu''$
TYPE I MECHANISMS	
Free radical derivations	
7. Hydrogen transfer	$^3S^* + RH \rightarrow SH^* + R^*$
8. Electron transfer	$^3S^* + RH \rightarrow S^{\cdot-} + RH^{\cdot+}$ $^3S^* + RH \rightarrow S^{\cdot+} + RH^{\cdot-}$
Reactant formations	
9. Peroxiradicals	$R^* + O_2 \rightarrow RO_2^*$ $RH^{\cdot+} + O_2 \rightarrow H^+ + RO_2^*$
10. Superoxide anion	$RH^{\cdot-} + O_2 \rightarrow RH + O_2^{\cdot-}$ $e_{aq}^{\cdot-} + O_2 \rightarrow O_2^{\cdot-}$
Oxidation	
11. Substrate stabilization	$RH, RO_2^* \rightarrow R(O_2)$
TYPE II MECHANISM	
Reactant formation	
7. Intermolecular exchange	$^3S^* + ^3O_2 \rightarrow ^1S + ^1O_2$
Oxidation	
8. Cellular oxidation	$^1O_2 + X \rightarrow X(O)$
CAROTENOID PROTECTION	
1. Singlet oxygen extinction	$^1O_2 + ^1CAR \rightarrow ^3O_2 + ^3CAR$

Sensitizer s: ^1S singlet ground-state; $^1S^*$, excited singlet state; $^3S^*$, excited state. Oxygen O_2 : $^3O_2$, triplet ground-state; $^1O_2$, excited singlet state. Substrate RH: $R(O_2)$, stable oxidized form. Cellular target X: $X(O)$, oxidized target. Carotenoid CAR: ^1CAR , singlet ground-state; ^3CAR , excited triplet state.

The photosensitizer, once excited, undergoes a series of simultaneous or sequential decays which result in *intramolecular transfer reactions*.

The decays may ultimately culminate in the release of highly reactive cytotoxic species, which cause irreversible exudation of some essential cellular component and destroy affected host tissues.



Reaction 3) is a **multi-step** process, where the initial photoexcitation of a **chromophore** (photosensitizer) S gives rise to an energy transfer to a target molecule T ($=^3O_2$), whose excitation will be responsible for subsequent molecular processes.

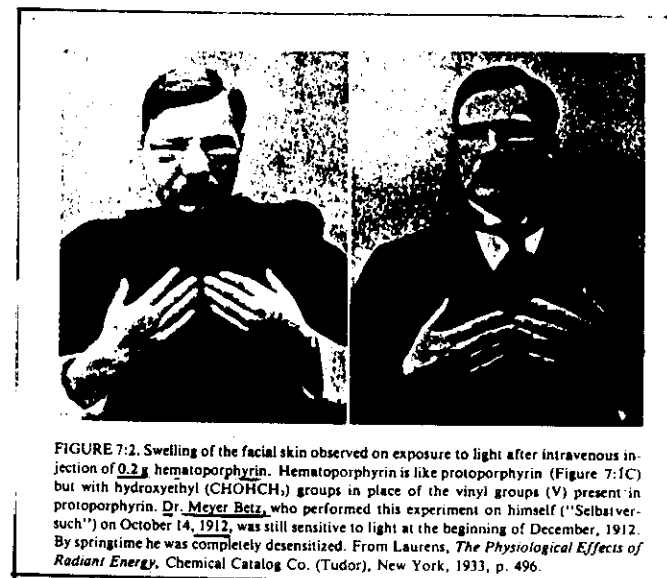
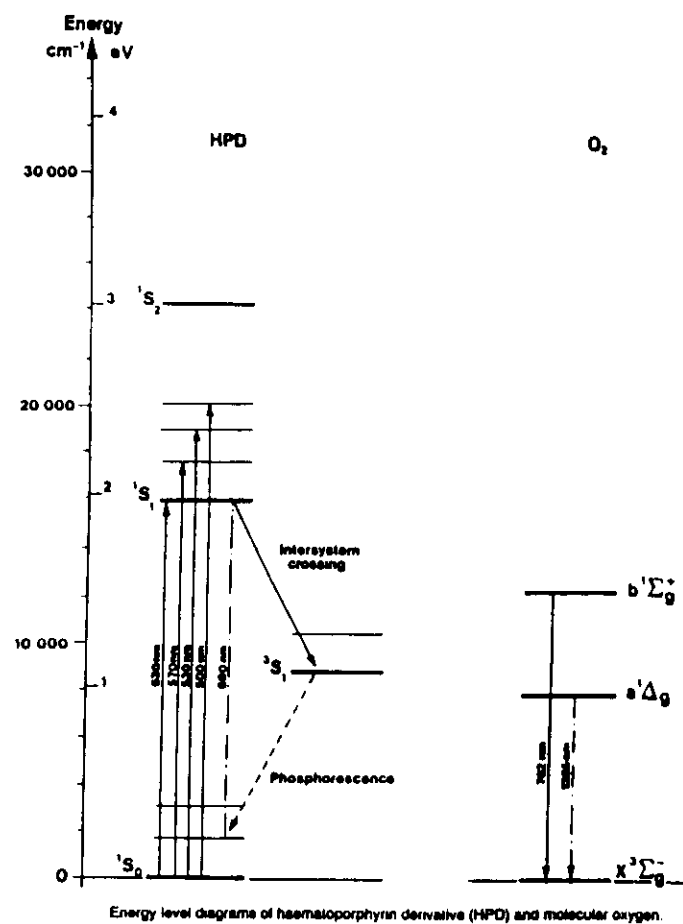
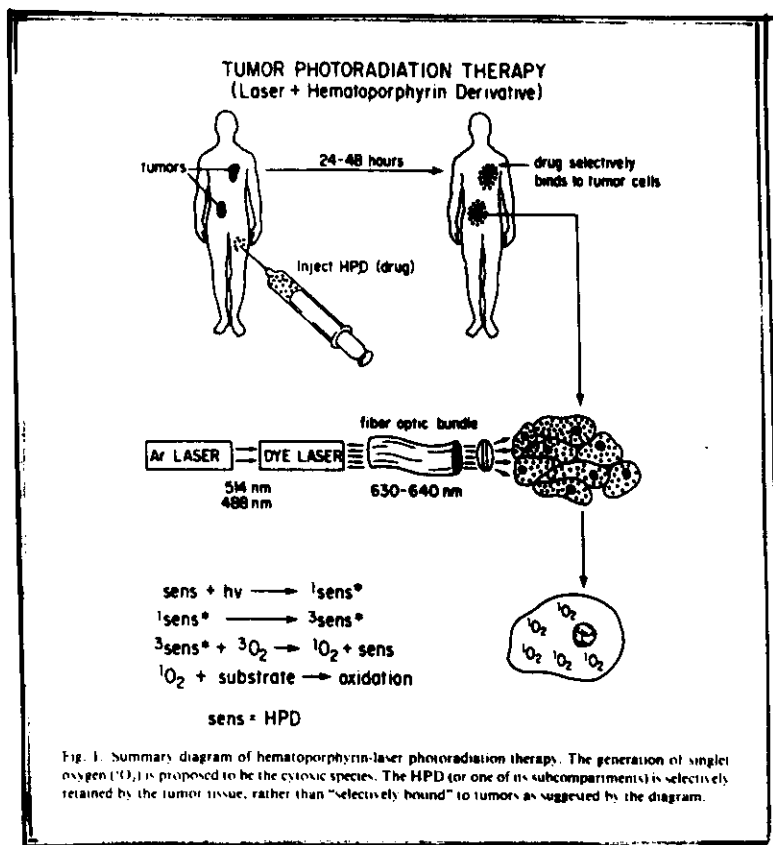
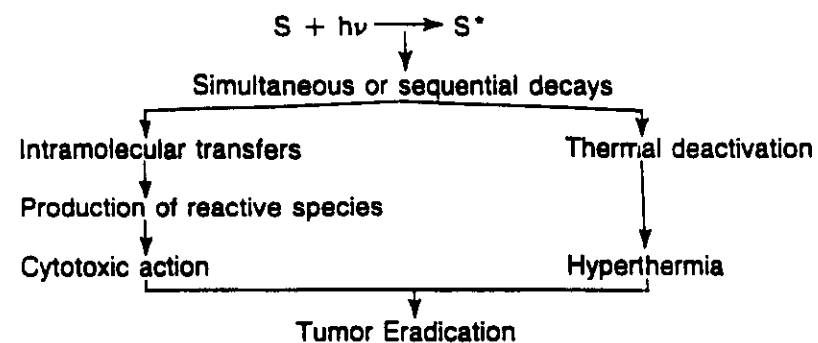


FIGURE 7:2. Swelling of the facial skin observed on exposure to light after intravenous injection of 0.2 g hematoporphyrin. Hematoporphyrin is like protoporphyrin (Figure 7:1C) but with hydroxyethyl ($CHOHCH_3$) groups in place of the vinyl groups (V) present in protoporphyrin. Dr. Meyer Betz, who performed this experiment on himself ("Selbstversuch") on October 14, 1912, was still sensitive to light at the beginning of December, 1912. By springtime he was completely desensitized. From Laurens, *The Physiological Effects of Radiant Energy*, Chemical Catalog Co. (Tudor), New York, 1933, p. 496.



Physical Principles of Photodynamic Therapy

- Administration of photosensitizer S
- Selective tumor retention of photosensitizer
- Irradiation by monochromatic source (laser)
- Resonant excitation of Photosensitizer



Photomechanical Interaction

The interaction of laser radiation with matter can lead to the generation of acoustic waves.

The electromechanical interaction involves a number of processes:

- * **thermoelastic expansion**
- * **mechanical recoil from ejected materials**
- * **plasma formation.**

Depending upon the type of interaction, the generated pressure waves can be either:

- * **acoustic waves**
i.e. low-pressure waves propagating with the speed of sound

or

- * **shock waves**
i.e. high-pressure waves propagating at supersonic speed.

The **intensity** of the laser pulse determines the mechanisms of the generation of acoustic waves.

Low intensity

* **thermoelastic effect**

At the lowest levels of energy input, the thermoelastic effect operates:

thermal expansion of heated material working againsts specimen inertia generates stresses at the boundary of, and within, the heated layer, sending **elastic waves** into the bulk of the material.

Intermediate intensity

* Vaporization

As absorbed energy increases, **vaporization** takes place:

* free surface

the recoils of atoms leaving **free surfaces** generates elastic waves, whilst

* inertial confinement

confinement and **expansion** in a liquid can produce high-amplitude pressure-waves.

Acoustic generation from the **thermoeleastic effect** is much weaker than the contribution from **vaporization**, but its onset is virtually **instantaneous**.

High intensity

* Ionization and plasma

Where energy densities or deposition rates are high enough **ionization** of the target medium and subsequent **plasma** formation can occur.

Plasma can be initiated by a variety of mechanisms in uniform media or by absorption at impurities.

Very high temperatures and pressures can be reached in such a plasma, e.g.:

- * **thausands** of degrees Kelvin, and
- * **millions** of atmospheres pressure

Plasma formation is followed by the generation of a shock-wave, which can disrupt tissue locally.

A **shock wave** differs *qualitatively* from an acoustic pressure transient.

It is characterized by a **supersonic speed** and a **very steep front** that for all practical purposes can be treated as a discontinuity in pressure, density, particle velocity and internal energy.

At the shock front pressure raises a few **kbars** within a distance of a few **nanometers**, resulting in pressure transients with risetimes of a few **picoseconds** (water).

A shock also changes the **thermodynamics state** of the medium in which it propagates in a different way than an adiabatic process does.

The large pressure gradients and the high translational velocity of the molecules within the shock front account for the **unique interactions** of the shock waves with matter.

