Lasers in medicine

2008 Rep. Prog. Phys. 71 056701

(http://iopscience.iop.org/0034-4885/71/5/056701)

Rep. Prog. Phys. **71** (2008) 056701 (28pp) doi:10.1088/0034-4885/71/5/056701

Lasers in medicine

Qian Peng[1,2,7], Asta Juzeniene[3], Jiyao Chen[2,4], Lars O Svaasand[5], Trond Warloe[6], Karl-Erik Giercksky[6] and Johan Moan[3]

[1] Department of Pathology, The Norwegian Radium Hospital, University of Oslo, Montebello, 0310 Oslo, Norway
[2] State Key Laboratory for Advanced Photonic Materials and Devices, Fudan University, 200433 Shanghai, People's Republic of China
[3] Department of Radiation Biology, The Norwegian Radium Hospital, University of Oslo, Montebello, 0310 Oslo, Norway
[4] Department of Physics, Fudan University, 200433 Shanghai, People's Republic of China
[5] Department of Electronics and Telecommunications, Norwegian University of Science and Technology, O.S. Bragstads Plass 2A, 7491 Trondheim, Norway
[6] Department of Surgical Oncology, The Norwegian Radium Hospital, University of Oslo, Montebello, 0310 Oslo, Norway

E-mail: Qian.Peng@rr-research.no

Received 17 January 2008, in final form 5 March 2008
Published 11 April 2008
Online at stacks.iop.org/RoPP/71/056701

Abstract

It is hard to imagine that a narrow, one-way, coherent, moving, amplified beam of light fired by excited atoms is powerful enough to slice through steel. In 1917, Albert Einstein speculated that under certain conditions atoms could absorb light and be stimulated to shed their borrowed energy. Charles Townes coined the term laser (light amplification by stimulated emission of radiation) in 1951. Theodore Maiman investigated the glare of a flash lamp in a rod of synthetic ruby, creating the first human-made laser in 1960. The laser involves exciting atoms and passing them through a medium such as crystal, gas or liquid. As the cascade of photon energy sweeps through the medium, bouncing off mirrors, it is reflected back and forth, and gains energy to produce a high wattage beam of light. Although lasers are today used by a large variety of professions, one of the most meaningful applications of laser technology has been through its use in medicine. Being faster and less invasive with a high precision, lasers have penetrated into most medical disciplines during the last half century including dermatology, ophthalmology, dentistry, otolaryngology, gastroenterology, urology, gynaecology, cardiology, neurosurgery and orthopaedics. In many ways the laser has revolutionized the diagnosis and treatment of a disease. As a surgical tool the laser is capable of three basic functions. When focused on a point it can cauterize deeply as it cuts, reducing the surgical trauma caused by a knife. It can vaporize the surface of a tissue. Or, through optical fibres, it can permit a doctor to see inside the body. Lasers have also become an indispensable tool in biological applications from high-resolution microscopy to subcellular nanosurgery. Indeed, medical lasers are a prime example of how the movement of an idea can truly change the medical world. This review will survey various applications of lasers in medicine including four major categories: types of lasers, laser-tissue interactions, therapeutics and diagnostics.

(Some figures in this article are in colour only in the electronic version)

This article was invited by Professor G Gillies

[7] Author to whom any correspondence should be addressed.

Contents

Abbreviations

ALA	5-aminolevulinic acid
AMD	age-related macular degeneration
BPH	benign prostate hyperplasia
CIN	cervical intraepithelial neoplasia
CNS	central nervous system
CNV	choroidal neovascularization
CT	computer tomography
CW	continuous wave
DNA	deoxyribonucleic acid
Er : YAG	erbium : yttrium–aluminium–garnet
HeCd	helium cadmium
HeNe	helium–neon
Ho : YAG	holmium : yttrium–aluminium–garnet
HPD	hematoporphyrin derivative
ILP	interstitial laser photocoagulation
KTP	potassium titanium oxide phosphate
Laser	light amplification by stimulated emission of radiation
LASIK	laser-assisted *in situ* keratomileusis
LDF	laser Doppler flowmetry
LDV	laser Doppler velocimetry
LED	light-emitting diode
LEDLLT	LED low-level therapy
LIF	laser-induced fluorescence
LIFE	lung imaging fluorescence endoscopy
LITT	laser-induced interstitial thermotherapy
LLLT	low laser level therapies
LPDL	long-pulsed dye lasers
LTK	laser thermal keratoplasty
Maser	microwave amplification by stimulated emission of radiation
MPE	maximum permissible exposure
MRI	magnetic resonance imaging
NAD	nicotinamide adenine dinucleotide
Nd : YAG	neodymium doped yttrium–aluminium–garnet
PD	photodetection
PDL	pulsed dye laser
PDT	photodynamic therapy
PLDD	percutaneous laser disc decompression
PpIX	protoporphyrin IX
PRK	photorefractive keratectomy
PWS	port-wine stain
ROS	reactive oxygen species
VAIN	vaginal intraepithelial neoplasia
VIN	vulvar intraepithelial neoplasia
YSAG	yttrium scandium aluminium garnet

1. Historical perspective

Albert Einstein (1879–1955) did not invent the laser, but he certainly paved the way towards its invention. In his ‘golden year of 1905’, he published several papers, one of which brought him the Nobel Prize in physics in 1921. It was a paper on the photoelectric effect: light can liberate electrons from certain metal surfaces [1]. This was an unequivocal manifestation that light can be described as particles, photons. Its wave nature was already known. In certain settings the wave nature is revealed, in other settings the particulate nature shows up. In 1924 an Indian physicist Satyendra Nath Bose (1894–1974) published a paper extending Max Planck’s work on photons [2]. Einstein found this report interesting and he extended the ideas further in two articles [3, 4]. A key feature was that photons, in contrast to electrons, prefer to occupy exactly the same energy state. The thermodynamics of such particles, called bosons, can be described by Bose–Einstein statistics. It is worth noting that Planck in his work on blackbody radiation in 1900 had already suggested such

Table 1. The commonly used medical CW lasers[a].

Laser	Medium	λ (nm)	Power	δ^{b}_{water}	δ_{tissue} (Ref. [15])	$\delta_{pigm.\ tissue}$
HeCd	Gas	325.0	<100 mW	3.2 m	8 μm	
		442.0	<200 mW	20 m	0.3 mm	
Argon ion	Gas	488.0	2–10 W	23 m	0.8 mm	
		514.5	10–100 W	18 m	1 mm	
Kr ion	Gas	530.9	0.1–10 W	16 m	1.1 mm	
		568.2	0.1–10 W	13 m	1.6 mm	
		676.4	0.1–10 W	12 m	5 mm	
KTP/Nd : YAG	Solid state	532.0	1–10 W	16 m	1.1 mm	0.2 mm
HeNe	Gas	632.8	100 mW	4.8 m	3.5 mm	
Dye	Liquid	400–500	1–100 W	11–20 m	0.1–0.9 mm	
		550–700		14–2 m	1–5 mm	
GaAlAs	Semiconductor	780	1–100 W	60 cm	7 mm	
		820		46 cm	8 mm	
		870		25 cm	7 mm	
Nd : YAG	Solid state	1 064	100 W	4 cm	4 mm	0.9 mm
Nd : YAP	Solid state	1 080	10–100 W	5 cm	4 mm	
		1341		8 mm	4 mm	
Ho : YAG	Solid state	2100	10–100 W	0.2 mm	1 mm	
HF	Chemical	2600–3000	150 W	200–0.5 μm	300–1 μm	
CO_2	Gas	10 600	100 W	10 μm	20 μm	

[a] The optical penetration depth (δ) is the tissue thickness that causes light to attenuate to 37% of its initial value.
[b] http://omlc.ogi.edu/spectra/water/data/warren95.dat

an energy distribution for the photons. Einstein's model was used to investigate the properties of large collections of excited atoms. Such excited atoms can spontaneously emit a photon with a characteristic wavelength (λ) when returning to their non-excited ground state. When such a photon passes close to another identical excited atom it can stimulate this atom to emit a photon that is an exact replica of the incoming one. This process, which thus behaves like an amplification process, has been termed light amplification by stimulated emission of radiation, or for short: 'LASER'.

However, identical atoms in the ground state can also absorb the photons. In thermal equilibrium, there are always more electrons in the lower energy states than in the upper ones. Therefore, the probability for absorption of incoming photons is larger than for amplification. To get net amplification one needs to have more atoms in the excited state than in the ground state. This state, which is called population inversion, can be obtained by delivering energy, e.g. electrical, chemical or radiation, to the system. The principle of stimulated emission was demonstrated experimentally for microwaves before it was shown for light. In 1954, the first microwave amplification by stimulated emission of radiation (MASER) was constructed [5,6]. In 1964, Townes, Basov and Prokhorov shared the Nobel Prize in physics for developing the maser principle.

The possibility to extend the principle into the infrared and visible regions was proposed by Schawlow and Townes in 1958 [7] and the first laser was constructed by Maiman in 1960 [8]. He used a ruby crystal surrounded by flashtubes to generate population inversion and lasing. The red light ($\lambda = 694$ nm) of this laser is emitted by chromium present as an impurity in the Al_2O_3 crystal. In the same year the helium–neon (HeNe) laser was developed by Javan *et al* [9]. The neodymium doped yttrium–aluminium–garnet laser (Nd : YAG) was constructed by Johnson in 1961 [10], the argon ion laser (Ar^+) was invented by Bennett *et al* in 1962 [11] and the carbon dioxide (CO_2) laser was created by Patel in 1964 [12].

Different types of solid-state lasers such as semiconductor lasers, metal vapour lasers and free electron lasers were invented later, as described below. The wavelength domain was gradually developed into the ultraviolet range, which made ionization and bond-rupturing of target molecules possible.

The medical potential of the laser has been explored since its invention. Today, lasers are widely used in almost all fields in medicine for diagnostics and therapeutics.

2. Types of lasers

Lasers were taken from invention in the laboratory in 1960 to the clinic in the course of 2–4 years [13, 14]. In table 1 and figure 1 some physical parameters are listed for the most important medical and biological lasers [15]. A wide range of wavelengths and fluence rates are available for different applications. Furthermore, pulsed and CW lasers are available. This adds to the medical applicability of the lasers. As will be discussed, both pulse length and frequency and wavelength can be tailored for targeting different tissues and cell compartments.

2.1. Gas lasers

2.1.1. Carbon dioxide laser. Invented in 1964 [12], the CO_2 gas laser is still one of the most widely used medical lasers [16]. It contains a mixture of helium (60–80%), nitrogen (~25%) and CO_2 (~5%). The gas is excited with either an electrical ac or dc discharge or with a radio frequency (RF) field. It is broken down to CO and O_2 and is usually replenished by a continuous flow, or the gas products are allowed to recombine in sealed tubes. Carbon dioxide lasers can be made with

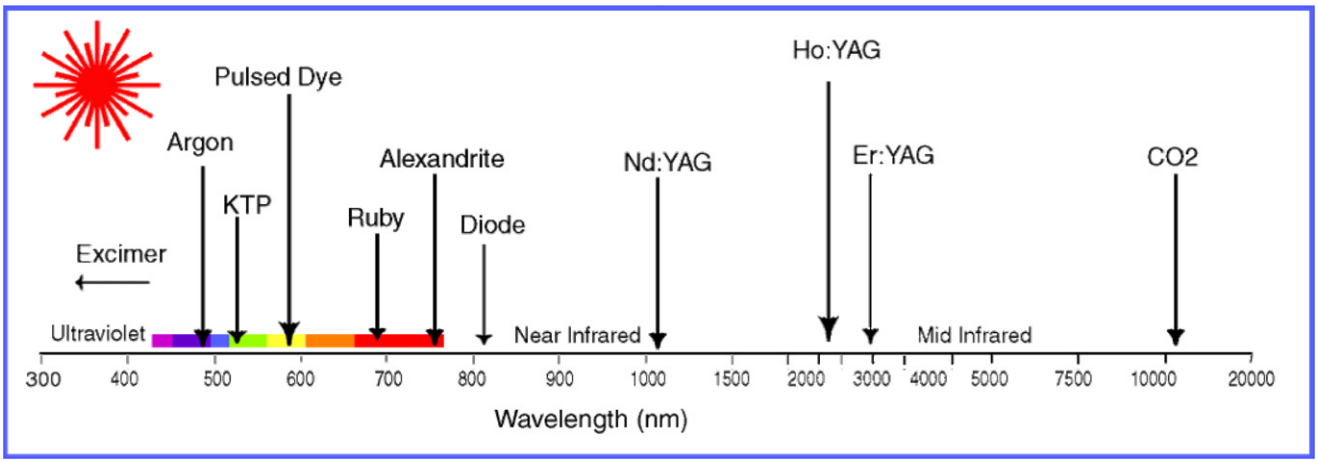

Figure 1. Wavelengths of common medical lasers (courtesy of Dr Albert Poet, Shore Laser Center).

Table 2. The commonly used medical pulsed lasers[a].

Laser	Medium	λ (nm)	Pulse duration	δ^{b}_{water}	δ_{tissue} (Ref. [15])	$\delta_{pigm.\ tissue}$
Excimer ArF	Gas	193	5–25 ns	25 cm	<1 μm	
Excimer KrCl	Gas	222	250 ns	90 cm	1 μm	
Excimer KrF	Gas	248	2–50 ns	1.5 m	1.2 μm	
Excimer XeCl	Gas	308	20–300 ns	2.5 m	5 μm	
Excimer XeF	Gas	351	1–30 ns	5 m	20 μm	
Cu	Metal	511	2.5–20 ns	19 m	0.9 mm	
	vapour	578		5 m	1.6 mm	
KTP/Nd : YAG	Solid state	532	100 ns–250 μs	10 m	1.1 mm	0.2 mm
Nd : YAG	Solid state	1064	30–100 ps	3 cm	4 mm	0.9 mm
Ruby	Solid state	694	20 ns–1 ms	60 cm	5 mm	0.4 mm
Alexandrite	Solid state	720–800	0.1 ms	0.2 m	6–8 mm	0.5 mm
GaAS	Semiconductor	904	150 fs	5 cm	4 mm	
Ti : sapphire	Solid state	700–1000	10–100 fs	60–1 cm	5–8 mm	
Ho : YAG	Solid state	2100	100 ns–250 μs	0.1 mm	1 mm	0.4 mm
Er : YAG	Solid state	2940	10 ns	0.3 μm	1 μm	
Free electron laser	Electrons	800–6000	2–10 ps	20 cm–2 μm	8 mm–30 μm	
CO_2	Gas	10 600	100 ns–1 ms	10 μm	20 μm	

[a] The optical penetration depth (δ) is the tissue thickness that causes light to attenuate to 37% its initial value.
[b] http://omlc.ogi.edu/spectra/water/data/warren95.dat

emission up to several kilowatts, but 10–20 W are sufficient for most surgical procedures. The wavelength is 10.6 μm and the beam is of high quality with respect to monochromaticity and collimation. They operate either in the CW or pulsed mode, depending on the application. The radiation of this laser cannot be transmitted through standard silica optical fibres. However, a system of mirrors, hollow waveguides or fibres made of metal halides, e.g. thallium bromide, can be used. The efficiency is high: 10–15% of the input power is converted to laser emission. Since the infrared radiation at 10.6 μm is invisible, HeNe lasers are used to generate aiming beams. The penetration depth in water is about 10 μm, and the penetration depths in tissues are largely dependent on the water content (tables 1 and 2, figures 2 and 3) [15]. The laser is used for a number of surgical-, ophthalmologic- and cosmetic applications [16–23].

2.1.2. Carbon monoxide laser. The carbon monoxide (CO) laser operates in the CW mode and has emission lines between 5 and 6 μm. Light in this wavelength region is strongly absorbed by tissues, and the laser has been used for thermal welding of vessels [24].

2.1.3. Argon- and krypton ion lasers. Unlike the carbon oxide lasers, the gases in these lasers must be ionized by electrical discharge to operate. They are not very efficient and a large fraction of the input energy is lost as heat, which requires efficient cooling systems. The Ar ion laser has its main output lines at 488 and at 514.5 nm, while the main lines of the krypton laser are at 530.9, 568.2 and 676.4 nm [16]. While the argon ion laser can give outputs larger than 20 W, the output at each of the krypton lines is lower than 10 W. The emission from these lasers is mainly in the visible range, can be transmitted through optical fibres and is absorbed by numerous tissue chromophores. Notably, haemoglobin absorbs argon lines strongly. Therefore, the laser has excellent coagulative properties and can be used for vaporization of pigmented lesions in the skin, endometric lesions and retina [16].

2.1.4. Helium–neon laser. The basic constituents of this laser are helium and neon. It operates in a continuous mode and has an average output of a few milliwatts. The laser can be made emitting at various wavelengths, e.g. 543 nm (green), 594 nm

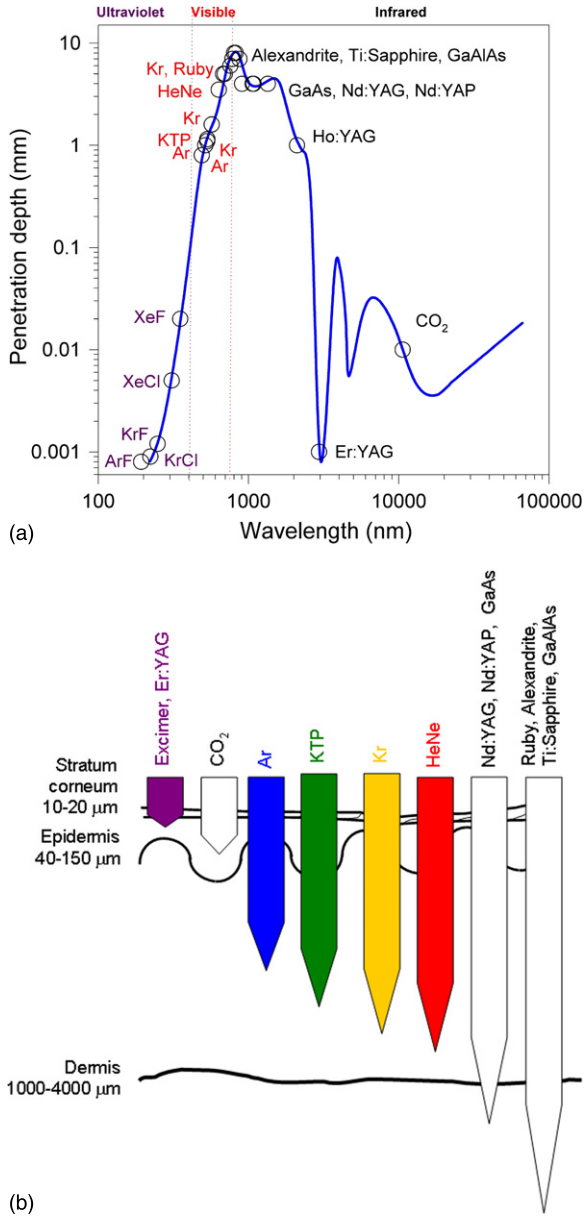

Figure 2. (*a*) Estimated penetration depth in bloodless, unpigmented tissue (see [15]) (solid [blue] line). The open circles indicate some common medical lasers. (*b*) Penetration depth of some common medical lasers in human skin tissue.

(yellow) and 633 nm (red). Its reliability, light weight and good beam qualities make it suitable for alignment and analytical purposes.

2.1.5. Helium cadmium laser. The helium cadmium (HeCd) laser is one of a class of gas lasers using helium in conjunction with a metal that vaporizes at a relatively low temperature. It is weak and has a low efficiency (<0.05%) and a low output of about 50 mW and 150 mW at the two main lines 325 nm and 442 nm, respectively.

2.1.6. Hydrogen fluoride laser. These types of lasers are called chemical lasers, since they generate population inversion from exothermic chemical reactions between free

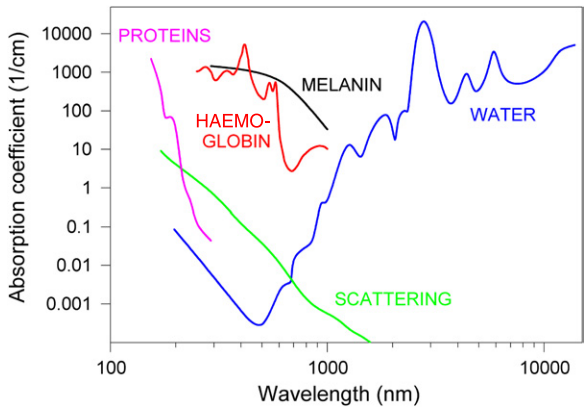

Figure 3. Absorption spectra of water, haemoglobin, melanin and proteins together with scattering in tissue.

fluorine and hydrogen to produce excited hydrogen fluorine. Outputs of more than 100 W can be obtained in modes of nanosecond pulses. During operation they consume SF_6, O_2, He and H_2, and generate radiation in the wavelength region 2.6–3.0 μm [25], where water has a strong absorption (figure 3). Therefore, they are interesting for surgical application of similar types as mentioned for the CO_2 and CO lasers [26].

2.1.7. Excimer lasers. In 1971, the first excimer laser was discovered using a xenon dimer (Xe_2) excited by an electron beam to produce stimulated emission at 172 nm wavelength [27]. Excimer is a short form of the expression 'excited dimers'. Some molecules, such as rare gas halides (ArF, KrF, XeCl, XeF), are stable only in their excited states, and not in their ground state. The laser medium consists of such molecules in a buffer gas (helium or neon). They have low efficiency (~2%), give short pulses (10–100 ns) and emit in the UV region. Typical wavelengths are 193 nm (ArF), 249 nm (KrF), 308 nm (XeCl) and 351 nm (XeF). The penetration of radiation at these wavelengths in tissues is low, which makes the lasers suitable for many surgical applications. UV radiation, notably at 193 and 249 nm, can ionize molecules in tissue, break bonds and lead to abrasive reactions. High energy (average power up to 200 W) and short pulses are excellently suited for this including some applications in the field of ophthalmology [28, 29]. Because of the high quantum energy low average fluence rates are needed for the lasers to enable them to cut without heating [30, 31]. Therefore, they are sometimes classified as 'cold lasers' [30, 31].

2.2. Metal vapour lasers

2.2.1. Copper vapour and gold vapour lasers. The lasing medium of these lasers is a mixture of neon and the vapour of a metal, usually copper or gold. They are excited by electric discharge, have rather low efficiencies (less than 1%), emit a few tens of watts at 511 and 578 nm (copper) and 628 nm (gold). To keep the metals in a vaporized state the temperature must be kept above 1500 °C. The gold lasers have been used for photosensitizer-mediated photodynamic therapy (PDT), since the porphyrin photosensitizers most frequently used in this

therapy have an absorption band around 630 nm. The copper vapour laser has been used as a pump source for dye lasers or for surgery and tissue destruction, since its lines overlap absorption peaks of haemoglobin. Both lasers are pulsed with repetition rates around 5–10 kHz.