Plasma formation and evolution by Optical breakdown (water)

The high peak intensity of short duration laser pulses leads to **optical breakdown**, followed by the formation of plasma.

a. plasma initiation

ionization + avalanche growth

The high absorbance of plasma facilitates the deposition of laser energy in the focal zone even in transparent media.

b. plasma expansion

Once generated, the plasma expands adiabatically with supersonic velocity, creating a high-pressure front.

c. shock wave separation

As the gases in the cavity cool, the expansion velocity of the plasma rapidly decreases and the high-pressure front (shock wave) separates from the cavity or bubble.

The expansion of the bubble continues until all the initial kinetic energy is transformed into the potential energy of the cavitation.

d. bubble collapse

Subsequently, the bubble implodes adiabatically under the external pressure of the liquid.

No The temperature and pressure inside the bubble rise again leading to a second explosion and the formation of a second shock wave.

Schematic representation of the shock wave generation during optical breakdown:

a. plasma initiation

b. plasma expansion

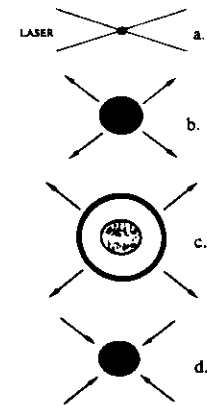
the hot plasma expands adiabatically with supersonic velocity

c. separation of the shock wave from the plasma

as the gas in the cavity cools, the expansion velocity of the plasma decreases and the shock wave separates from the bubble

d. collapse of the bubble

the bubble implodes adiabatically under the external pressure of the liquid.



Microscopic mechanism of optical breakdown

A high peak power laser pulse focused at a target locally generates high electric fields (10^6 - 10^7 V/cm), comparable to average atomic or intramolecular Coulomb electric fields.

Typical peak power densities:

- * 10^{10} W/cm² for nanosecond pulses
- * 10^{12} W/cm² for picosecond pulses

Such large fields induce a massive generation of free electrons, with a two step process.

- * the *initial phase* corresponds to a localized electron **seeding** by ionization involving a few electrons only;
- * the *second step* is represented by a **massive electron photoproduction**.

Ionization

For ionization mechanisms, energies of about 7 to 10 eV must be supplied to bound electrons in order to separate them from individual molecules.

In this initiation phase, ionization mechanisms differ, depending on pulse duration.

* Thermoionic emission

For short pulses (3-10 ns duration), ionization is caused by thermionic emission resulting from focal heating of the target, where local *temperatures* exceeding several 10,000°C is reached;

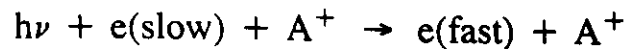
* Multiple photon absorption

For ultra-short pulses (20 ps), molecular ionization is obtained by non-linear processes (**multiple photon absorption**).

Electron avalanche growth

In the electric field of molecules or ions (required for energy/momentum conservation), already seeded free electrons absorb incoming photons and convert this energy into kinetic energy, thereby increasing their velocity.

The microscopic process is basically a **free-free absorption**:



(*inverse Bremsstrahlung effect*)

On colliding with neighboring molecules, rapidly moving free electrons ionize collision partners when their relative kinetic energy is sufficient and, hence, create extraneous free electrons:



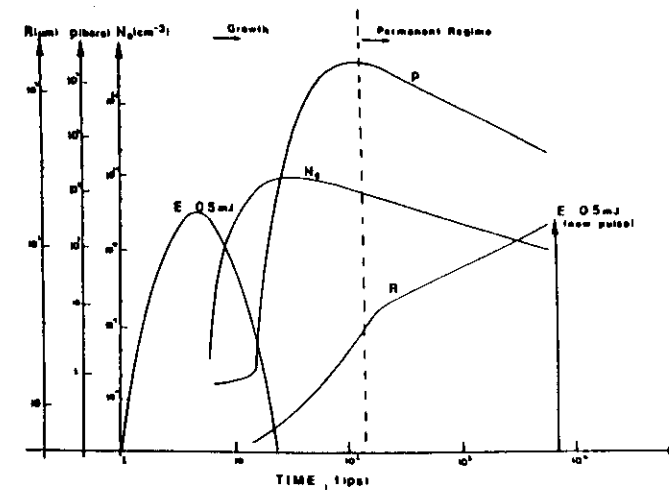
Each electron in turn absorbs more photons, accelerates, strikes more atoms or molecules, and ionizes them in an avalanche process with exponential growth.

In a few hundred picoseconds a very large free electron density (typically 10^{21} cm^{-3}) is thus created in the focal volume of the pulsed laser beam.

The process is termed **electron avalanche growth**.

Physical Principles of Laser-Induced Breakdown

• Short laser pulse focused at target	$I \sim \frac{(E_p / \tau_p)}{W_s^2}$
• High power density	$I \sim 10^{12} \text{ W/cm}^2$
• High electric field	$E = \left(\frac{2}{c\epsilon_0} I \right)^{1/2} \sim 10^8 \text{ V/cm}$
• Dielectric breakdown (multiphoton process)	$E_{\text{laser}} \sim E_{\text{ionization molecules}}$
• Plasma formation free electrons	$N_e \sim 10^{21} / \text{cm}^3 \quad T > 20000^\circ\text{C}$
• Spherical shock wave propagating at sound velocity	$P \text{ (bars)} \sim 13 E_p \frac{E_p \text{ (mJ)}}{R \text{ (mm)}}$ $A \sim 15 \cdot 10^8 \text{ mm/s}$
• Localized mechanical rupture for small radius	$P > \text{Yield strength of tissues}$



Temporal evolution of plasma parameters (electron number density N_e , plasma radius R , and pressure p), following a laser-induced breakdown with 0.5 mJ energy in a 25 psec pulse.

Threshold

The threshold for optical breakdown is higher for picosecond than for nanosecond pulses ~~than for nanosecond pulses~~:

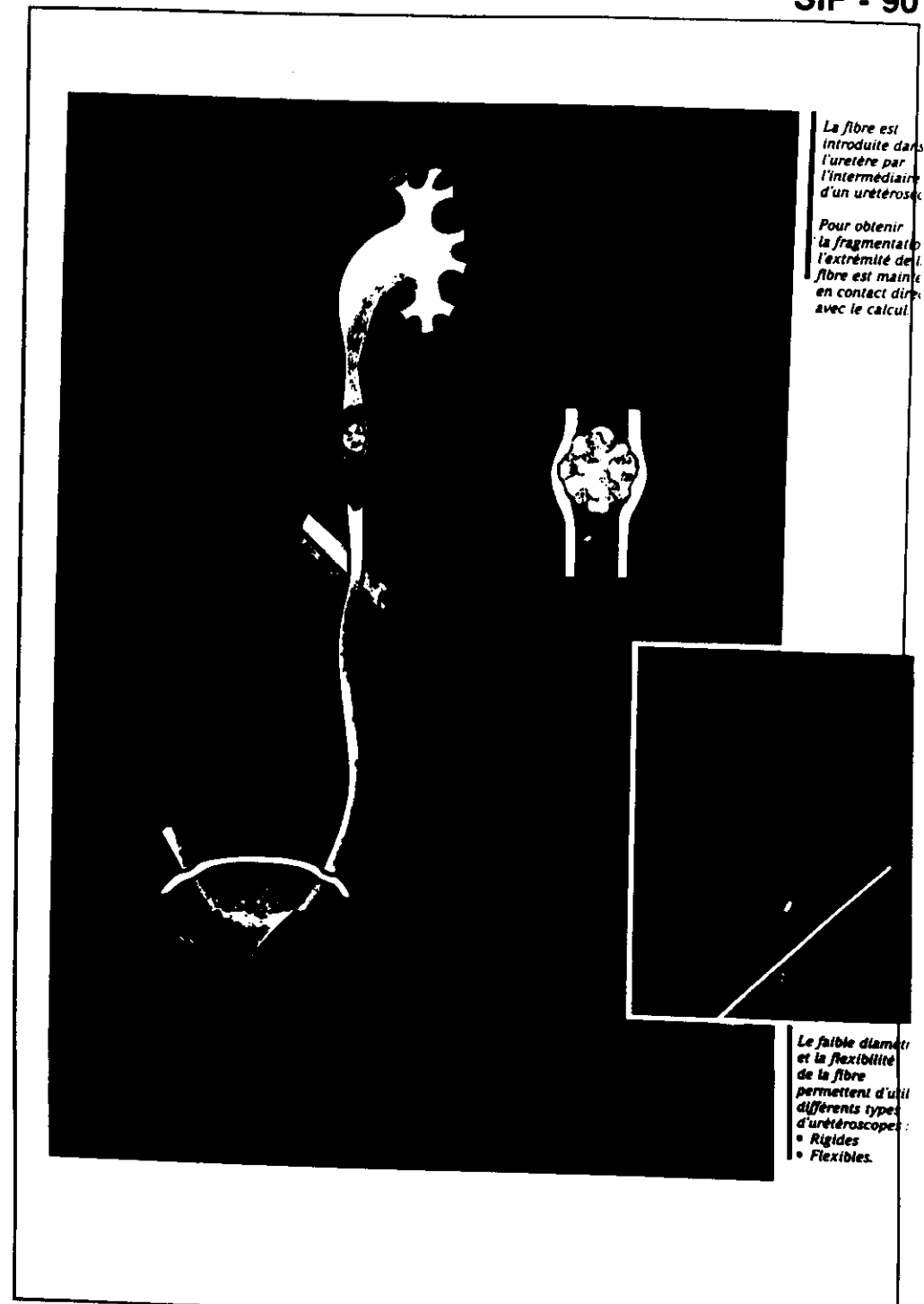
Air; Nd:YAG laser, $\lambda = 1.06 \mu\text{m}$:

$\sim 10^{14} \text{ W/cm}^2$ (single 25 ps pulse)

$\sim 10^{11} \text{ W/cm}^2$ (10 ns pulse)

In biologic solutions, these numbers are reduced by a factor of 100.

The total energy density delivered in achieving optical breakdown ($\sim 10 \text{ J/cm}^2$) is ultimately the same for a mode-locked pulse train and a Q-switched pulse, even though peak power density is, on the average, 100 times higher for picosecond pulses.

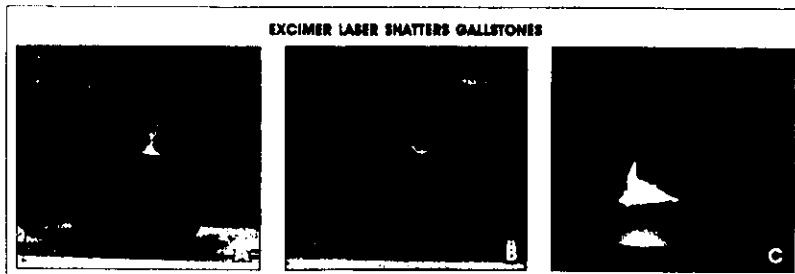


Fotoframmentazione UV
di calcolo in acqua

Laser UV : $\lambda = 308 \text{ nm}$

$E = 27 \text{ mJ/impulso}$

$\Delta t = 230 \text{ ns}$

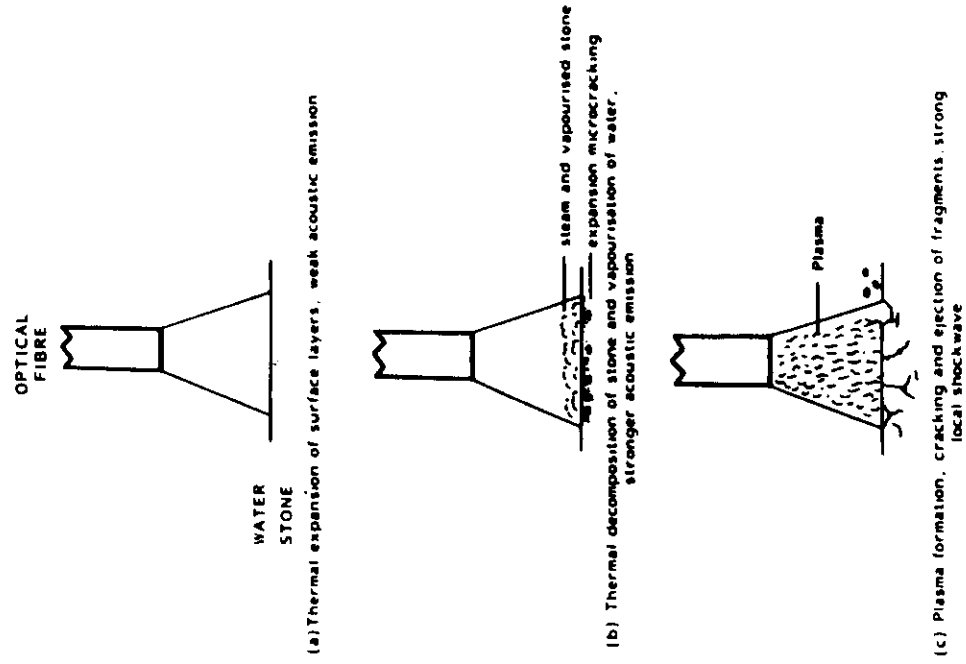


- a) Initial pulses penetrate the gallstone shell
- b) A hole is drilled after 100 pulses, enabling the fiber to enter the gallstone
- c) An additional 50 to 70 pulses crack the gallstone.



INTERAZIONE FOTOMECCANICA/6

Schema del meccanismo di FOTOROTTURA di un calcolo in acqua



SILC 91/lez

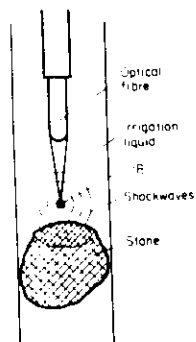


Fig. 2 Principle of the laser-induced shock wave lithotripsy (LISL). In front of the spherically shaped fibre tip a laser-induced breakdown (LIB) is released and in consequence shock waves are emitted which fragment the stone.

Tissue ablation

In this context the term **ablation** simply means the removal of tissue.

This may be by vaporization of the liquid and solid components by pyrolysis of macromolecules and/or spallation where tissue fragments are ejected during the the ablation process.

NO

The sequence of events that leads to laser ablation of tissue may vary depending on the optical and mechanical properties of tissue as well as the temporal and spatial characteristics of the laser beam.

Thermal ablation

Thermal ablation is a **non-equilibrium** thermodynamic process.

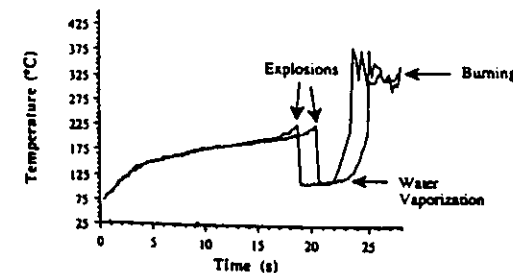
Continuous wave and pulsed laser ablation of tissue is described as an **explosive event**.

Continuous wave ablation

Phenomenology

- * **Absorption** of laser radiation rises tissue temperature over 100°C , where the onset of ablation occurs;
- * initially, **maximum** temperatures are at the **surface**; once ablation starts, the maximum temperature shifts **inside** the tissue;
- * tissue fluid is converted into steam at a pressure over 1 atm (**subsurface superheating**); fluids become **superheated**, pressure increases until an **explosive** event remove the tissue;

- * as hot tissue is **removed**, a cooler layer is exposed to the laser irradiation;
- * the temperature of the exposed layer **remains** at approximately 100°C while continued irradiation dehydrates the tissue;
- * the removal of water **decreases** the local **thermal conductivity** reducing heat conduction to the surrounding area;
- * Continued radiation rapidly **increases** the tissue temperature until it reaches about 300°C ; the tissue burns and carbonizes as nucleation sites form on the surface.



Surface temperatures of porcine aorta samples at center of 8 W argon irradiation. The beam diameter is 1.8 mm (LeCarpentier *et al.*, 1990).

Photosurgery

In the **clinical** procedure **coagulation** and/or **ablation** of the tissue must be obtained with **minimum thermal damage** to the non-irradiated healthy tissue.

This requires a **precise control** of temperature rise in the irradiated volume and in the surrounding zones: the temperature in the irradiated volume must reach the coagulation or ablation limit, while it must remain below the irreversible damage limit in the untreated tissue.

For this reason, there is a growing interest in the use of **short duration** (less than a few **ms**) pulses to ablate tissue.

Pulsed laser ablation

The rationale for favoring pulsed to cw irradiation are

- * the desire to produce a thermal event that is **shorter** than the **thermal relaxation** time of the tissue to reduce the zone of thermal damage;
- * the delivery of sufficient energy to ablate tissue with each pulse which removes the hot tissue **before** heat is transferred to surrounding tissue;
- * **precise** tissue cutting control; and
- * ablation of **dense** tissue such as bone or tooth by rapid heating and/or plasma formation.

Absorption coefficient and penetration depth

The photophysical parameter of interest is the

absorption coefficient α

and its

reciprocal $1/\alpha$

which measures the characteristic

absorption length

or

penetration depth

or

extinction length

of the biological tissue.

Thermal diffusion length

Another important parameter of interest is represented by the

thermal diffusion length, L

of the sample, defined as

$$L^2 \sim 4 \kappa t$$

where:

t = time

κ = thermal diffusivity (which depends on thermal conductivity, specific heat, and density).

Thermal relaxation time τ

If the pulse duration is **much shorter** than the characteristic time τ that the heat needs to diffuse along a length nearly equal to the penetration depth $1/\alpha$ of the optical radiation,

the optical energy of the pulse remains **trapped** in a volume S/α (S = beam cross-section), where it produces a high temperature increase.

By equating the thermal diffusion length L to $1/\alpha$ we obtain the expression of τ

$$\tau \sim 1/4\kappa\alpha^2$$

τ = thermal relaxation time of the tissue

Table 2 Optical Data on Basic Coefficients (in cm^{-1}) for Absorption (α), Scattering (β), and Attenuation (μ)^a

		KrF (248 nm)	Ar (514 nm)	He-Ne (633 nm)	Nd:YAG (1060 nm)	CO ₂ (10.6 μm)
Water	α				0.3	1200
Human dermis in vitro	α		8	7.1	5	
	β		83	60.7	20	
	μ		37.4	30.2	15	
Blood thrombus	α	850 ^(a)	110	4.5	6	200 ^(a)
	β	100 ^(a)	13	9	3	2
	μ	940	122.3	10.1	8.5	202
Fibrous plaque	α		18	2	1.4	200 ^(a)
	β		19	12	2.3	2
	μ		31.7	7.2	2.9	202
Vessel wall	α		11	1.8	0.9	
	β		11	6.3	2.8	
	μ		19	5.1	2.4	

^a Computed from the Kubelka-Munk theory applied to various biological media^{28,29} at KrF, argon, He-Ne, Nd:YAG, and CO₂ laser wavelengths.
(a) Estimated values.

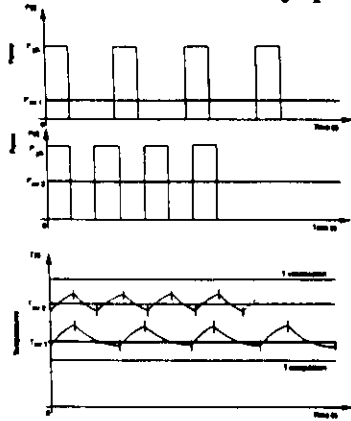
Table 3 Target Relaxation Times (in sec) for Various Biological Media at KrF, Argon, He-Ne, Nd:YAG, and CO₂ Laser Wavelengths

	KrF (248 nm)	Ar (514 nm)	He-Ne (633 nm)	Nd:YAG (1060 nm)	CO ₂ (10.6 μm)
Water				2×10^3	12×10^{-6}
Human dermis in vitro		0.12	0.2	0.78	
Blood thrombus	0.2×10^{-3}	12×10^{-3}	1.7	2.4	4.3×10^{-3}
Fibrous plaque		0.17	3.4	21	4.3×10^{-3}
Vessel wall		0.48	6.7	30	

Photocoagulative necrosis

For applications where a **photocoagulative necrosis** is needed, the temperature of the biologic material must be kept **above** the coagulation value for a certain time.

By adjusting the **duration**, the **energy content**, and the **repetition rate** of the light pulse, the **temperature rise** in the irradiated volume and in the adjacent zones can be **controlled** in a sufficiently precise way.



According to the following scheme, the average tissue temperature can be maintained above the **coagulation** temperature and below the **ablation** limit by adjusting the repetition rate of a suitably pulsed laser system.

Selective photothermolysis

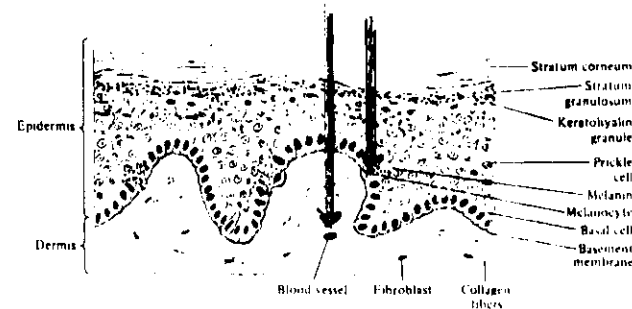
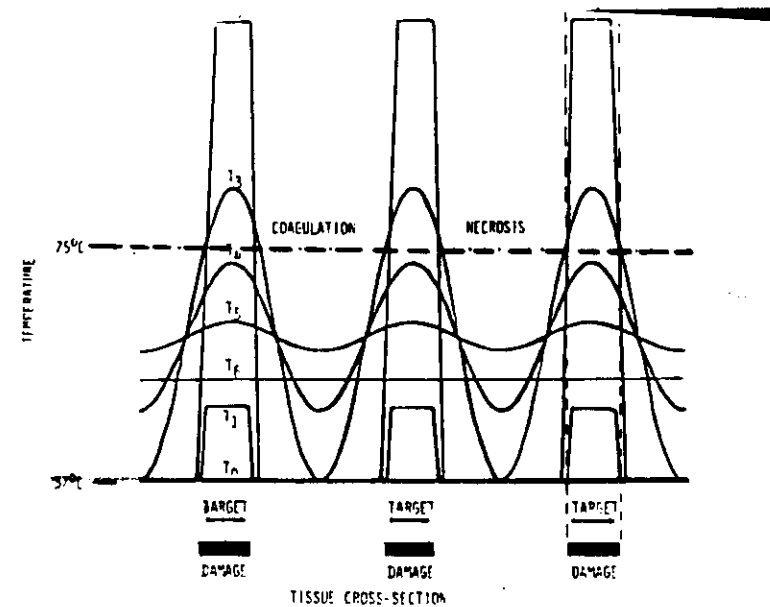


Fig. 4-2 Diagrammatic cross section of epidermis. This drawing is a magnification of part of Fig. 4-1. (From Partish, J.A. *Dermatology and Skin Care*. Copyright McGraw-Hill, Inc., 1975. Used with permission.)



High irradiance delivery

If the irradiance delivered to the target is above 10^8 W/cm^2 , the strong electric field forms a **plasma**.

The plasma can develop in a few ns and once it forms, the **laser irradiation** is **absorbed** in the plasma and **does not** penetrate the tissue.

As a results, the amount of tissue ablated as a function of fluence per pulse **plateaus**.

The phenomenon occurs at **all wavelengths**, and the threshold for plasma formation is a function of the absorption properties of the material.

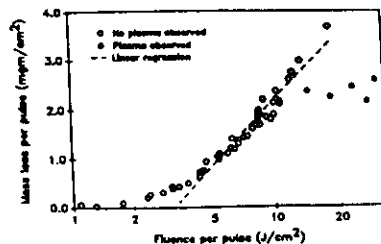


Figure 13. The mass of guinea pig skin removed per unit area by a TEA CO_2 laser focused to a $1.6 \times 2.0 \text{ mm}$ spot on the tissue surface. The dotted line represents a linear relationship between the mass of tissue removed and the logarithm of the fluence (Walah and Deutsch, 1988 with permission).