2.3. Solid-state lasers

2.3.1. Ruby laser. The ruby laser was the first laser, developed in 1960 by Theodore Maiman [32]. The red 694 nm light comes from a small amount of chromium (0.01–0.5%) in an aluminium oxide crystal. In 1962, the dermatologist, Leon Goldman, was the first physician to test the ruby laser on human skin [33]. Ablation of a melanoma metastasis with the ruby laser was first reported by McGuff *et al* in 1964 [34]. At the same time, they reported an ability to vaporize atherosclerotic plaque in cadaver vessels with the laser [35, 36]. The ruby laser was first used by ophthalmologists in 1964 for photocoagulating the retina [37]. Being outside the haemoglobin absorption band, the pulsed light from a ruby laser is mainly absorbed by melanin-containing tissue structures. Destruction of deep lying hair follicles can be achieved without significant scarring [38]. Likewise, dermal scarring from removal of tattoos can be minimized [39–42].

2.3.2. Neodymium : yttrium aluminium garnet (Nd : YAG) laser. The Nd : YAG laser is probably the most widely used medical laser [10, 38, 43–45]. The lasing medium is 1–2% neodymium (Nd^{3+}) doped into an yttrium–aluminium–garnet crystal. The medium is excited by continuous or flashed Xe lamps or, more recently, by diode lasers. The laser can emit at several wavelengths in the near infrared, and the most frequently used wavelength is 1064 nm. Since the efficiency is usually below 2%, water-cooling is necessary. It can be operated either in pulsed or CW mode. The so-called Q-switching can be applied to generate ultrashort pulses. When a non-linear optical crystal is placed in the beam, second harmonics of the main line can be obtained, i.e. light at 532 nm. Frequency doubling crystals of potassium titanium oxide phosphate ($KTiOPO_4$), or KTP in short, is often used. The so-called KTP laser (532 nm) has low penetration depths in tissue, but good coagulative properties [46]. The Nd : YAG laser itself has large penetration depths (3–5 mm) and also has acceptable haemostatic properties [47]. Because of its deep penetration Nd : YAG laser radiation can work via hyperthermal action mechanisms. By endoscopic delivery modes it can be used in urology [48–50], pulmonology [51] and gastroenterology [52, 53]. With ultrashort pulses it can act via the electromechanical mode, which is utilized in ophthalmology for the treatment of secondary cataract of the posterior capsule (see below). This type of opaqueness often occurs after lens implant treatment for primary cataract [54].

2.3.3. Erbium : YAG laser. The erbium : YAG laser gives radiation at 2940 nm, which is close to the main absorption of water. Thus the penetration depth in water is extremely small, and the laser works via evaporation and ablation. Osseous minerals also absorb strongly at this wavelength, which makes sawing and drilling in bone and teeth possible. This laser can be adapted for dermatology and used for smoothing of skin [55, 56]. A slightly different type of erbium laser is obtained when erbium is doped into a crystal of yttrium scandium aluminium garnet (YSAG). It has an emission wavelength of 2780 nm.

2.3.4. Holmium : YAG laser. The holmium : YAG (Ho : YAG) laser gives radiation in the mid-infrared at 2100 nm and operates either CW or pulsed. This laser is used in a refractive surgery procedure called laser thermal keratoplasty (LTK) to correct mild to moderate cases of farsightedness and some cases of astigmatism [57–59].

2.3.5. Titanium–sapphire laser. The titanium–sapphire laser ($Ti : Al_2O_3$) was developed by Moulton [60] in the early 1980s and first reported by him in 1986. The lasing medium of this solid-state laser is titanium-doped sapphire. It can be tuned between about 660 nm in the deep red and 1160 nm in the infrared. Tunability is obtained by introducing a wavelength-selective element in the cavity, thereby separating out a narrow wavelength band from the broader wavelength range of the lasing process. An important use of titanium–sapphire laser is in two-photon spectroscopy. In traditional fluorescence spectroscopy the exciting photons must have higher energy than the fluorescent emitted ones. In the case of fluorescent studies of tissues the excitation wavelength is usually in the ultraviolet or blue/green part of the spectrum with emission in the yellow/red region. These excitation wavelengths are strongly absorbed by haemoglobin and other proteins. This makes it very difficult to study deeper structures since the excitation light is strongly reduced as well as the backscattered light is strongly dominated by fluorescence in the upper layers. However, in non-centrosymmetrical molecules there is a small probability that two photons combine, thus generating twice the energy of a single photon. This process is closely related to the second harmonic generation process as discussed for the KTP lasers. Because the probability is very small this will occur only for very high photons densities, i.e. for very high electrical fields.

Two-photon generation can be obtained in the highly focused region of a high intensity near infrared beam, and the fluorescence is therefore generated only in this region. Furthermore, since the incident photons are in the red/near infrared region they can induce fluorescence deeper in the tissue than is possible with UV or blue/green light. In order to maximize the electrical field without too high energy in the beam a train of very short pulses is generated by running the Ti-sapphire laser in the so-called mode-locked operation.

2.3.6. Alexandrite laser. This solid-state laser, which is tunable in the wavelength range 700–830 nm, can operate in CW or pulsed mode. The laser medium is chromium-doped chrystoberyl (alexandrite) ($Cr : BeAl_2O_4$). Its average fluence rate can be up to 100 W. Since light in this wavelength region is absorbed by melanin and dyes, but not significantly by

blood, it can be used to destroy melanin-containing structures (hair-roots, moles) [61–65], remove tattoos [39, 40, 42] and to fragment kidney stones (lithotripsy) [66, 67].

2.3.7. Dye lasers. Fluorescing dyes can be used as laser medium within the emission band of the dye. Some of the dyes used in dye lasers are rhodamine 6G, fluorescein, coumarin, stilbene, umbelliferone, tetracene and malachite green [68]. Optical elements can be used to select a narrow wavelength band. Other lasers, the so-called 'pump lasers' (often Ar lasers) are used to excite the dye and thus generate population inversion. Due to the wide tunability in the visible range such lasers have a number of medical and biological applications. Dye lasers are generally used in PDT [69–73].

2.4. Diode lasers

Bands in semiconductors replace the discrete gap between different atomic energy levels, which is used in most other lasers. An electron excited into the conduction band of a semiconductor can recombine with a positive hole in the valence band and emit a photon with an energy corresponding to the band gap energy. This is the reverse process of that taking place in a solar cell. Diode lasers are very efficient and reliable, and will probably lead to a silent revolution in medical applications. Powerful ones, with fluence rates up to more than 50 W, are being constructed. Such lasers can act via a number of tissue reactions, such as hyperthermia, coagulation and evaporation. A typical example is the GaAs laser at 904 nm. By substituting aluminium for gallium in the lattice ($Ga_{1-x}Al_xAs$) the band gap will be increased, and the emission wavelength reduced accordingly. Typical commercially available diodes are AlGaAs diodes at 805 nm wavelength. Larger wavelength can be obtained with In substitution, e.g. InGaAs at 1000 nm wavelength. Percutaneous laser disc decompression (PLDD) with the latter laser seems to be an efficient method for the treatment of thoracic disc disorders [16, 74]. Diode lasers can be used as excitation sources for other lasers. Wavelengths from UV to infrared can be obtained. Fluorescence diagnostics and PDT are typical application fields [75, 76].

2.5. Free electron lasers

Free electrons emit radiation when forced to change direction by magnetic fields. When electrons accelerated to relativistic speed (i.e. speed close to that of light) wiggle through a periodic array of magnetic fields of alternating directions, emission occurs. The coherent emission, which is mainly in the forward direction, is of the same kind as the non-coherent emission from cyclotrons. Radiation wavelengths from the x-ray to the microwave region can in principle be obtained with pulse durations ranging from almost infinite (CW) to sub-picoseconds. A number of medical applications are possible and ablation of tissue in ophthalmologic, otolaryngologic, neurosurgical applications and wound healing applications has been proposed [77]. However, since laser operations require an electron particle accelerator, wide spread medical use is not feasible.

3. Lasers compared with conventional light sources

The special feature of a laser is high power radiation with high degree of monochromaticity and collimation. A high degree of monochromaticity and collimation can also be obtained by passing light from fluorescent tubes, discharge lamps and incandescent lamps through monochromators and narrow pinholes. In such a filtering process the power is strongly reduced as all unwanted radiation is filtered away. The optical quantity that distinguishes lasers from all other light sources is called spectral radiance, i.e. emitter power per unit area cross-section of the beam, per unit opening solid angle and per unit wavelength. Further on, the ability to make very short pulses in the region of picoseconds or femtoseconds ($1\,\text{ps} = 10^{-12}\,\text{s}$, $1\,\text{fs} = 10^{-15}\,\text{s}$) is a unique feature of lasers. It should, however, be pointed out that very short light pulses where the duration of the pulse is comparable or shorter than the period (c/λ where c is the velocity of light) in principle are not monochromatic, e.g. an infinitely short pulse of finite energy contains all wavelengths with the same power.

The high radiance of laser radiation enables focusing of high power to small spots with dimensions close to the wavelength. Thus, extremely high local fluence rates can be obtained, tissue can be ablated and precise surgery can be performed. Furthermore, large powers can be fed into thin optical fibres for endoscopic and interstitial applications. Finally, focusing of high power pulsed laser radiation enables two-photon spectroscopy and posterior capsulectomy of the eye.

Interference between two laser beams is a result of a constructive or destructive adding of the electric field resulting from fields with the same phase or 180° out of phase, respectively. If the phase fluctuates randomly in the beams the constructive interference is destroyed because it fluctuates rapidly between a constructive and a destructive mode. The time interval between the arrivals of two photons with randomized phase is called the coherence time, and the distance travelled along the beam during this interval is called the coherence length. Correspondingly, the distance across the beam corresponding to random phase is referred to as spatial coherence. The coherence length of solar light or light from an incandescent light bulb is in the order of 1 μm. The corresponding values for a super-radiant light emitting diode (LED) and a HeNe laser are 10 μm and 300 mm, respectively; whereas the coherence length can be several metres for specially constructed lasers (single-mode lasers).

The so-called optical coherence technique represents a very interesting modality for studying finer details of the retina and upper layers of the skin. This technique is a modern version of the classical Michelson–Morley interferometer where a light beam is split into two parts, which interfere when they are joined again provided that the difference in travelled paths is less than the coherence length of the source. This technique can be used for scanning objects below the tissue surface. Light from the reference path and light returned from a subsurface region will interfere only when coming from a region of extent equal to the coherence length, and by varying the length of the reference path various depths into the tissue will be

scanned. Thus the best spatial resolution is obtained for a source with a short coherence length, i.e. with a very broad banded source such as a super-radiant LED. The technique was correctly termed 'low-coherence tomography' when it was introduced in the early 1990s, whereas the present term 'coherence tomography' might be quite misleading.

The collimation of a laser beam is rapidly lost when propagating into tissues. Except for ocular media the inhomogeneous structure of the tissue on the cellular or subcellular level initiates scattering of the beam, and the region within the tissue will be irradiated from all directions by multiple scattered photons. An order of magnitude estimate of the scattering can be obtained by assuming one scattering event per cell. The scattering is usually forward directed, but the polarization and direction are completely randomized after five to ten scattering events, i.e. after about 0.1–0.2 mm. The main scatterers in tissue are collagen and elastin fibres, erythrocytes, subcellular organelles (most notably pigmented melanosomes, nuclei and mitochondria) and cell membranes. Since many scatterers are smaller than the wavelength the scattering will be wavelength dependent: the scattering from objects much smaller than the wavelength will be determined by Rayleigh scattering (proportional to λ^{-4}); whereas scattering from larger objects is more independent of wavelength [78]. Scattering cross-sections are maximal for particles of a similar size to the wavelength. Many scatterers are in the range 100–300 nm, i.e. in the UV range, so that UV is strongly scattered. This contributes, together with the high UV absorption coefficients of nucleic acids, proteins and aromatic molecules, to an extremely small UV penetration depth.

Although the scattering is a lossless process, it enhances the absorption of light. The reason for this is that the zigzag path of the scattered photons enhances the probability for absorption. The main absorbers in tissue are, as mentioned, nucleic acids, proteins and aromatic molecules in the UV, melanin and heme proteins in the visible range and water in the infrared range, i.e. that of Er-YAG or CO_2 laser. Absorption leads to electronically excited biomolecules, which are mainly deactivated by thermal processes. Thus, deactivation gives vibrational and translational energy, manifesting themselves as heat. The transformation of electronic energy to thermal energy takes place on the picosecond time scale.

Under certain conditions ultrashort pulses can travel deeper into tissues than CW radiation. This is because the first part of a powerful pulse may contain enough photons to take all chromophore molecules in the upper tissue layer to excited states, and, thus, make it more or less transparent for the rest of the pulse. The pulse can literally open a road for itself into tissue [79, 80].

LEDs are complex semiconductors that convert electrical current into incoherent narrow spectrum light. The conversion process is fairly efficient in which it generates little heat compared with incandescent lamps. The wavelengths of emitted light depend on the composition of semiconductor and are available from 247 to 1300 nm. LEDs have been frequently used to emit a low power, broad spectrum light of 25–30 nm bandwidths, but in recent years improvements in semiconductor technology have substantially increased the

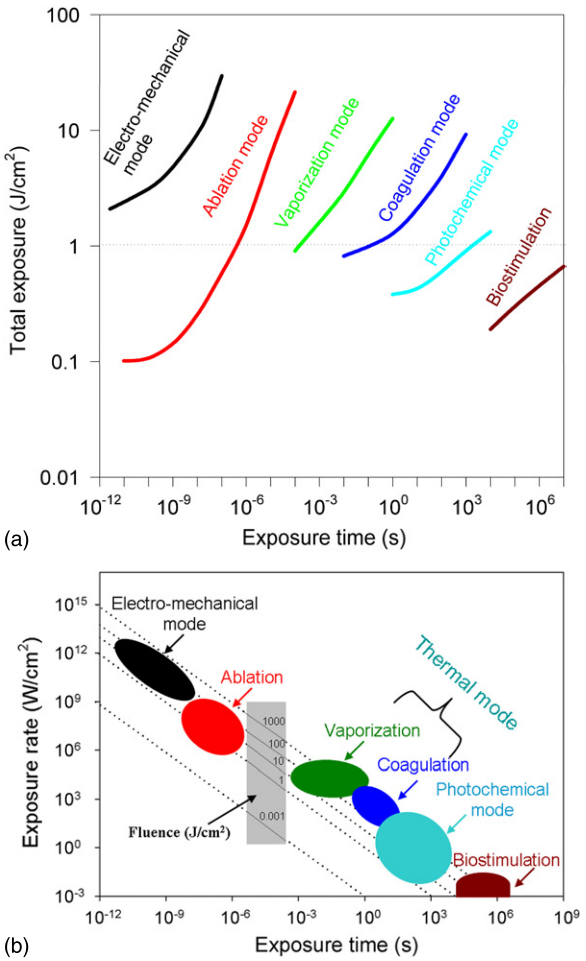

Figure 4. (*a*) Different types of laser–tissue interaction dependent on total exposure and exposure time. (*b*) Different types of laser–tissue interaction dependent on exposure rate and interaction time (figure is adapted from [95]).

light output of LED chips. Although LEDs cannot be used in the applications required for a highly collimated beam, they offer an effective alternative to laser treatments where large areas are targeted [81–90]. For example, LED-based low-level therapy (LEDLLT) can produce a biostimulative effect to promote wound healing [84–86, 91] and reversal of photoaging [92, 93]. In fact, coherent properties of laser light are not important when a thin layer of tissue surface is irradiated [94]. This is because the coherent and non-coherent light with the same wavelength, intensity and dose induces the same biological response [94]. Thus, well-designed LED devices should have a great future in phototherapy and PDT.

4. Models of laser–tissue interactions

4.1. Exposures and exposure rates

Basically, laser radiation can interact with biological tissue in six ways, as listed in figure 4(*a*). The modes of action are spread over more than 12 orders of magnitude with respect to exposure time, but only about two orders of magnitude with respect to total exposure. This becomes even clearer when the modes are approximately adjusted into a figure with exposure

time along the abscissa and exposure rate along the ordinate (figure 4(*b*)). Referring to figures 4(*a*) and (*b*) we will discuss the different modes.

4.2. The electromechanical (photomechanical or photodisruptive) mode

This mode, also often referred to as photomechanical or photodisruptive mode, requires nanosecond or shorter pulses with extremely high spatial density of photons, which have to be coherent so that their electrical fields can add constructively. A non-linear process of practically non-thermal origin can then occur. Focusing can result in local exposure rates of 10^{10}–10^{12} W cm^{-2} corresponding to local electric fields of 10^{6}–10^{7} V cm^{-1} [95]. These fields are comparable in strength to the intramolecular Coulomb fields and the molecule can therefore be torn apart. This is called optical breakdown and generates tiny spots of micro-plasma, ionized regions of extremely high electron density of the order of 10^{21} cm^{-3} [95]. As the micro-plasma expands a mechanical shockwave travelling at supersonic velocities arises, which can lead to mechanical rupture of the medium. With the high charge density in the focal point, a temperature exceeding 20 000 °C can arise as the tiny volume literally explodes. Secondary ionizations then occur. The power threshold for optical breakdown is higher for picosecond pulses ($\sim 10^{12}$ W cm^{-2}) than for nanosecond pulses ($\sim 10^{9}$ W cm^{-2}) [96]. The secondary electron production can be classified as a chain reaction or an electron avalanche formation. The basic reaction can be described as a transfer of energy between electrons in the vicinity of an ion or a neutral atom. The cross-section of the reaction increases with decreasing energy of the initial photon. Thus, a substance can absorb radiation outside its absorption spectrum: red light can drill holes in transparent glass or cornea and lenses. The main area of application of the photomechanical mode is ophthalmology, e.g. non-invasive treatment of iridectomies, removal of vitreous strands and capsulectomies for removal of opacities of the posterior capsule secondary to cataract surgery [97–100].

4.3. Ablation

Ablation is evaporation followed by expulsion of evaporated material. The absorption of strong laser pulses causes small explosions. The kinetic energy of molecules and molecular fragments is provided by the excess energy of the pulse after evaporation and/or fragmentation has been caused. The process is dependent on absorptive and elastic properties of tissue and on its viscosity. Furthermore, focusing and wavelength of the laser radiation are important. Excimer lasers give UV radiation of high energy. At 193 nm (ArF lasers) the quantum energy is 6.4 eV which is more than enough to break peptide bonds (3.0 eV) and carbon–carbon bonds of polypeptide chains like those in collagen (3.5 eV) [101]. In some cases heat may diffuse from the ablation crater and cause thermal damage, while in other cases, notably ablation with UV lasers, little heat is generated. This makes the process clean and sharply localized, which is sometimes highly desirable. The interaction tissue volume is determined by spot diameter and optical penetration depth. If the energy deposited in this volume is smaller than that needed to evaporate the tissue, i.e. below the ablation threshold, the energy is simply converted to thermal energy and results in thermal effects such as coagulation and hyperthermal damage. The low penetration of UV radiation makes ablation a likely process for excimer lasers.

Ablation is an important mode of action in ophthalmology (keratotomy, refractive keratophakia, epikeratophakia and corneal ablation) [102–107], surgery of joints [108], angioplasty [109–111] and lithotripsy [112]. In the latter case, stones are fragmented piece by piece by ablative processes.

Table 3. Thermal relaxation times (τ) of common laser targets.

Target	Size	τ
Melanosome	1 μm	1.7 μs
Erythrocyte	10 μm	170 μs
Microvessel	100 μm	17 ms
Vessel	1 mm	1.7 s

4.4. Photothermal (coagulative and vaporizing) processes

Diffusion of particles can be characterized by the Einstein–Smoluchowski equation: $L^2 = 4D\tau$, where L is the diffusion length, D is the diffusion constant and τ is the relaxation time. The self-diffusion coefficient of water is 2.3×10^{-9} m^2 s^{-1} and that of O_2 and haemoglobin in water are, respectively, 2×10^{-9} m^2 s^{-1} and 7×10^{-11} m^2 s^{-1}. The diffusion of heat is given by a corresponding expression where D is interpreted as the thermal diffusivity. The thermal diffusivity of water is 1.6×10^{-7} m^2 s^{-1}, and that of tissue is in the range (1.2–1.4) $\times 10^{-7}$ m^2 s^{-1}. This implies that in 1 s the diffusion length for O_2 in water at room temperature is 90 μm. The corresponding distance for haemoglobin molecules is 17 μm, whereas the distance for heat diffusion is 800 μm. Thus, a short laser pulse can deposit thermal energy in regions of high absorbance, such as microvessels and melanosomes, and the heat moves away faster than molecules diffuse.

Selective heating of a high absorbing region of dimension L will be obtained when the laser pulse duration τ is shorter than the thermal diffusion time across that region, i.e. $\tau < L^2/4D$. Table 3 shows typical laser pulse lengths that must not be exceeded if selective heating is attempted. A typical example is photothermolysis of ectatic vessels in port-wine stain. The wavelength is selected for high absorption in blood, e.g. 585 or 595 nm. The pulse duration is chosen long enough to allow heat to diffuse into the vessel wall from the site of absorption within the erythrocytes, but small enough to prevent heating of perivascular tissue. Thus the vessel wall can be selectively heated to 70 °C, which is required for thermal necrosis. Typical required pulse durations are in the region of 0.5–10 ms. Such long pulses can, however, also be obtained from pulsed Xe flash lamps. In fact, the treatment does not necessitate a laser, although long-pulsed dye lasers (LPDL) are most convenient tools. In the case of CW exposure the cooling efficiency by blood perfusion must be taken into account, as the contribution from blood perfusion becomes the predominant

Table 4. Laser–tissue interactions: photothermal effects.

Temperature	Molecular and tissue reactions
42–45 °C	Hyperthermia leading to protein structural changes, hydrogen bond breaking, retraction
45–50 °C	More drastical conformational changes, enzyme inactivation, changes in membrane permeabilization, oedema
50–60 °C	Coagulation, protein denaturation
∼80 °C	Collagen denaturation
80–100 °C	Dehydration
>100 °C	Boiling, steaming
100–300 °C	Vaporization, tissue ablation
>300 °C	Carbonization

heat transport mechanism for exposure times longer than the blood perfusion time, i.e. the time required for perfusing a volume of tissue with the same amount of blood. Typical blood perfusion times range from 20 s for cortex of the kidney, 120–400 s for the skin, 800–3000 s for muscle and 4000–5000 s for adipose tissue [113, 114]. If energy is deposited in a volume more than blood perfusion can remove, the temperature can rise to the hyperthermia threshold (∼42 °C) to the coagulation threshold (50–60 °C) or to the vaporization threshold (above 100 °C) [95]. Table 4 summarizes the most important cellular and tissue reactions. The relation between fluence and exposure times for the various mechanisms is illustrated in figures 4(*a*) and (*b*).