Models of pulsed laser ablation

Blow-off model

The simplest model for pulsed laser ablation is a **blow-off** model, in which ablation is assumed to occur **instantaneously** and extend to a **depth** at which the fluence falls to a **threshold value**.

The model ignores numerous dynamic effects, such as

- transient changes in the optical properties of tissue target
- absorption by the ablation plume
- heat conduction into the target, and
- phase changes.

The blow-off model often **fails** to describe the measured **etch depth vs fluence** curve over its entire range.

In addition, it **fails** to describe the observed **thermal damage** to tissue, which is uniform along the sides and bottom of the crater.

Liquid-layer model

The liquid-layer model remedies some of these defects.

It is a steady-state model, typically applicable to pulse durations of several **hundred microseconds**.

It considers the fact that laser heating, in addition to causing vaporization of tissue, results in a **liquid layer** which may be expelled from the ablation crater by radial pressure gradients resulting from a Gaussian beam profile.

The **hot liquid-layer** can act a **heat source** for tissue damage.

The model predicts a **uniform damage layer** along the walls of the ablation crater, in agreement with experiment.

Advanced models

More refined models take into account a variety of complicating phenomena, such as

- * **shielding of the target by plasma formation**
- * **transient changes in optical absorption for both UV and IR laser ablation, and**
- * **heat conduction during the ablating pulse.**

Both UV and IR pulsed laser ablation have explosive nature.

Wavelength effects

An important difference between **UV** and **IR** ablation is the **chromophore** that absorbs the laser light.

For **UV wavelengths** the chromophores are **protein** and **DNA**, whereas the absorbing chromophore for **IR radiation** is **water**.

Dehydration will **not** affect **UV ablation**, but it may **drastically** alter the **penetration depth** of **IR** wavelengths.

As dehydration takes place, the penetration depth will depend upon the concentration of **OH** and amine chromophores in the tissue.

Inertial confinement

Inertial confinement occurs when the laser pulse length is **short** enough that the laser heated volume **cannot expand** during the pulse.

This results in heat deposition at **constant volume**, with the resulting **rise** in internal pressure and finally, **fragmentation**.

This ablation pathway is substantially **more efficient** than the **constant pressure** path which require the vaporization of tissue water.

NO

Nonlinear effects

Nonlinear effects greatly complicate laser ablation.

Plasma formation can

- * impede delivery of laser energy to a target,
- * launch shock waves, and
- * initiate cavitation.

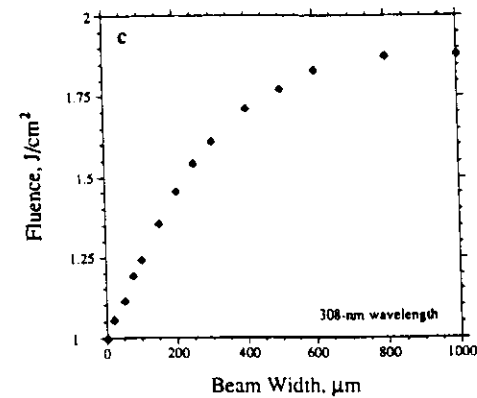
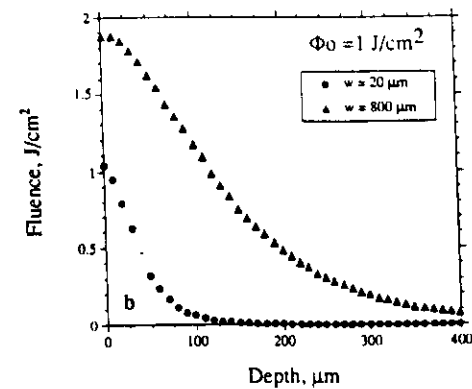
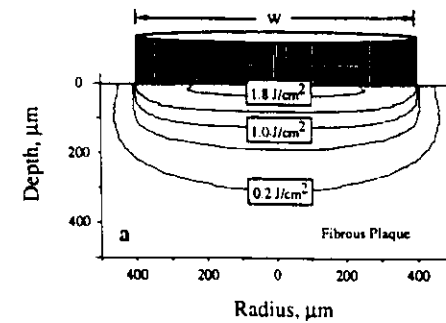


TABLE 1. Optical Properties of Aorta, Fibrous Plaque (FP), and Normal Zone (NZ) Measured at 308 nm*

Optical properties (coefficient)	NZ, FP	NZ, FP
	Room T $\leq 35^\circ\text{C}$	After 85°C heating
μ_a , cm^{-1}	33, 24	44, 34
$\mu_s(1-g)$, cm^{-1}	77, 81	270, 272
μ_{eff} , cm^{-1}	104, 87	204, 177
δ , μm	96, 115	49, 57
R_{eff} , %	11.5, 15.5	22, 26
Φ_{max} , %	1.75, 1.9	2.6, 2.8

*Natural variation in the optical properties of human aorta is about 30%.

Optical Properties and Energy Pathways

TABLE 2. Energy Pathways in Aorta, Normal Zone (NZ), and Fibrous Plaque (FP) During XeCl Laser Irradiation Under Experimental Conditions (Air/Quartz/Tissue)*

Aorta tissue type	Specular reflectance (R_{sp})	Diffuse reflectance (R_{ds})	Absorbed fraction (f_a)	Escaped fluorescence (F_{esc})	Photochemical modification (η)	Heat generation (q)
NZ	0.044	0.0115	0.841	0.008	0.02	0.972
FP	0.044	0.0155	0.801	0.016	0.02	0.964

* $1 = R_{\text{sp}} + R_{\text{ds}} + f_a(F_{\text{esc}} + \eta + q)$

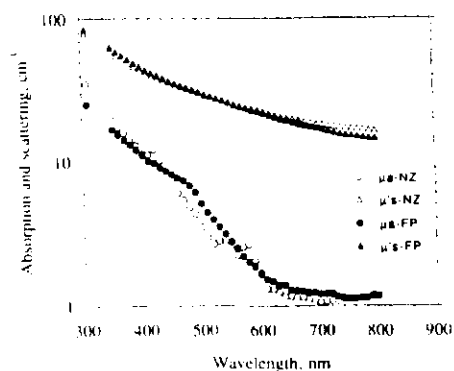


Fig. 4 Absorption (μ_a) and effective scattering (μ_s) spectra for normal arterial wall, NZ, and fibrous plaque, FP.

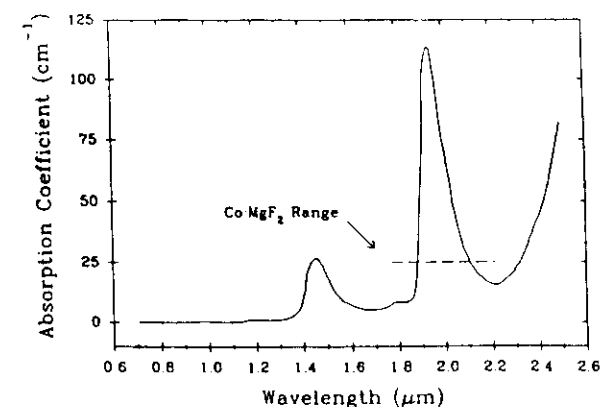
FOTOABLAZIONE IR /1

SPETTRO D' AZIONE

Intervallo spettrale : 1.81 - 2.14 μm

(picco principale H_2O : 1.94 μm)

(laser Co:MgF₂)



La densità di energia di soglia per l'ablazione risulta:

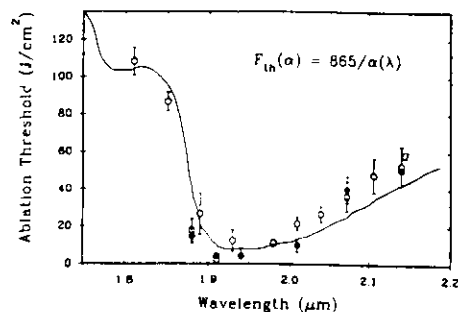
* tessuti soffici (alto contenuto H_2O)

inversamente proporzionale al coefficiente di assorbimento dell'acqua;

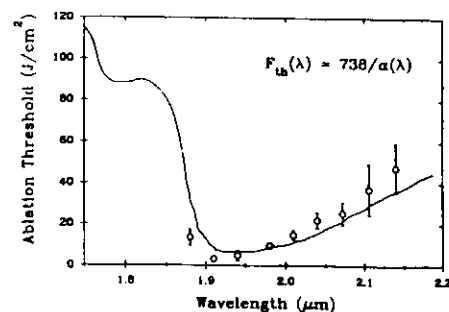
* tessuti ossei (basso contenuto di H_2O)

scarsa dipendenza dalla lunghezza d'onda.

SPETTRO D' AZIONE / 1

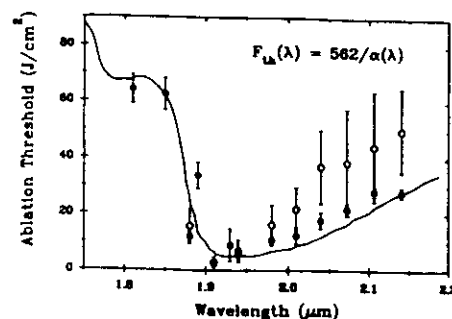


The dependence of ablation threshold on wavelength for resected calf corneas in situ. The data were recorded using the optical pump-probe technique (open circles) and framing camera technique (solid circles). The solid curve represents a least-squares fit to the optical pump-probe data assuming that $F_{th} = a/\alpha$.

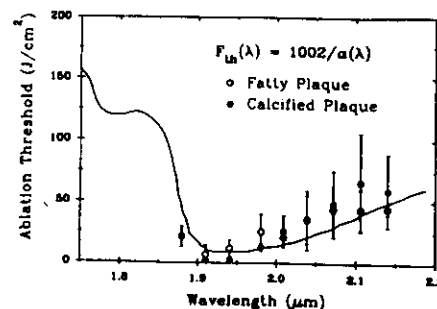


The dependence of ablation threshold on wavelength for resected human aortas. The data were recorded with the optical pump-probe technique only. The solid line represents a least-squares fit assuming that $F_{th} = a/\alpha$.

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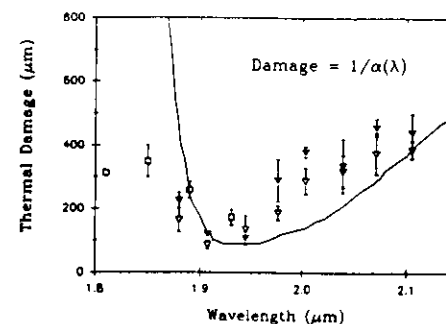
The dependence of ablation threshold on wavelength for resected chicken livers. The data were recorded using the optical pump-probe technique (open circles) and framing camera technique (solid circles). The solid curve represents a least-squares fit to the framing camera data assuming that $F_{th} = a/\alpha$.



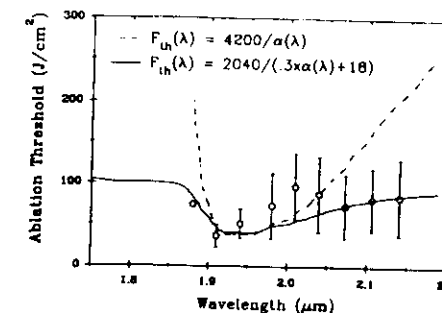
The dependence of ablation threshold on wavelength for resected diseased human aortas. The data were recorded with the optical pump-probe technique only. The solid line represents a least-squares fit to the fatty plaque data assuming that $F_{th} = a/\alpha$.

SPETTRO D' AZIONE : DANNO TERMICO

Intervallo spettrale : 1.81 - 2.14 μm

(picco principale H₂O : 1.94 μm)(laser Co:MgF₂)

The dependence of thermal damage on wavelength for resected calf corneas. The measurements were taken from tissue samples fixed in formalin (open triangles and open squares) and Bouin's solution (filled triangles). Except for the open squares, all fluences were 7.3 ± 2.6 times the ablation threshold found at each wavelength (see Fig. 4). The open squares used fluences of 2.6, 3.0, 12.8, and 36 times the ablation thresholds found at 1.81, 1.85, 1.89, and 1.93 μm respectively. The solid line represents a least-squares fit to the open and filled triangles, assuming that the damage depth varies as α^{-1} .



The dependence of ablation threshold on wavelength for the resected rabbit ulna bones. The data were recorded with the optical pump-probe technique only. The dashed line represents a least-squares fit assuming that $F_{th} = a/\alpha$. The solid curve represents a modified fit to the data assuming that a second chromophore having a constant absorption coefficient exists (see text).

Cornea : debole dipendenza da $1/\alpha$ Osso : indipendente da λ

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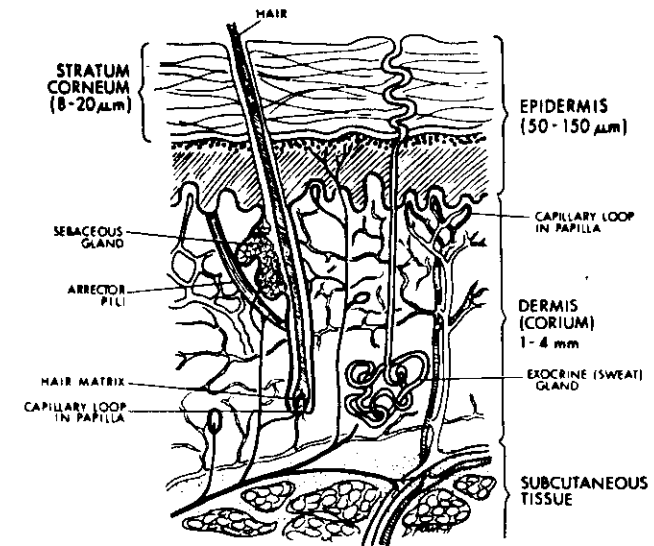
Optical models of tissues

Both diagnostic and therapeutic applications of light require **precise modelling** of tissues.

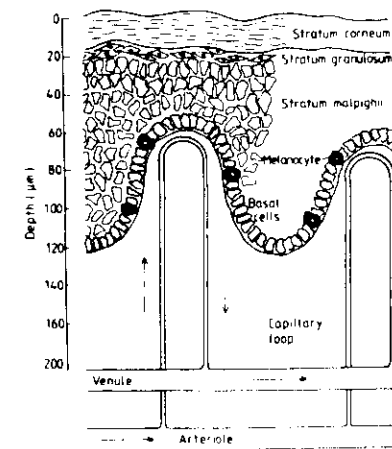
Diagnostic devices use some form of energy to interrogate the tissue being examined, e.g. sound, heat, microwaves, light, X-rays.

Until recently there have been **well-developed** theoretical backgrounds for propagation of all these energy forms in biological tissue **except light**.

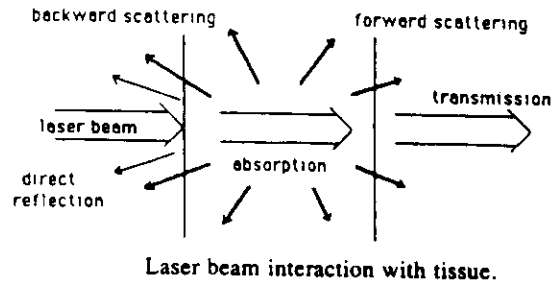
Biological tissues are **complex** optical media, and the study of light propagation in tissues is made difficult by the high inhomogeneities of the biological structures, the modification of the optical and thermal properties of these structures produced by the therapeutic light, etc..



Anatomical structure of the skin. The actual thicknesses of different layers vary with individuals and depend upon the region of the body. See Table 3-3 for thickness of various layers of human skin.



A schematic cross section of human skin perpendicular to the skin surface

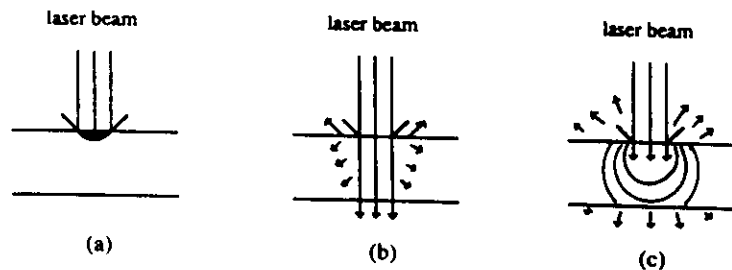


The **EM wave interaction** with biological media varies depending upon **wavelength** and the **optical properties** of the tissue.

For wavelengths that are **much longer** than **cell diameters** (frequencies lower than 300 GHz) where there is little scattering from the cellular structures, and therefore reflection,

absorption and transmission

are described best using **EM theory**.



Scattering and absorption of laser light. (a) Absorption dominant. (b) Equal scattering and absorption. (c) Scattering dominant.

In the optical spectral band substantial *multiple scattering* in tissue occurs due to the comparable size of cells with respect to the irradiation wavelength.

For optical wavelengths, the **radiative transfer theory** (Chandrasekhar, 1960; Ishimaru, 1978) provides a practical description for the optical propagation of light in tissue.

Radiative transfer theory

Radiative transfer theory gives an adequate description of light **absorption** and **scattering**.

The theory requires that the scatterers are far enough apart to scatter **independently** from each other.

The **radiative transfer** equation originates from an energy balance of the radiance, incident upon a cylindrical volume with infinitesimal length:

$$\frac{dL(r, \hat{s})}{ds} = -(\mu_a + \mu_s) L(r, \hat{s}) + \mu_s \int_{4\pi} p(\hat{s}, \hat{s}') L(r, \hat{s}') d\omega'$$

$L(r, \hat{s})$ = **radiance** at r and in direction $\hat{s}$ [i.e., the (local) power density, flowing in a certain direction $\hat{s}$, confined within an infinitesimal solid angle, $d\omega$]

$$\frac{dL(r, \hat{s})}{ds} = -(\mu_a + \mu_s) L(r, \hat{s}) +$$

$$+ \mu_s \int_{4\pi} p(\hat{s}, \hat{s}') L(r, \hat{s}') d\omega'$$

κ

- * the left hand side term represents the **rate of change** of the radiance $L(r, \hat{s})$ at r and in direction $\hat{s}$, after traversing a cylindrical volume of infinitesimal cross section and infinitesimal length ds (in the direction of $\hat{s}$);
- * the first terms in the right hand side represents the **decrease** in the radiance transversing the length ds due to **absorption and scattering**;
- * the second in the right hand side represents the **increase** in the radiance due to **scattering** from the radiance from all other directions $\hat{s}'$ into $\hat{s}$ at position r .

In this model the propagation medium is specified by three quantities:

- * **absorption coefficient, μ_a ;**
- * **scattering coefficient, μ_s ;**
- * **phase function $p(\hat{s}, \hat{s}') = p(\theta)$**

[probability density function giving the probability of photon scatter from an initial propagation direction to a final direction $\hat{s}'$].

The first moment of the phase function is the average cosine of scattering angle, denoted by **g (anisotropy factor)** :

$$g = \int_0^\pi \int_0^{2\pi} p(\theta) \cos\theta \sin\theta \, d\theta \, d\phi$$

$g = 1$ means totally forward scattering;

$g = 0$ means isotropic scattering.

Typical tissues have g values in the range:

$$0.7 - 0.95$$

($\cos 45^\circ = 0.71$, $\cos 18^\circ = 0.95$).

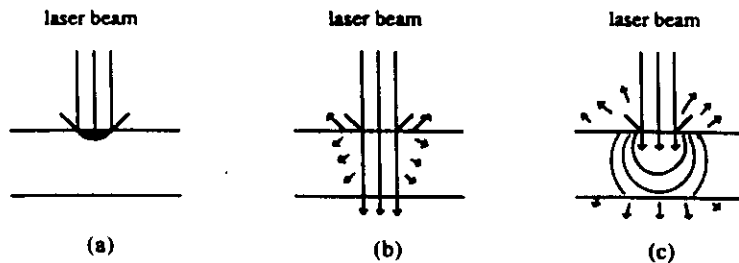
Possible interactions of light and tissue are illustrated in the Figure.

Fresnel reflection

A small percentage, usually about 5% of a normally incident laser beam is reflected (Fresnel reflection) from the surface due to a mismatch in refractive index.

Multiple scattering and absorption

The rest of the beam is transmitted into the tissue and encounters the process of multiple scattering and absorption.



Scattering and absorption of laser light. (a) Absorption dominant. (b) Equal scattering and absorption. (c) Scattering dominant.

The **degree of scattering** depends upon the **wavelength** of the laser beam and the **optical properties** of the tissue.

Absorption >> scattering

UV wavelengths of the excimer lasers:

190 - 300 nm

and the **IR** wavelengths of Ho:YAG, Er:YAG and CO₂ lasers:

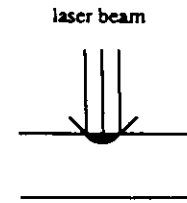
2 - 10 μm

are highly absorbed in tissue.

Penetration depth of these wavelengths is

$\sim 1 - 20 \mu\text{m}$

At these wavelengths, scattering is not significant compared to absorption.



Absorption ~ scattering

For wavelengths between

450 and 590 nm

the penetration depth of the laser beam is approximately

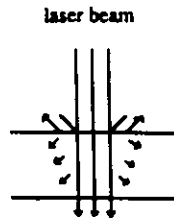
0.5 - 2.5 mm.

Both absorption and scattering are substantial, and light in tissue has a strongly collimated component surrounded by a region where light is multiply scattered.

The **back scattered** component of light is a major component of the total measured reflectance. Measurements of

15 - 40 %

of the incident beam are typical for these wavelengths.



Absorption < < scattering

Between

590 nm and 1.5 μ m

scattering dominates absorption and the penetration depth varies from

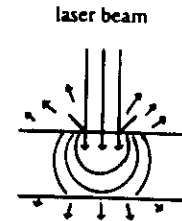
2.0 - 8.0 mm.

As the light passes through the tissue, the collimated structure of the beam is replaced by a completely diffuse light.

Backscattering is markedly increased and the range of total measured reflected light is as high as

35 - 70%

of the incident light.



Solutions of the Transport Equation

A **general** solution of the integro-differential *radiative transfer equation* is not known.

Analytical solutions for situations of interest in clinical laser medicine are generally not available.

Solutions are available under restricted conditions: **uniform irradiation**, **absorption** or **scattering strongly dominant**.

Approximate solutions

The solutions in transport theory are based on

1-D models,

where **uniform** irradiation is assumed,
and

3-D models,

like the *diffusion approximation*, where the scattering coefficient μ_s , the absorption coefficient μ_a , and the light scattering anisotropy, g , are calculated.

Other models, such as

Monte-Carlo simulation

have become popular.

Both these models, Monte Carlo simulation and diffusion theory, are based on the assumption that **photons** propagating through tissue can be treated as **neutral particles** and that wave phenomena can be disregarded.

This assumption is not strictly justified, but, nevertheless, models based on it have been **successfully** applied to tissue optics.

In both models, **polarization**, **inelastic scattering**, and **fluorescence** are **ignored**, and the propagation medium is specified by the three quantities: μ_a , μ_s and g .

Strong absorption

When tissue absorption is substantially larger than scattering transport theory is simple. The fluence rate in tissue decreases **exponentially** with increasing depth according to Beer's law:

$$I_c(z, r) = I_L(r) (1 - r_{sp}) \exp(-\mu_a z)$$

where r_{sp} is the specular reflection coefficient (Fresnel reflection).

Experimentally μ_a can be determined by measuring the **transmittance** through a slab of material. An experimental problem can be that the thickness should be **extremely small** when μ_a is **large** (for example, soft tissue has at $10.6 \mu\text{m}$ an absorption coefficient of $\sim 60 \text{ mm}^{-1}$; in this case a thickness of $38 \mu\text{m}$ yields a 10% transmittance).