Photothermal damage of tissues may be induced by pulsed irradiation through absorption in either endogenous chromophores (amino acid at 200–300 nm, NADH at 250–400 nm, collagens at 300–700 nm, flavins at 340–500 nm, porphyrins at 380–650 nm, haemoglobin at 400–650 nm and melanin with non-selective absorption) or in externally added dyes (metallo-porphyrins, azo dyes, triphenylmethane derivatives) [115]. The damage depends on the absorption coefficient of the target and of its thermal relaxation time. Selective photothermal damage of macromolecules or subcellular organelles requires pulsed excitation at picosecond or nanosecond regimes, while microsecond or millisecond domains are effective in the case of cells or similar structures [115]. Dyes that can convert electronic energy of the excited states to thermal energy can be used for tumour treatment [115–120].

Application of the interaction of laser radiation with absorbing nanoparticles, such as carbon nanotubes, metal nanospheres, nanoshells or others is a rapidly expanding area in laser medicine [121–123]. Absorption of laser energy by nanoparticles causes a very localized vaporization of the fluid surrounding the particles, leading to the generation of transient vapour bubbles (microcavitation) [122, 124]. Cell killing by microcavitation is a selective process, restricted to cells containing the nanoparticles, thus leaving other cells unaffected [122].

There are several applications of such new photothermal sensitizers (nanoparticles) heated with short laser pulses: (a) selective cancer-cell targeting by the conjugation of absorbing particles (e.g. gold nanoparticles) with specific antibodies [123, 125], (b) localized tumour destruction without harmful effects on surrounding healthy tissue [122], (c) absorption of radiation at longer wavelengths, i.e. centrally in the window of transparency of most tissues, (d) few or no undesired side-effects are expected (e.g. cytotoxicity).

Laser immunotherapy is a novel approach for the treatment of metastatic tumours [126]. It combines a selective photothermal laser–tissue interaction for direct tumour destruction and an immunoadjuvant-directed stimulation of immune responses [118, 126–130]. This involves intratumour administration of an absorbing dye (indocyanine green) and an immunoadjuvant (glycated chitosan) followed by non-invasive near infrared laser exposure.

4.5. Photochemical (photodynamic) reactions

Fluence rates below the hyperthermia threshold can be used for PDT, a two-step modality in which the delivery of a light-activated and lesion-localizing photosensitizer is followed by a low, non-thermal dose of light irradiation. Almost all photochemical reactions of biological relevance are dependent on generation of reactive oxygen species (ROS) [131, 132]. Out of these ROS singlet oxygen, $^1O_2$, is by far the most important one [133]. $^1O_2$ is believed to be the major cytotoxic agent involved in PDT [134]. The energy of a $^1O_2$ molecule is about 1 eV above the ground state. Thus, under favorable conditions phosphorescence at 1270 nm can be observed when the excited oxygen entity returns to the ground state. However, useful concentrations of $^1O_2$ cannot be generated by 1270 nm exposure, since the generation necessitates energy transfer from a sensitizer molecule in the lowest excited triplet state. Taking into account that this triplet state has a significantly lower energy than the lowest excited singlet state from which it originates (due to electronic interactions), it is not possible to generate $^1O_2$ by light of higher wavelengths than about 800 nm [135]. Thus, for PDT one has to use radiation in the UV or visible range. Because of the optical window of tissue 'between' 620 and 1100 nm, yielding optimal penetration depths (∼1–3 mm at 630 nm), red light is most frequently used for PDT [135, 136]. Porphyrins, chlorines and phthalocyanins all absorb beyond 620 nm, the red band of heme proteins, and are being used for laser PDT. Several lasers can be applied, notably dye lasers and diode laser [137]. For topical PDT traditional fluorescent, incandescent and vapour light sources, as well as LEDs, can be used [137]; while for PDT of internal organs through fibres lasers are needed. Figure 5 shows a scheme of the processes involved in PDT, from light absorption, via triplet state formation, to energy transfer to oxygen and singlet oxygen formation. Absorption of 10 light quanta can give as many as six $^1O_2$ molecules, so the process is extremely efficient, and sub-hyperthermal fluence rates can be efficient. However, to avoid too long exposure times (>30 min) one has to approach the hyperthermia limit if low sensitizer concentrations are present in the target tissue. This is often the case for PDT with 5-aminolevulinic acid (ALA) generated protoporphyrin IX (PpIX) [138–143]. Mild hyperthermia during the light exposure can give good results, possibly even of synergistic nature [144–150]. Synergism is

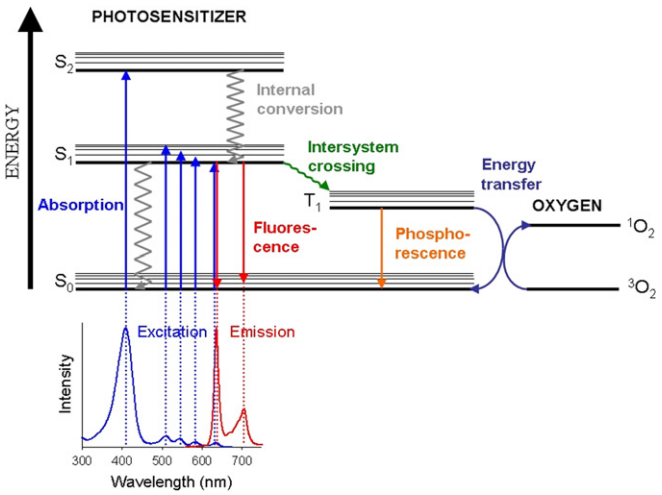

Figure 5. Modified Jablonski diagram. Fluorescence excitation and emission bands of a porphyrin type photosensitiser shown in the left lower corner.

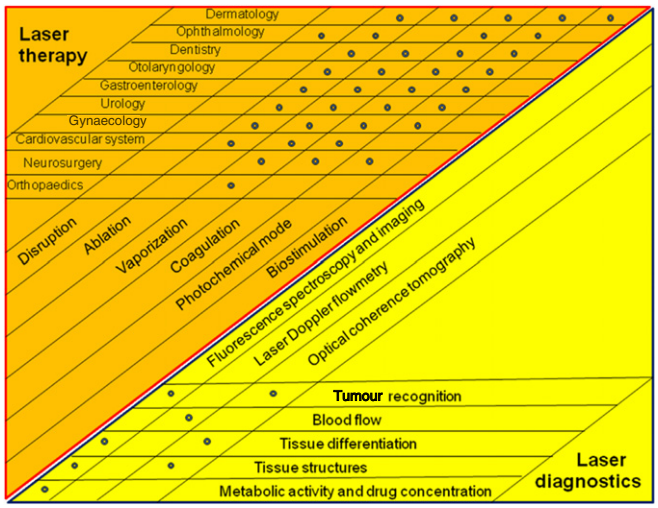

Figure 6. Therapeutic and diagnostic applications of medical lasers (adapted from [169]).

believed to be related to hyperthermia effects on repair of sub-lethal PDT damages, and cell signalling pathway may also be involved [146, 148].

Singlet oxygen has a short lifetime of 10–40 ns in cells and tissues [136]. Thus, its radius of action is only about 10–20 nm [151]. This means that PDT acts selectively on targets with high concentrations of sensitizer [152]. Tumour selectivity of PDT is based on this principle. The tumour selectivity of sensitizer accumulation can be related to a number of factors: a low tumour pH (several sensitizers protonate and get more lipophilic below pH 7), a high concentration of lipoprotein receptors in tumours (many sensitizers are bound to lipoprotein in the blood), the presence of leaky microvessels with low lymphatic drainage in tumours, and a high concentration of macrophages (taking up aggregated sensitizers) in tumours [153].

Light exposure shortly after sensitizer application predominantly leads to vascular damage in the tumours, notably if the sensitizers are not too lipophilic [154, 155]. At longer times after application tumour cells are destroyed. Furthermore, PDT affects the immune system [156, 157]. This can explain why less metastasis sometimes occurs after PDT than after surgical removal of tumours [158].

4.6. Biostimulation and wound healing

Biostimulation and wound healing have been reported for even lower CW light fluence rates and doses than those used in PDT. Since the polarization and collimation are lost within a few tenths of a millimetre of penetration into tissues, lasers are not needed for such applications. Nevertheless, they are being used, and the treatments are often termed 'low laser level therapies', LLLTs, also known as photobiomodulation, cold laser therapy and laser biostimulation. Notably in Eastern European countries LLLT seems to be accepted to some extent [159–164]. The following applications have been proposed: tumour treatment, treatment of tinnitus, epilepsy, pain, thrombosis, relief of light hypersensitivity, reduction of the recovery time after traumas or surgery, treatment of hyperlipidemia and strengthening of the immune system [165]. The chromophores for possible biostimulative effects are unknown, and so are the cell reactions. Action spectra for biostimulation of cells in culture have been reported [166]. They have many peaks and do not point to any well-defined and known chromophore. Effects on mitochondrial and respiratory involved enzymes have been proposed. It may be concluded that biostimulation and wound healing by low fluence rates of light are still controversial and not scientifically proven [167, 168].

5. Practical considerations of lasers in medicine

The utilities of lasers in medical treatments consist mainly of photothermal therapy and PDT. Today, the laser is applied in both cases to almost all disciplines of medicine including dermatology, ophthalmology, dentistry, otolaryngology, gastroenterology, urology, gynaecology, cardiovascular system, neurosurgery and orthopaedics (figure 6) [169]. Although photothermal therapy still plays a major role in medical laser treatment, PDT has been established as a treatment modality for a number of non-oncological and oncological diseases. At least seven photosensitizers and porphyrin precursors have been approved by regulatory health agencies in many countries for PDT and photodetection of diseases (table 5). In addition, several second-generation photosensitizers are being investigated in clinical trials (table 6). The major advantage of PDT over photothermal therapy is the selective effect without hyperthermia, so that the surrounding healthy tissues are undamaged (table 7).

5.1. Factors influencing laser choice

Choosing a suitable laser for a given application depends on (a) the absorptive characteristics of the tissue to be destroyed, (b) the wavelength of the emitted radiation, (c) the temporal parameters of the delivered energy including the level of applied power (power density), the total energy delivered over

Table 5. Approved photosensitizers and porphyrin precursors in PD and PDT.