Strong scattering

Diffusion theory

The diffusion equation is a differential equation for the fluence rate which can be derived from the full Boltzmann transport equation when **scattering events are much more probable than absorption events**.

This is the case for mammalian tissues, in the **RED** and **NIR** regions of the spectrum.

$$\left[\frac{d^2 \phi_d(z,r)}{dz^2} + \frac{d^2 \phi_d(z,r)}{dr^2} + \frac{1}{r} \frac{d\phi_d(z,r)}{dr} \right] - 3\sigma_a [\mu_a + \sigma_s(1-g)] \phi_d(z,r) = -3\sigma_a [\mu_a + (1+g)\sigma_s] I_c(z,r) \quad (7)$$

(for cylindrical symmetry)

$\phi_d(z,r)$ = diffuse light fluence rate.

The derivation of the diffusion equation requires the assumption that the radiance is **weakly anisotropic**.

Unfortunately, the diffusion approximation is **not accurate** for values of $g > 0.9$. This is due in part to difficulties in modelling backscattering.

The diffusion equation can be solved **analytically** or **numerically** with appropriate boundary values conditions such as the specular reflectance of the collimated source and internal reflection of diffuse light at tissue-air interfaces.

Inverse problem

Determination of the optical parameters (absorption, scattering, and phase function) requires **not only** the solution to the transport equation (or a suitable approximation) for an experimental geometry (e.g. a thin slab of tissue), but also an

inverse solution

that relates measurements such as reflection and transmission to the optical properties.

Such methods have only be derived recently, usually under conditions that **scattering dominates over absorption** (diffusion approximation).

Because of the simple form of the analytic solution, the **inverse** problem of determining the **absorption** and **scattering** coefficients from **reflection**, **transmission**, and tissue thickness measurements has been frequently used.

$$S_{KM} = \frac{1}{bt} \left[\frac{1 - R_d (a - b)}{T_d} \right]$$
$$K_{KM} = S_{KM} (a - 1)$$

where

$$a \equiv \frac{1 + R_d^2 - T_d^2}{2R_d}$$
$$b \equiv \sqrt{a^2 - 1}$$

$R_d \equiv$ diffuse reflection coefficient

$T_d \equiv$ diffuse transmission coefficient

$t \equiv$ tissue thickness

Strong scattering

For collimated irradiation, Beer's law and K-M model fail to account for the beam broadening of laser light in tissue.

Beer's law does not include a component for back scattering: local space irradiance is **always less** than the incident intensity.

Conversely, K-M model **overestimates** the space irradiance, especially at the **center** of the beam.

Strong scattering

Slab geometry

Transport equation:

$$\mu \frac{dI(z, \mu)}{dz} = -(\sigma_a + \sigma_s)I(z, \mu) + \frac{(\sigma_s + \sigma_a)}{2} \int_{-1}^1 d\mu' I(z, \mu') p(\mu, \mu'),$$

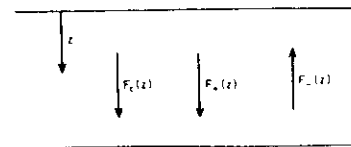
Diffusion approximation:

$$I(z, \mu) = I_c(z) \delta(1-\mu) + I_d(z, \mu)$$

$$I_c(z) \equiv \text{collimated intensity}$$

$$I_d(z, \mu) \equiv \text{slightly anisotropic intensity}$$

$$\mu \equiv \cos \theta$$



Slab geometry

Diffusion approximation

$$\frac{dF_c(z)}{dz} = -(\sigma_a + \sigma_s)F_c(z),$$

$$\frac{dF_+(z)}{dz} = -\{2\sigma_a + \frac{1}{2}(\sigma_a + (1-g)\sigma_s) - \sigma_s\}F_+(z) + \{\frac{1}{2}(\sigma_a + (1-g)\sigma_s) - \sigma_s\}F_-(z) + \frac{\sigma_s}{4}(2+3g)F_c(z),$$

*

$$\frac{dF_-(z)}{dz} = -\{2\sigma_a + \frac{1}{2}(\sigma_a + (1-g)\sigma_s) - \sigma_s\}F_-(z) + \{\frac{1}{2}(\sigma_a + (1-g)\sigma_s) - \sigma_s\}F_+(z) + \frac{\sigma_s}{4}(2-3g)F_c(z).$$

The diffusion part of eq.(*):

$$U_d \equiv 2[F^+ + F^-]$$

(diffuse fluence rate) obeys to a diffusion equation with $F_c(z)$ as source (neutron diffusion).

Experimental determinations

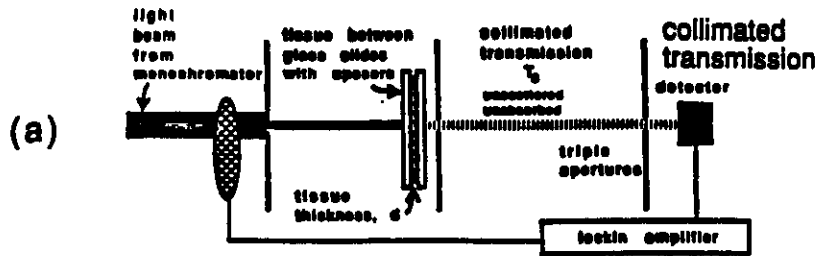
Reliable methods to measure the optical parameters for strongly scattering materials have **only recently** been developed.

Determination of the three independent parameters μ_a , μ_s , and g requires **three independent** measurements, usually:

- * the collimated attenuation coefficient for a thin slab of tissue
- * the diffuse reflectance
- * the diffuse transmittance.

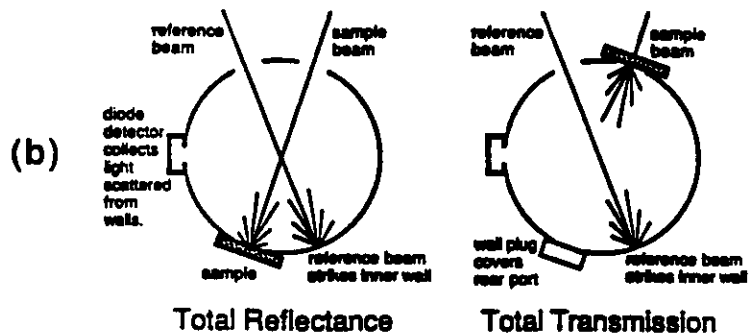
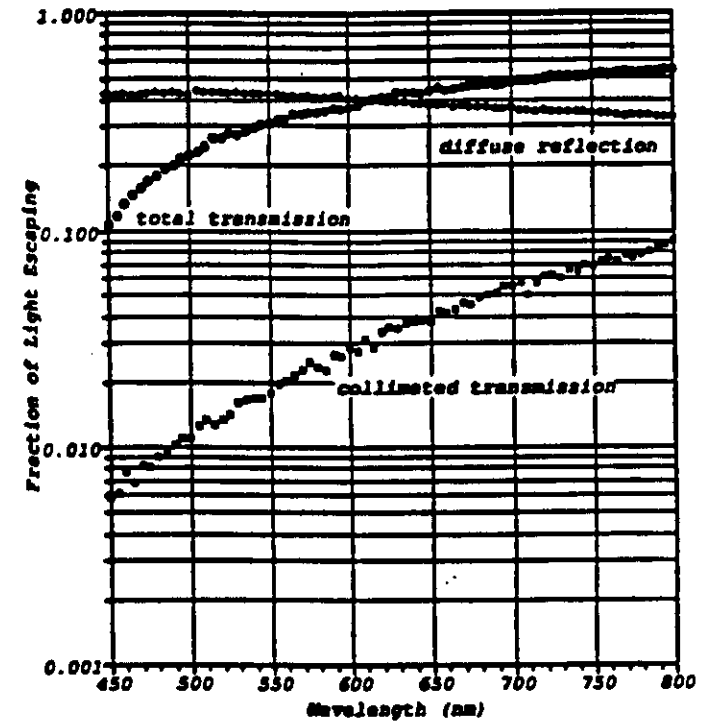
Experimental determination of the optical properties of (*in vitro*) tissues can be performed in an **integrating sphere** arrangement by measuring the percentages of light reflected and transmitted as a function of wavelength.

sfera



(a) Total attenuation experiments measure the attenuation of a narrow beam by both absorption and scattering in a thin sample ($\leq 100 \mu\text{m}$ thickness).

Optical measurements of bloodless dermis



(b) Integrating sphere

experiments measure the total transmission (T_t) and total reflectance (R_t) from a thick sample ($200\text{--}1000 \mu\text{m}$ thickness). The diffuse reflectance (R_d) is calculated: $R_d = R_t - r_{sp}$, where r_{sp} is the specular reflectance from the sample surface.

Method to determine the transport parameters

$$\mu_a (\equiv \sigma_a), \mu_s (\equiv \sigma_s), g \equiv \langle \mu \rangle \equiv \cos \theta$$

Diffuse irradiation

Thin slab of tissue; integrating sphere:

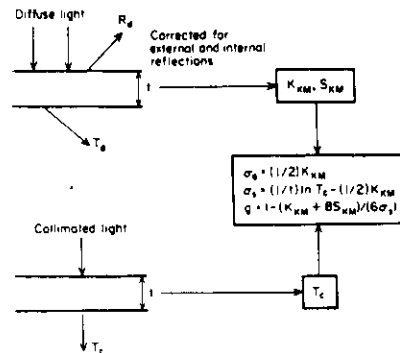
$$K_{KM} = 2 \mu_a$$

$$S_{KM} = (3/4)(1-g)\mu_s - (1/4)\mu_a$$

Collimated irradiation

$$-\ln[T_c(t)] = \mu_q t \quad \mu_q \equiv \mu_a + \mu_s$$

(any scattering event causes the photon to miss the detector).



Scattering about equal to absorption

No analytical solution or reasonable approximation is available to the transport equation for $\mu_a \sim \mu_s$ for an incident finite laser beam.

Such solutions are now available however from Monte Carlo numerical techniques.

Methods to determine μ_a, μ_s and $p(\theta)$ or g when $\mu_a \sim \mu_s$ have not received the attention that has been given to the condition $\mu_a \gg \mu_s$.

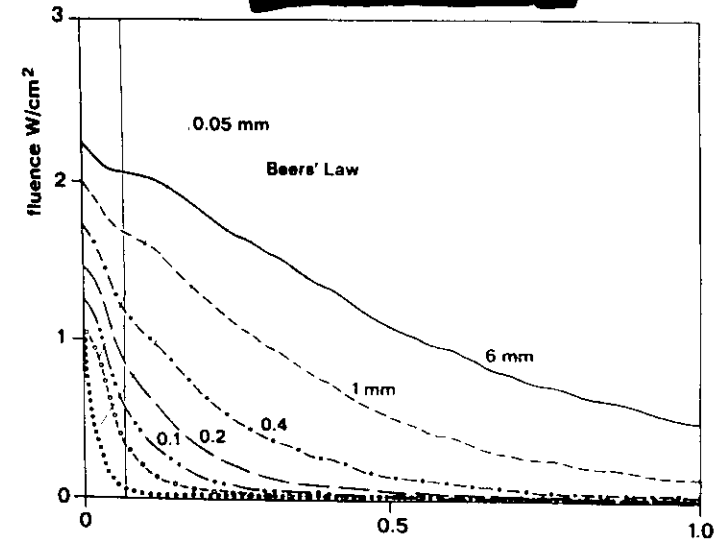
Monte Carlo simulation

Recently, numerical Monte Carlo computations have become available that produce solutions to the transport equation under **clinical laser conditions**.

The chief **advantage** of this approach is that **complex geometries** and **inhomogeneities** can be modeled in a straightforward manner, and that a variety of **physical quantities** can be scored during the same run.

The main **drawback** of MC simulation is that **many photon histories** are required to obtain precise results.