Compound	Trade mark	Producer	λ (nm)	Indication (country and year)
Porfimer sodium	Photofrin	Axcan Pharma http://www.axcan.com http://www.photofrin.com	632	Superficial bladder, endobronchial, esophageal, gastric, cervical cancers (>120 countries, since 1993)
Benzoporphyrin derivative monoacid ring A (BPD-MA)	Visudyne	QLT Inc. & Novartis Opthalmics http://www.qltinc.com/Qltinc/main/mainhome.cfm http://www.visudyne.com	690	Choroidal neovascularization (CNV) secondary to wet type of age-related macular degeneration (AMD), pathological myopia or presumed ocular histoplasmosis (>70 countries, since 2001).
Tetra(meta-hydroxyphenyl) chlorin (mTHPC)	Foscan	Biolitec AG http://www.biolitec.com	652	Head and neck cancer (EU, Norway and Iceland, since 2001)
5-Aminolevulinic acid (ALA)	Levulan	DUSA Pharmaceuticals, Inc. http://www.dusapharma.com http://www.levulanpdt.com	blue	Actinic keratosis of face and scalp (USA, 1999)
5-Aminolevulinic acid (ALA)	Giolan	Medac GmbH http://www.medac.de	375–400	Intraoperative PD of residual malignant glioma (EU, 2007)
Methyl aminolevulinate	Metvix	PhotoCure ASA http://www.photocure.com	632	Actinic keratosis, basal cell carcinoma (EU, Australia, New Zealand, since 2001)
Hexyl aminolevulinate	Hexvix	PhotoCure ASA http://www.photocure.com	370–400	Fluorescence detection of bladder cancer (Sweden, 2004; EU, 2005)

Table 6. Photosensitizers and porphyrin precursors used in PD and PDT clinical trials.

Compound	Trade mark	Producer	λ (nm)	Indication
5-Aminolevulinic acid (ALA)		Shanghai Fudan-Zhangjiang Bio-Pharmaceutical Co., Ltd	630	Urethral condylomata acuminata
5-Aminolevulinic acid (ALA)		Cosmo Oil Co., Ltd	630	Acne
Pd-bacteriopheophorbide	Tookad	Negma-Lerads Laboratories, Toussus Le Nobel	762	Prostate cancer
Tin ethyletiopurpurin (SnET2)	Purlytin	Miravant Medical Technologies	660	CNV due to AMD AIDS-related Kaposis Prostate cancer
2-(1-Hexyloxyethyl)-2-devinyl pyropheophorbide-a (HPPH)	Photochlor	Roswell Park Cancer Institute	660	Barrett's esophagus Esophageal and lung cancer Skin basal cell carcinoma
Lutetium-texaphyrin (Lu-tex)	LUTRIN ANTRIN	Pharmacyclics Inc.	732	Locally recurrent breast cancer Photoangioplasty of peripheral arterial diseases
Boronated porphyrin	BOPP	Pacific Pharmaceuticals Inc.	628	Brain cancer
Mono-N-Aspartyl chlorine e6 (NPe6)	Talaporfin	Light Sciences Corporation, Inc.	664	Head and neck, lung, rectal, prostate cancer
Chlorin e6 conjugated with polyvinyl pyrrolidone	Fotolon	Apocare Pharma GmbH	665	Bowen's disease
Hypericin	VIMRxyn	VIMRX Pharmaceuticals Inc.	600–1000	Glioblastoma. HIV-infected diseases. Cutaneous T-cell lymphoma, Kaposi's sarcoma, warts and psoriasis
Hematoporphyrin derivative	Hiporfin	Chongqing Huading Modern Biopharmaceutics Co., Ltd (China)	630	Skin, lung, bladder, liver, gastrointestinal and other cancer
Sulphonated aluminium phthalocyanine (AlPcS)	Photosense	State Research Center (Russia)	675	Skin, breast, lung, gastrointestinal and other cancer
Porphycene (ATMPn)		Glaxo-Wellcome Inc.	630	Psoriasis
Dibromorhodamine derivative	TH9402	Theratechnologies	515	Bone marrow purging

a given surface area (energy density) and the rate and duration of the exposure (pulse repetition) and (d) the mode of beam energy delivery to a target tissue (i.e. continuous versus pulsed energy and direct contact or no contact with the target tissue).

5.2. Laser delivery systems

The laser delivery system transmits the laser beam to a targeted tissue. Several laser delivery systems are available and their choice depends on wavelength, operating power, desired spot size and accessibility of the treatment site, and transmission/absorption characteristics of optical elements. Generally, the systems can be classified into two types: non-contact and contact. In the non-contact type only the laser beam interacts with targeted tissue with a predominant optic effect. There are mainly three various systems of this type. (a) Articulated arm and lens system: an articulating arm is a series of hollow tubes and mirrors. The laser beam is transmitted through a tube and then reflected into the next tube by an appropriately angled mirror. This system can be adapted

Table 7. Comparison between photothermal therapy and PDT.

	Photothermal therapy	PDT
Laser (most)	Nd : YAG	Diode
Laser wavelength	805–1064 nm	510–530 or 630–730 nm
Laser power	3–5 W	0.1–0.3 W or higher for hollow organs
Light fluence rate	$>300\,\mathrm{mW\,cm^{-2}}$	$<200\,\mathrm{mW\,cm^{-2}}$
Tissue penetration of light	>4 mm	<4 mm
Nature of effect	Thermal	Photochemical
Destruction of connective tissue	Yes	No
Selective effect	None	To a high extent
Healing	Scarring	Often no scarring
Toxicity	None	Skin photosensitization (weeks)

to an operating microscope or handpiece providing excellent precision. (b) Fibre optics: fibre optics are thin, flexible optical fibres coated with opaque nylon or metal casings, which can transmit visible and near infrared radiation by reflection off the opaque casing. The optical fibres can be used in conjunction with rigid or flexible scopes to provide minimally invasive surgery. Recently flexible, biocompatible silica optical fibres with side-firing and diffusing tips for high power delivery of laser irradiation have been shown to be promising for a number of medical indications. (c) Waveguide: waveguides are semi-flexible steel tubes lined by ceramic tile. Laser energy is reflected down the tube by bouncing the beam off the lateral walls. In the type of contact, the laser energy is mainly concentrated at a tip to induce a cautery effect.

It should be pointed out that high energy lasers can damage optical fibres during their delivery. Often, the laser-induced damage occurs on either of the end faces, or at the point of the first focus, a point at which the light has its highest intensity inside the fibre. Such damage is associated with gradual heating of the fibres partly as a result of fibre-beam misalignment [170], and largely limits the applications of endoscopic cauterization systems.

5.3. Laser safety

As lasers are potentially hazardous tools, devastating thermal injuries can occur with improper use. Regulatory agencies worldwide have thus proposed safety guidelines for the operation of lasers by setting limits for laser exposure and maximum permissible exposure (MPE) [171]. In US and UK regulations have been established since the mid-1980s and they are continuously updated [172, 173]. As various tissues tolerate different levels of laser power at different wavelengths, various MPE standards have been made for different tissues such as skin and eye. Based on the MPE standard for a specific laser with a known beam diameter and divergence, the safety working distance for the specific laser beam in clinics and laboratories can be calculated as a laser safety document [174]. All personnel involved must be fully conversant with the safety document and also obtain laser safety practical training. Although laser safety regulations do not apply to the exposure of the patient at the target site, accidental exposure to the patient from misdirection of the laser beam that can injure the skin and eye should be avoided.

Generally, the skin is an easy target for a laser beam because of its high chance of laser exposure. Once damaged, the laser thermal effect-induced collagenation in the dermis can last for several months, that further delays healing and promotes fibrosis. Before the reepitheliation process starts heat damaged epithelial tissue must be remodelled, either by sloughing of coagulative necrosis or by biochemical repair of sub-lethally injured cells. As long as the dermis is exposed to air, more and more fibroblasts are activated, resulting in an increase in collagen deposition. Fortunately, the skin is relatively resistant to light due to the protection of the pigmented epidermal layer.

The most vulnerable organ of the human body is the eye. Unlike the skin, the cornea of the eye does not have the externally protective layer of pigmented cells. In particular, the ocular lens focuses the incident laser beam on the retina with a very small spot to produce a high power density. This can burn a hole on the retina. Since the laser beam irradiance at the retina can be multiplied by a factor of 100 000 compared with the irradiance on the cornea [175], even a low power laser can result in retinal damage without harming the cornea or other eye tissues. It should be pointed out that only the visible and near infrared lasers can damage the retina, as the light of such wavelengths can penetrate the watery layers in front of the retina and finally reach the pigmented epithelium of the retina. The UV and far infrared lasers, on the other hand, can be absorbed by the cornea giving rise to corneal damage when the power density of a laser is over the threshold. Thus, the MPE standard for the retina is different from those for the cornea and other eye tissues [176]. Today, laser safety goggles for a specific laser are available and the use of eye goggles is mandatory, because the blink reflex of the eyes is not fast enough to prevent the laser light reaching the delicate retina. In addition, windows of the laser room should be covered and doors be locked during laser use. Appropriate hazard warning signs should be posted in the vicinity of the laser room.

Lasers can produce potentially hazardous airborne contaminants from the photovaporization of tissue. The vaporized tissue has been referred to as laser plume. The laser-induced pyrolytic products are similar to those resulting from the barbecue of meats. They contain toxic by-products and known carcinogens such as nitrosamines. A local exhaust ventilation system should be required in a laser operating room to reduce the risk of chronic breathing of the laser plume.

6. Therapeutic applications of lasers

6.1. Lasers in dermatology

Lasers were introduced in the specialty of dermatology in the mid-1960s. Because of the accessibility of the skin to examination and study by lasers, dermatologists play an extremely important role in defining the clinical usefulness and limitations of laser systems. They have also helped to define the specificity of laser–tissue interaction that further improved the usefulness of these devices. When the absorptive

characteristics of a targeted tissue are precisely matched with an ideal laser wavelength, the maximal specificity of the laser–tissue interaction can occur. The optical property of the skin is an important determinant for the selectivity of laser effects. There are two main chromophores in the skin: oxygenated haemoglobin with three absorption peaks at 418, 542 and 577 nm; and melanin which has a very broad range of absorption. In addition, water is the key component of the skin tissue that can affect the quality of the thermal effects ranging from structural changes of protein at temperatures of 42–45 °C, to coagulation at 50–60 °C and vaporization at above 100 °C.

There are a large number of lasers used for various types of dermatological indications including visible wavelengths of pulsed dye, ruby, KTP, diode, alexandrite and infrared wavelengths of CO_2, Nd : YAG. The major effect of lasers on skin tissue is photothermolysis [177] and the common skin indications treated with lasers are vascular lesions, benign and malignant tumours, infectious lesions, pigmented lesions and tattoos and a number of cosmetic conditions [178]. Generally, lasers used correctly cause limited side-effects with little discomfort, no risk of infection and no scarring.

One of the most common cutaneous vascular lesions treated with lasers is the port-wine stain (PWS). PWSs with an incidence of about 0.4% of newborns are benign vascular birthmarks consisting of superficial and deep dilated capillaries in the skin resulting in a reddish to purplish discoloration. PWS can cause significant psychological trauma and a reduction in the quality of life. Treatment of PWS includes ionizing radiation, cryosurgery, skin grafting, but lasers provide the treatment of choice for most patients today. Being absorbed by intravascular oxyhaemoglobin within the visible-light range a laser can induce photothermolysis to destroy the diseased blood vessels selectively without affecting the surrounding tissues and causing scarring. Various types of lasers have been used for PWS, but the flashlamp-pumped pulsed dye laser (PDL) is the treatment of choice with the wavelengths from 585 to 600 nm [179, 180]. In addition, the KTP laser at the shorter wavelength of 532 nm is still used for the PWS treatment with the advantage of causing less purpura. PDT is now also applied for PWS. Unlike PDL-induced coagulation, PDT uses continuous low light irradiation with no photothermal effect to activate a photosensitizer that has accumulated in diseased vessels and thus selectively destroys the vessels.

Although thermal laser therapy is used for the treatment of skin tumours, PDT with ALA or its methylester has recently been applied for the treatment of cutaneous premalignant and malignant lesions [141]. The principle of ALA-PDT is that in the initial step of the heme biosynthetic pathway in cells ALA is formed from glycine and succinyl CoA. The last step is that the rate-limiting enzyme, ferrochelatase, catalyzes the insertion of ferrous iron into PpIX (a potent photosensitizer) in the mitochondria. By adding exogenous ALA, the naturally occurring PpIX accumulates with a high degree of selectivity in tumours possibly because of limited capacity and/or low activity of ferrochelatase. Such a selectivity has therefore been exploited for its application in photodetection (figure 7) and PDT of tumour as an alternative to administration of exogenous photosensitizers. The benefits

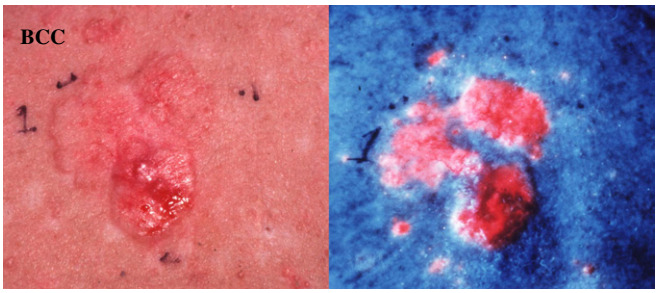

Figure 7. Highly selective ALA methylester (Metvix)-induced PpIX fluorescence (right) in human skin basal cell carcinoma.

of ALA-based PDT include reduced skin photosensitivity (1 or 2 days compared with 1 or 2 months with some other photosensitizers), easy administration (topical or oral) and repeat use if necessary [181]. PDT with topically applied ALA or its methyl ester has already been approved by regulatory agencies of many governments for the treatment of actinic keratosis and basal cell carcinoma [141, 182].

Q-switched lasers with short-pulsed and high intensity are used to bleach the dyes in unwanted tattoos and fade the pigments in age spots and moles. The 308 nm excimer laser is effective to clear psoriasis. In addition, lasers are applied for resurfacing, hair removal and wound healing [183].

6.2. *Lasers in ophthalmology*

No field has seen greater accomplishments with lasers than ophthalmology. The advantage in this field is the ability of a laser beam to enter the eye without causing injury. In the 1940s, Gerd Meyer-Schwickerath, a German ophthalmologist, pioneered to use the energy of the sun to 'weld' the retina to the underlying epithelium [184]. This was the first eye surgery with light coagulation of the retina. Ophthalmology was perhaps the first subspecialty in medicine to use laser light to treat patients. Immediately after the invention of the first laser in 1960, Campbell used a confocal laser transmission system for the first retinal laser coagulation in 1961. Today, lasers are indispensable for effective and minimally invasive microsurgery of the eye. The focusing system of the cornea and lens brings laser beams to a sharp focus inside the eye. This actually carries a risk of injury, but also has considerable therapeutic possibilities. Generally, laser energy has four different effects of light–tissue interaction on the eye: photodisruption, photoablation, photocoagulation and photochemical reactions.

Photodisruption uses the mechanical energy of a laser to create microexplosions, expanded plasma formation, acoustic waves and cavitations in order to cut intraocular structures with minimal thermal damage. The Nd : YAG laser, that can induce a photodisruptive effect to make tiny holes, is applied for iridotomy in the pupillary-block glaucoma caused by increased pressure in the eye, and also for lens capsulotomies.

Photoablation involves minimal thermal damage. Hyperopia (longsightedness), myopia (shortsightedness) and astigmatism can be corrected by photorefractive keratectomy (PRK) with non-thermal excimer laser ablation in the far ultraviolet. The laser-assisted *in situ* keratomileusis (LASIK) is a common

type of the PRK and is done in the stromal bed by creating a plano-hinged flap with a keratome. Myopia up to 12 dioptres and hyperopia up to 5 dioptres, each with a certain degree of astigmatism, can be treated effectively in this way. Patients choose LASIK as an alternative to wearing corrective eyeglasses or contact lens. In addition, the laser ablation can be used as phototherapeutic keratectomy to remove superficial corneal opacifications in scars and dystrophies and to close the epithelium in non-infectious corneal ulcers.

Photocoagulation uses the thermal energy of a laser to seal leaking blood vessels. The argon laser is a standard modality for retinal coagulation of diseases such as diabetic retinopathy and vascular diseases. In the treatment of glaucoma, focal coagulation can be induced within the trabecular meshwork of the anterior-chamber angle with the argon laser using a high energy to cause the outflow of the aqueous humour, thus lowering the intraocular pressure. The excimer and Er-YAG lasers can also be used to produce a few tiny holes in the trabecular meshwork. In vascular and pigmented eyelid lesions including tumours CO_2 and Er-YAG lasers are used for tissue coagulation to reduce bleeding, making the surgical field easy to survey.

The photochemical effect generated by PDT with verteporfin and a low-energy laser is used to treat choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD). Until recently, the only treatment proven beneficial was thermal laser photocoagulation. However, the thermal laser damages the retina overlying the CNV, making it problematic for lesions involving the foveal centre. The photochemical application has shown to reduce the risk of moderate and severe vision loss in patients with predominantly classic subfoveal CNV secondary to AMD.

A scanning laser ophthalmoscope is a diagnostic tool for eye disorders. The principle is that a focused low-level laser beam is used to scan the fundus of the eye to provide a digital and fluorescent image of the retina, in which the depth of the optic cup and the thickness of the retinal nerve fibre layer can be measured.

6.3. Lasers in dentistry

The common lasers used today in different fields of clinical dentistry are argon, KTP, HeNe, diode, Nd : YAG, ErCr : YSGG, Er : YAG and CO_2. Among them He–Ne laser and diode laser (632 nm) with a low power are applied for photodetection and PDT. These fields mainly include periodontology, endodontics, hard tissue applications, soft tissue surgery and esthetic dentistry.

Periodontal diseases are among the most prevalent infectious diseases, with 75% of people aged between 35–44 and 95% of the population over 65-year olds being affected [185]. Most pathogenic bacteria in the oral cavity are present as complex aggregates (biofilms) on the surfaces of the teeth (known as dental plaques). The accumulation of these bacterial biofilms on the tooth surface above the level of the gingival margin causes the progressive dissolution of enamel and the underlying dentine to induce caries. Treatments of carious lesions include the elimination of infected dentine by drilling and restoration of the tooth by filling with a variety of materials. However, instead of the removal of the infecting microorganisms by drilling, a more attractive alternative approach is to kill the bacteria *in situ*. Recent studies have shown that the bacteria present in dental plaques and caries are susceptible to lethal photosensitisation of the photosensitizer Toluidine Blue O or aluminium disulfonated phthalocyanine to a laser [186–190]. This would help not only to prevent dental caries but also to eliminate infected dentine. Periodontitis is a chronic inflammation due to the accumulation of bacterial biofilms on the root surface of the tooth below the level of the gum margin (subgingival plaque). The bacterial biofilm induces destruction of the periodontal ligament and a gap between the tooth and the gum (periodontal pocket), resulting in the loosening and eventually loss of the tooth. The physical removal of the subgingival biofilms combined with topical application of antimicrobial agents to the periodontal pocket is the conventional therapy. However, it is difficult to maintain therapeutic concentrations of the antimicrobial agents due to the dilution by the saliva and gingival crevicular fluid. PDT is feasible, as a photosensitizer can be directly applied to the periodontal pocket followed by light irradiation either through the thin gingival tissues or via an optical fibre placed into the pocket. A number of studies have shown that PDT can effectively kill periodontopathogenic bacteria [191–195].

In the case of infected root canal system the routine endodontic treatment procedures are to mechanically enlarge the canals followed by irrigation with an antibiotic agent and filling of the affected space. However, the complex anatomy of the root canals makes it difficult or virtually impossible for the routine procedures to completely remove the bacteria. PDT may offer an alternative to disinfect and sterilize the canals due to the easy access of a photosensitizer and light.

Overall, the advantages of PDT over conventional antimicrobial agents are (a) a faster process of killing bacteria (seconds to minutes), (b) can be repeated without inducing drug-resistance and (c) sparing surrounding tissues. Argon and diode lasers with a low power are used to excite hydroxyapatite and bacterial by-products for fluorescence detection and quantification of incipient occlusal and dental carious lesions in pits and fissures. This fluorescence technique has greater sensitivity than conventional visual and tactile methods [196, 197]. Since laser exposure lacks the risks of ionizing radiation, this allows its frequent use for monitoring dental lesions [198, 199]. Apparently, the best is the combination of a fluorescence detection system with a therapeutic laser to allow diagnosis and treatment of dental diseases in a single device.

ErCr : YSGG and Er : YAG lasers, operating at the wavelengths of 2780 nm and 2940 nm, respectively, are used for dental hard tissues including caries removal and cavity preparation without significant thermal effects, collateral damage to tooth structure and patient discomfort [200–202]. This is because normal dental enamel contains sufficient water and these Er-based laser wavelengths correspond to the peak absorption of water, so that they can achieve effective ablation at temperatures well below the melting and vaporization temperatures of the enamel [200]. For example, the most

uncomfortable component in dental treatment is probably the drill (handpiece). Er : YAG and CrEr : YSGG lasers can drill into the enamel and dentin, and may replace the dental drill with the advantages of minimal pain and no noise or vibration. The CO_2 laser is also highly absorbed by dental hard tissues, but it is not suitable for drilling and cutting enamel and dentine because its deeper thermal absorption can damage the dental pulp.

Numerous surgical procedures for soft tissues can be performed with lasers including gingivectomy, gingivoplasty, removal of gingival pigmentation, frenectomy, vestibuloplasty, aphthous removal, tumour excision, etc. Argon, KTP, Nd : YAG, ErCr : YSGG and Er : YAG lasers are usually used for minor soft tissue surgery, whereas CO_2 lasers are suitable for major soft tissue procedures [203–205]. This is due to the efficient absorption of many commonly used dental lasers by water and haemoglobin in oral tissues. The main advantages of laser soft tissue surgery are reduced bleeding and less pain.

Lasers can also be used for aesthetic dentistry such as tooth whitening. Diode (810–980 nm) and CO_2 (10 600 nm) lasers are used to induce photothermal bleaching; while argon (514.5 nm) and KTP (532 nm) lasers are used for photochemical bleaching due to the fact that their wavelengths fit well with the maximal absorption (510–540 nm) of those chelate compounds formed between apatites, porphyrins and tetracycline compounds [206].

6.4. Lasers in otolaryngology

Experimentally, the first laser in otolaryngology was the ruby laser that was used on the inner ear of pigeons in 1965. A Nd : YAG laser was then applied to the otosclerotic footplate in 1967 and an argon laser to the otic capsule in 1972. Today, laser technology is used in virtually all areas of the ear, nose and throat specialty. Although a number of lasers including CO_2, argon, KTP, Ho : YAG, Nd : YAG, diode lasers are available today, only the CO_2 laser is in routine use as a workhorse laser in otolaryngology because of its excellent cutting properties with little lateral tissue damage. The major advantage of the laser over a scalpel is, for example, that any damage to the voice box by larynx surgery can severely impair speech; while the laser enables lesions to be vaporized without additional damage to the larynx. Lasers have also been used to treat snoring by trimming away part of the uvula.