Monte Carlo computations are currently considered as the **method of choice** for estimation of the spatial fluence rate distribution in an absorbing and scattering tissue.



Monte Carlo computations of fluence rate versus skin depth, for various spot sizes (from S.L. Jacques, Houston, unpublished, 1989).

[TISSUE OPTICS]

The [redacted] has been modeling the [redacted]

Several functions have been developed to account for the high forward scattering of tissue:

- * the [redacted] (which approximates Mie scattering) :

$$p(\theta) = (1-g^2) [1 + g^2 - 2g \cos \theta]^{-1.5}$$

- * the [redacted]

$$p(\cos \theta) = (\sigma/\gamma) [u + (1-u)(1-g_H^2) \cdot (1 + g_H^2 - 2g_H \cos \theta)^{-1.5}]$$

where the first term u represents the [redacted] g and the second term is the Henyey-Greenstein formula.

- * the [redacted]

The delta-Eddington function is mathematically pleasing for tissue, because it gives values of g from 0.7 to 0.95.

[TISSUE OPTICS]

The main concern has been modeling the correct anisotropy.

Several functions have been developed to account for the high forward scattering of tissue:

- * the Henyey-Greenstein function (which approximates Mie scattering) :

$$p(\theta) = (1-g^2) [1 + g^2 - 2g \cos \theta]^{-1.5}$$

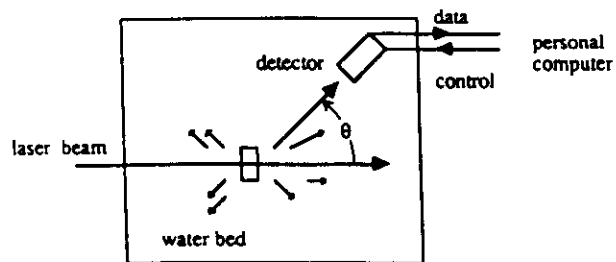
- * the modified Henyey-Greenstein function

$$p(\cos \theta) = (\sigma/\gamma) [u + (1-u)(1-g_H^2) \cdot (1 + g_H^2 - 2g_H \cos \theta)^{-1.5}]$$

where the first term u represents the isotropic scattering and the second term is the Henyey-Greenstein formula.

- * the delta-Eddington function.

The delta-Eddington function is mathematically pleasing for tissue, because it gives values of g from 0.7 to 0.95.



Experimental setup of phase function measurement.

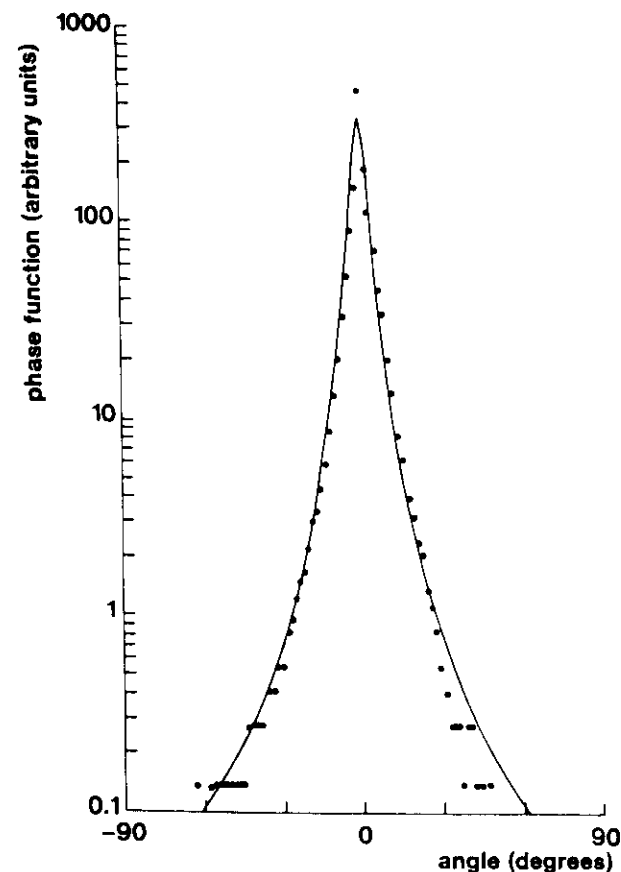
Phase Function Measurement

Experimental Setup: The setup for measuring angular distributions of light scattered from a laser beam passing through a thin tissue sample is illustrated in Fig. 5. Samples placed in the center of a water-filled tank were irradiated by a 1 mm diameter beam from a He-Ne laser. Scattered light was measured with a photodiode detector (1 mm aperture) that was rotated through 360°, with the midpoint of tissue as the center point of the circle. The sample and the detector were submerged in the water tank to minimize the difference of indexes of refraction and the inside-walls of the tank were painted black. The radius of the circle was 24 cm and the angular step size was 0.6°, except for the use of a 0.3° step for alignment of the detector precisely with the collimated beam, and for measurements of light intensities in regions of highly-peaked forward scattering. An IBM XT personal computer was used to control angular stepping of the detector and to acquire data.

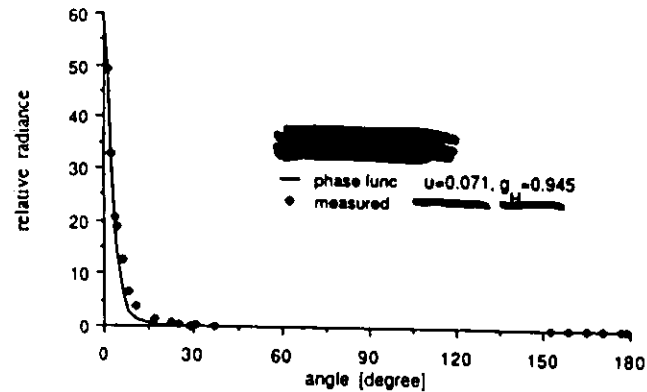
[TISSUE OPTICS]

Experimentally, it has been found that *in vitro* tissues have a scattering probability that is close to the Henyey-Greenstein function.

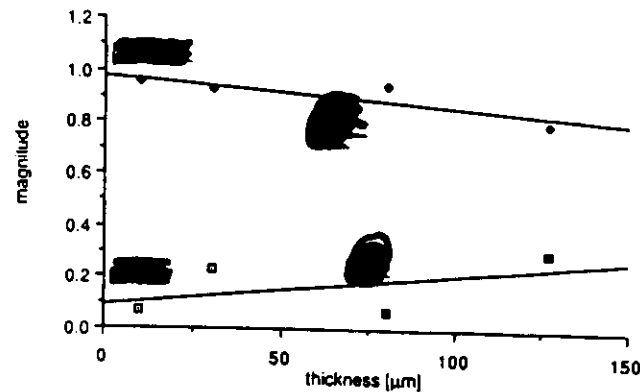
An experimentally obtained example is shown in Figure.



The Henyey-Greenstein phase function as a fit to goniophotometer measurements of 0.02 mm thick human dermis (from Prahl, 1988)



(a)



(b)

(a) Angular distributions of measured light intensities (in dots) and the phase function described by (7) fit by the least squares method (in solid line) for an $80\ \mu\text{m}$ thick sample of aortic wall. (b) Measured values of g_H and u for thin tissue samples. The linear regressions (in solid lines) give 0.976 and 0.094 as the asymptotic values for g_H and u , respectively.

Therapeutic applications

Photothermal surgery

- * Photocoagulative necrosis
- * Tissue ablation
 - * cutting (*optical knife*)
 - * "vaporization" (hot)
 - * "ablation" (cold)

Photomechanical surgery

- * Photodisruption of pathological structures

Photochemical therapy

- * Phototherapy
 - light alone
- * Photochemiotherapy
 - light + endogenous/exogenous drugs

Potential advantages claimed for laser surgery

- * *No-touch*
- * Reduced blood loss
- * Reduced oedema
- * Reduced post-operative pain
- * Less invasive techniques possible
- * Easier access to awkward sites
- * Surgical field free of instruments
- * Precision
- * Selective absorption (in some cases)
- * Sterile procedure
- * ...

*** Photocoagulative necrosis**

Oncology

- * Open air/endoscopic treatment of tumors
- * Recanalization of obstructed tracts
[bronchology, gastroenterology
(palliation)]
- * Urology: bladder tumors
- * Neurosurgery: NMR assisted stereotactic
coagulation

Dermatology

- * Photosclerosis: photobleaching of
pigmented lesions (**portwine stains,**
tatoos, ...)

- * **Tissue ablation**

- * cutting/excision (*optical knife*)
 - * bloodless incision/excision of highly vascularized tissues (hemostasis)
vocal cords, head and neck surgery, gynecology, ...

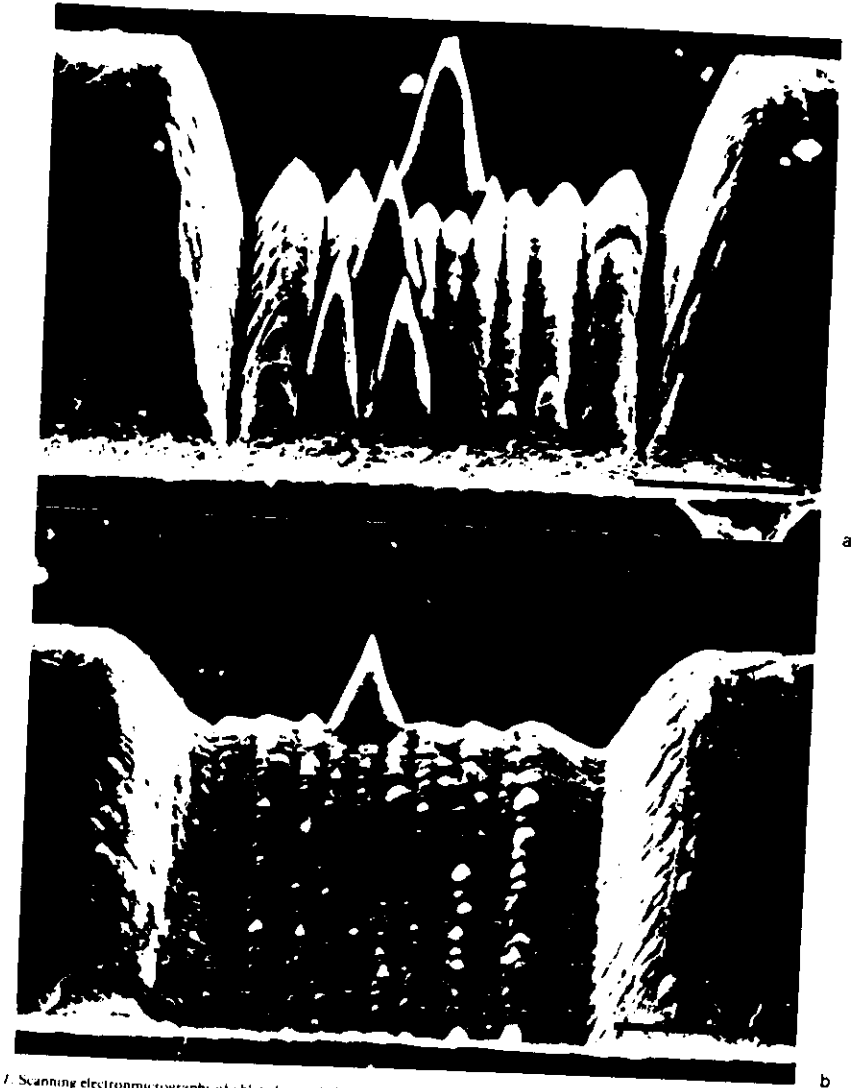
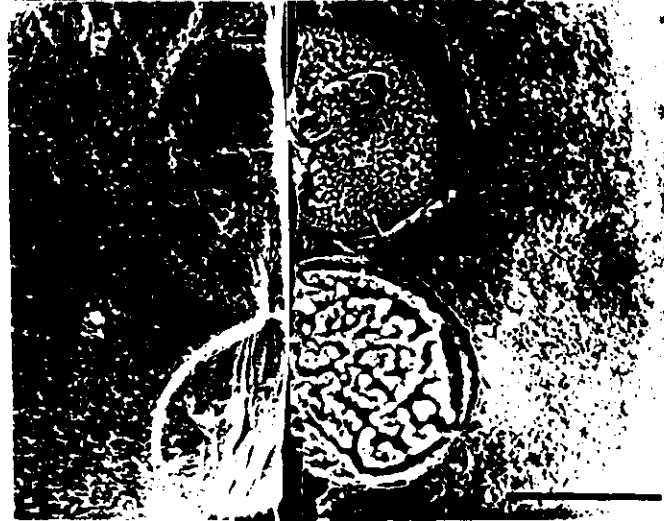
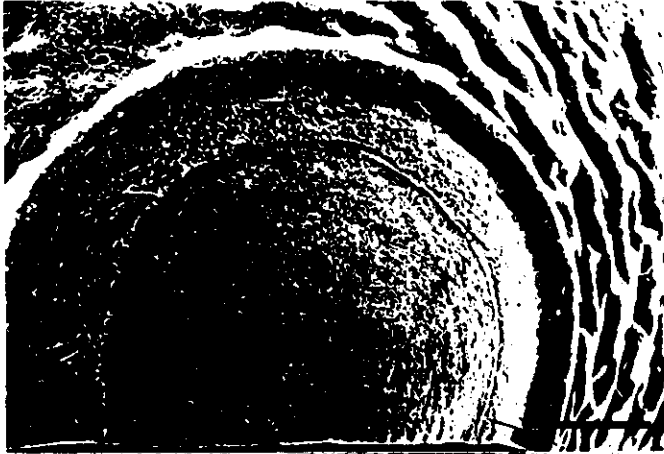


Fig. 1. Scanning electronmicrographs of ablated areas in human hairs. Both (a) and (b) were produced by exposure to 193nm radiation passing through a slit aperture. The parallel ridges are caused by diffraction of the laser beam and the pyramids are induced by inhomogeneities in the primary ablating surface. The bar marker is 25 μ m.



c

micrographs of discs eroded on rabbit cornea. All pictures are derived from acute specimens. (a) Disc ablated by short exposure at low fluence at 193nm. This exposure only involved the epithelium and superficial stroma but note the smoothness of the ablated surface. The peripheral folding and corrugations outside the area of ablation are artifacts of the preparative technique induced by 193nm and 248nm respectively. In each case the upper ablation was produced by low fluence and the lower ablation by high fluence. Note the poor surface quality produced at 248nm and compare these illustrations with Fig. 3. The bar markers are (a) 500 μ m, (b) & (c) 1 mm.

32



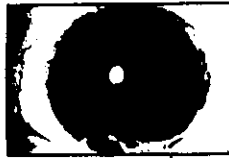
a



b

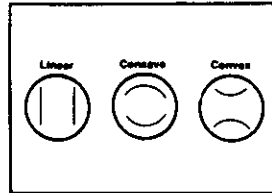
c

Fig. 6. Scanning electron micrographs of discs eroded on rabbit cornea. All pictures are derived from acute specimens. (a) Disc ablated by short exposure at low fluence at 193nm. This exposure only involved the epithelium and superficial stroma but note the smoothness of the ablated surface. The peripheral folding and corrugations outside the area of ablation are artifacts of the preparative technique induced by 193nm and 248nm respectively. In each case the upper ablation was produced by low fluence and the lower ablation by high fluence. Note the poor surface quality produced at 248nm and compare these illustrations with Fig. 3. The bar markers are (a) 500 μ m, (b) & (c) 1 mm.



Linear Transverse Excisions

The "T"-excision procedure is a form of refractive surgery in which astigmatism is corrected by creating transverse excisions in the cornea. The placement and depth of the excision is dependent upon the location of the axis of astigmatism and the degree of correction required.



Diagrammatic representations of the three excision types shown in photographs at left. All excisions are made perpendicular to the steepest meridian of astigmatism.

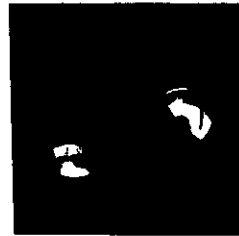


Concave Transverse Excisions

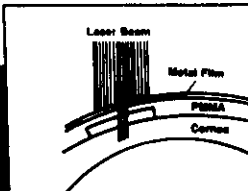
The unique properties of the excimer laser make it possible to create curved excisions which are believed to provide higher diopter correction when compared to straight cuts using a surgical knife. The accurate excimer laser control over the excision cut depth into the cornea is also anticipated to add increased predictability to this type of procedure.



Convex Transverse Excisions



These custom contact lens masks (FRG Patent number 3536072) manufactured by Summit Technology, are used to accomplish the concave excisions shown at left.



A view, in cross-section of the contact mask in place during an excimer laser "T"-excision procedure.



3 mm diameter excimer laser ablation in human cornea. 5 diopters correction. 40x magnification. Photo courtesy of Prof. John Marshall, PhD.



100x: With a mechanical iris, refractive correction is achieved by stepped ablation. The resultant ablated area has the appearance of a Fresnel lens.

Photomechanical surgery

Ophthalmology

The photodisruption process is of particular interest for the noninvasive treatment of several ocular pathologies:

such as **capsulotomies**, certain **peripheral iridotomies**, the removal of **vitreous strands**, or the dissociation of **opacified membranes** which frequently develop following cataract surgery.

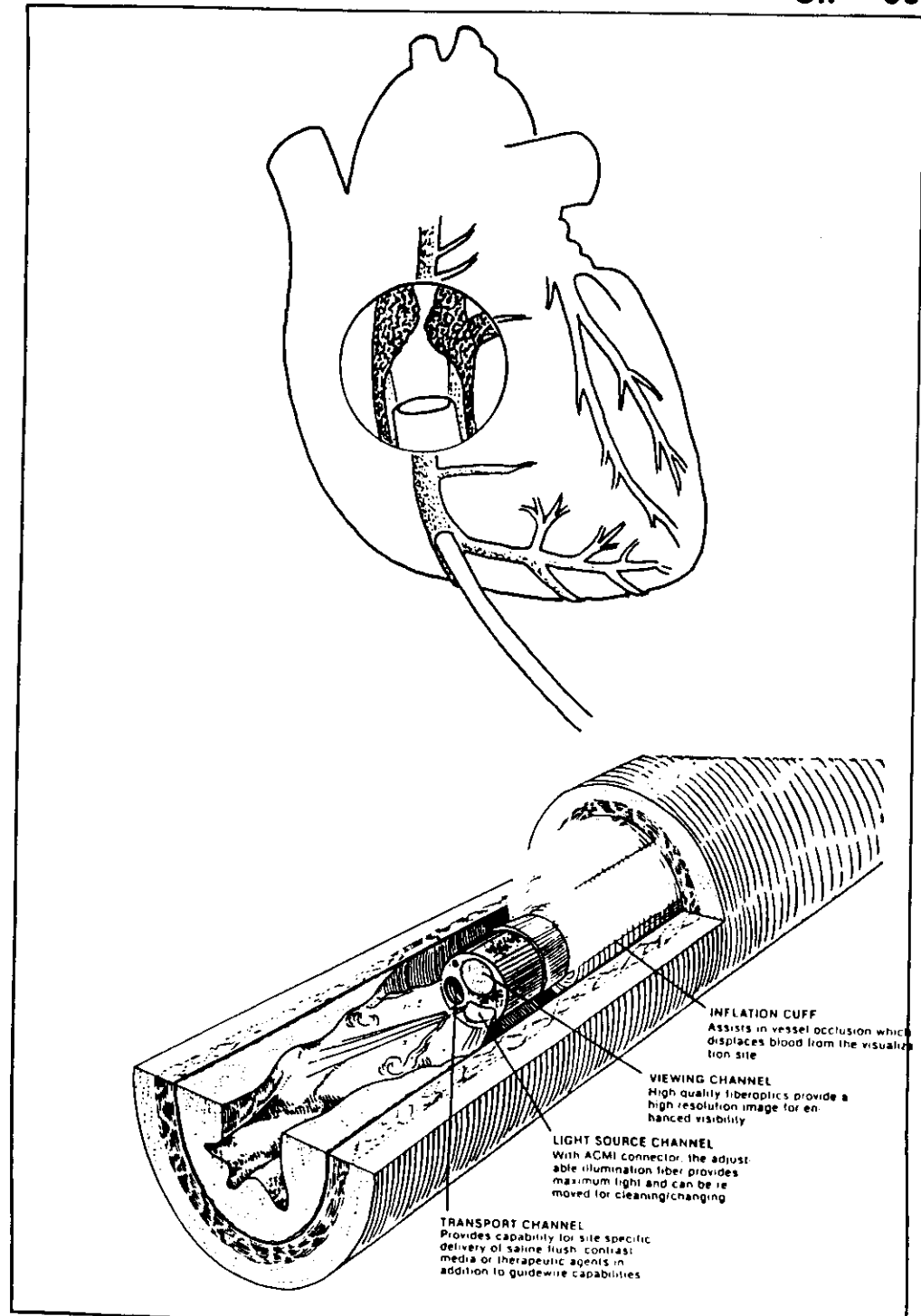
This technique which, owing to its simplicity, can be implemented in ambulatory treatments.

Photomechanical surgery

Cardiovascular angioplasty

Recently, optical breakdown techniques have been used in cardiovascular models to investigate possible disintegration of atheromatous plaques or stenosis in small arteries.

Although preliminary results suggest feasibility of the recanalization technique, a main difficulty remaining is the transport within fibers of the necessary high peak powers.



Photomechanical surgery

Urology

* Lithotripsy

One spectacular development of the photomechanical effect pertains to the field of intracorporeal laser **lithotripsy**, particularly for the fragmentation of ureteric calculi.

This **minimally invasive** kidney stone laser shattering procedure is well suited to remove stones lodged in the lower part of the ureter, a problem traditionally corrected by surgery; it is complementary to the lithotripter noninvasive shockwave therapy which cannot reach this region because of anatomic configuration.

Laser anastomosis of small vessels

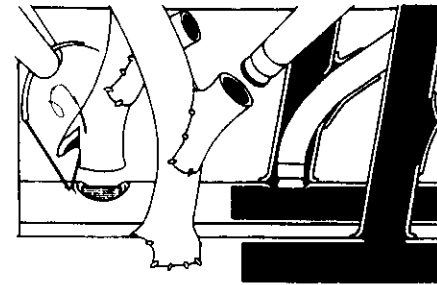


FIG. 1. Drawing depicting the different steps of the end-to-side anastomosis. *Left Rear:* After removal of the adventitial and muscular layers at the spot where the anastomosis is planned, the distal end of the donor artery is connected with the exterior of the recipient artery, just outside the prepared area. About 2 cm proximally from the anastomosis site an artificial side branch is made in the recipient artery, utilizing a conventional end-to-side technique. *Left Front:* The Nd:YAG laser catheter with the hemispherical contact probe on top is introduced via the artificial side branch. *Right Rear:* The hemispherical probe makes contact with the wall of the recipient artery at the site where adventitial and medial layers are removed. The recipient artery is temporarily occluded with vessel clips on both sides of the anastomosis. A hole with a diameter of 1.8 or 2.2 mm is created in the recipient artery with a laser pulse of 0.5 sec at 18 W. *Right Front:* After withdrawal of the laser catheter, the anastomosis side is flushed with a heparin-salt solution, the temporary clips are removed, and the artificial side branch is occluded with a hemoclip. The proximal temporary clip on the donor artery is also removed.

Diagnostic applications

- * Doppler flowmetry
- * Doppler interferometry
- * Laser-induced fluorescence (LIF)
- * Diffuse transmittance spectroscopy
- * Diffuse reflectance spectroscopy
 - * transcutaneous bilirubinometers
 - * transcutaneous oxymeters
- * Holographic techniques
- * Optical tomography
- * ...