The CO_2 laser, with the help of a microlaryngoscope as well as a delivery system, offers a distinct advantage in the management of polyps, nodules, cysts, leukoplakia, subglottic stenosis, webs, capillary hemangiomas, etc in laryngology [207]. Treatment of these conditions needs careful attention to preserve the phonatory mechanism, as the vocal ligament may be involved. Micro-point manipulators on the newer generation of CO_2 lasers provide an excellent precision [208] in the management of certain conditions such as haemorrhagic polyp and Reinke's oedema [209, 210]. With an appropriate power setting in a pulsed mode, the capillaries are sealed off during surgery, facilitating the incision and dissection. The bilateral abductor paralysis, a neuromuscular disorder causing dyspnoea, can be treated with a laser to obtain satisfactory airways on phonation. Treatment of laryngeal tumours with a laser has been the subject of much debate and controversy, although lasers are the method of choice for treating recurrent respiratory papillomatosis.

In rhinology, almost any lesion in the nasal cavity can be treated with a laser. The nasal mucosa is extremely vascular and conventional surgical procedures (punch and grasping forceps) in the nose cause profuse bleeding, which obscures the view and makes the procedures become somewhat 'blind'. The relatively bloodless field offered by a laser and an endoscopic application device provides the surgical procedure with a better visual control of the surgical field and surrounding structures. Generally, effective preoperative decongestion of the nasal mucosa with a laser is almost universally useful. The benefits of nasal laser management are dependent on the nature of the lesion, laser energy as well as wavelength, surgical technique and the operator's experience.

In otology, laser applications for ear surgery are still very limited. The operative procedure on the ear largely involves gross bone removal. The energy provided by a laser may be utilized to undertake certain steps of the procedure where an extreme degree of finesse is required or where conventional procedures can produce unwanted effects. At a low intensity, argon laser radiation penetrates through the bone without altering it, and may thus be used to devitalise extensions of cholesteatoma within the cell spaces of the mastoid bone. At a high energy, it vaporizes the bone, and has been used to undertake fenestration of the footplate in otosclerosis.

PDT has been tried to treat head and neck cancer for more than two decades, and Foscan as a photosensitizer has recently been approved for such PDT treatment (table 5).

6.5. Lasers in gastroenterology

Gastroenterology was one of the earliest specialties to examine the use of lasers in the early 1970s for the arrest of gastrointestinal haemorrhage. Because of the developments in gastrointestinal endoscopic techniques and the optic fibres inserted through the instrument channels of endoscopes, laser light can be easily delivered to the upper and lower gastrointestinal tracts in a safe and relatively non-invasive fashion [211].

The most important laser used today in gastroenterology is Nd : YAG. Short shots from this laser obtain good haemostasis due to thermal contraction of soft tissue. Longer shots at high powers can vaporize tissue and coagulate the underlying layers for effective debulking of advanced tumours; while those at much lower powers can coagulate a larger volume of tissue without vaporization. Thermal lasers in current practice are used for palliation of advanced, inoperable cancers of the upper and lower gastrointestinal tract. Under direct vision with the laser fibre held away from the surface of the target, nodules of exophytic tumour can be vaporized and the underlying tumour coagulated either to relieve obstruction or to reduce blood loss. Laser therapy can improve dysphagia in patients with cancers of the esophagus and gastric cardia, but several treatments and the introduction of expanding stents are often needed to achieve optimum recanalization [212, 213].

The tip of the laser fibre can also be directly inserted into a targeted tissue with a much lower power to gently 'cook' the targeted area over a period of several minutes. This is called interstitial laser photocoagulation (ILP). ILP can be used for the percutaneous treatment of small hepatic metastases under the guidance of ultrasound, computerised tomography or magnetic resonance imaging in patients who are unsuitable for partial hepatectomy [214]. Because of the simple and cheap sclerotherapy for haemostasis, lasers are not often used for the control of haemorrhage today, but they still play an important role in controlling blood loss in vascular lesions such as hereditary telangiectasia and angiodysplasia. The Q-switched or pulsed Nd : YAG laser is often used for fragmenting biliary stones.

Perhaps the most important new applications of lasers in gastroenterology are PDT being developed for the treatment of dysplasia in Barrett's esophagus and small tumours in the gastrointestinal tract. Potential applications of PDT also include tumours of the pancreas and bile duct. The major advantage of PDT over thermal laser therapy is the selective effect on the mucosal layer of the gastrointestinal tract with little damage to underlying connective and muscular tissues, thus leading to minimal risk of perforation.

6.6. Lasers in urology

Since the first report on the use of a ruby laser to fragment urinary calculi in 1968, this technology has been extensively applied by urologists. Laser lithotripsy in the 1980s and now laser prostatectomy have dominated laser usage in urology. Because of improvements in endourology, nephroscopy, perinephroscopy, laparoscopy, pelviscopy and retroperitoneoscopy, almost all urologic organs have become visually accessible via fibreoptic laser delivery. Laser applications in urology are based on several mechanisms for laser–tissue interactions including photomechanical, photothermal and photochemical effects [48, 215–217].

Clinical applications of laser lithotripsy began in the mid-1980s with the introduction of the pulsed dye laser. The laser operates with a short pulse of 1 μs at a wavelength of 504 nm [218]. This is based on a photomechanical mechanism. The optical fibre is placed in direct contact with the stone, and a short laser pulse is delivered, resulting in a shockwave at the stone surface to fragment most types of stone. However, due to its large size and high cost as well as maintenance, the dye laser has been replaced with the Ho : YAG laser. Unlike the dye laser, the Ho : YAG laser operates with a long pulse of approximately 500 μs, generating a photothermal mechanism of stone fragmentation with chemical decomposition of the irradiated calculus components [219].

The Ho : YAG laser wavelength of 2120 nm is strongly absorbed by water in the tissue, allowing the laser to cut and coagulate tissue with a minimum zone of 0.3–0.4 mm. This property makes the laser also ideal for a range of soft tissue procedures including benign prostate hyperplasia (BPH) and bladder tumour as well as strictures. BPH, or enlargement of the prostate gland, is a common benign disease that occurs with increasing age in the male population. Recently, the frequency-doubled KTP and Nd : YAG lasers with a high power have been introduced for vaporization of BPH. The KTP laser wavelength of 532 nm is strongly absorbed by haemoglobin and therefore provides excellent haemostatic properties during vaporization and coagulation of the prostate, although with a larger thermal damage zone (1–2 mm) than the Ho : YAG laser. Thus, the KTP laser represents a higher power, less expensive, more reliable solid-state alternative.

Other common applications of lasers in urology include Ho : YAG laser incision of urethral strictures caused by surgery-induced tissue trauma, Ho : YAG laser ablation of superficial bladder transitional cell carcinoma [220], Nd : YAG and CO_2 laser ablation of penile carcinoma [221] and Nd : YAG and Ho : YAG laser incision of ureteroceles [222].

Although PDT is still under clinical development [223], it has shown promising results in the treatment of bladder cancer and small prostate and penile cancers with several photosensitizers including Photofrin and Tookad. Hexvix, a porphyrin precursor, has recently been approved by the EU for the photodetection of bladder cancer [224].

6.7. Lasers in gynaecology

Since the CO_2 laser was first used in gynaecology more than 20 years ago, a number of other lasers have been used in this field such as Nd : YAG, KTP, dye and diode lasers. As more gynaecological procedures move to laparoscopic, colposcopic and hysteroscopic surgery, the use of lasers continues to increase. Advances in laser technique have improved precision and minimized thermal damage. These make it possible to use a laser for incision, excision, resection, ablation, vaporization, coagulation and haemostasis of soft tissues in the field of gynaecology. With colposcopy and CO_2 laser ablation, for example, condyloma, leukoplakia and high-grade cervical, vulvar and vaginal intraepithelial neoplasia (CIN, VIN and VAIN) can be treated. A number of reports have shown this laser to be effective at treating VIN with a success rate of approximately 85% [225–228]. By laparoscopy/hysteroscopy and photovaporizing diseased or excess tissue, CO_2 and KTP lasers have also been used to treat ectopic pregnancies, dysmenorrhea, endometriosis, ovarian cysts, etc. In addition, lasers have been employed to perform hysterectomies and to reconstruct damaged or blocked fallopian tubes, thus allowing infertile women to conceive. The major advantage of laser treatment is the eradication of any volume of diseased epithelium, with negligible risk of scarring. Recently, fluorescent-dyed tissue samples with porphyrin precursors have been shown to reveal abnormal cells when excited by laser light, leading to early detection of cancer such as cervical cancer.

6.8. Lasers in the cardiovascular system

By fibreoptics laser radiation can be transmitted to anywhere in the cardiovascular system. This makes laser-based modalities attractive, and today laser technology is available for the treatment of artery disease, ventricular and superventricular arrhythmias, hypertrophic cardiomyopathy and congenital heart disease. The first laser application to treat cardiovascular diseases was made by McGuff *et al* [35] in 1963. They

used a laser to vaporize atherosclerotic plaques. Choy *et al* used argon laser radiation to treat thrombosis in animals, and then performed the first clinical coronary argon laser angioplasty with a bare fibre in 1983 [229]. In contrast to balloon angioplasty where plaque material is fractured, compressed, or displaced, laser angioplasty vaporizes the plaque material and thereby has a high success rate for treating chronic coronary artery occlusions. This approach is often referred to as laser thermal angioplasty, since the tips of optical fibres can convert the laser light energy into heat energy to achieve recanalization by mechanical compression and tissue vaporization of the plaque material. The results reported for excimer laser angioplasty show success rates of 82–85% with major complication rates of only 5–7% [230–233]. Failures of laser angioplasty occur often due to the inability to advance the catheter to the lesion because of prestenotic vessel tortuosity.

A laser can also ablate thrombi and emboli by photovaporization. This is because light absorption by haemoglobin in thrombi is larger than that by vascular tissue at 482 nm, thus providing a degree of selective laser ablation of the thrombi without damage to vascular walls [234]. Gregory *et al* reported selective laser thrombolysis of coronary artery thrombi in 17 out of 18 patients with significantly improved coronary blood flow [235].

Transmyocardial laser revascularization is a technique for the treatment of patients with chronic angina pectoris. This procedure employs a laser to create multiple transmyocardial channels in the ischemic areas. The procedure can also be performed by percutaneous myocardial laser revascularization with a less-invasive advantage. Clinical trials have shown a significant improvement in angina class, but it is too early to draw any clear conclusion, as the techniques have not yet indicated any significant increase in survival and myocardial functions [236].

Laser ablation has been studied in the treatment of ventricular and supraventricular arrhythmias. Saksena *et al* [237] and Isner *et al* [238] used argon and CO_2 lasers to achieve superficial vaporization of endocardial tissue responsible for ventricular tachycardia. Compared with argon and CO_2 lasers for tissue vaporization, the Nd : YAG laser has been proposed for antiarrhythmic therapy by *in situ* photocoagulation of the inciting focus. One of the advantages of Nd : YAG laser photocoagulation is that the treated tissues are left intact, preserving structural integrity of the myocardium. The major benefit in contrast to cryoablation is that Nd : YAG laser photocoagulation can be performed on the normothermic beating heart during ventricular tachycardia.

Although laser technology has been evaluated for the treatment of a number of cardiovascular disorders for several decades, it has not performed as well as hoped. The procedure may create dangerous blood clots and perforation of vascular wall due to laser ablation. Catheters have been reported to cause mechanical trauma and are also too stiff to pass through convoluted blood vessels. Further research on both laser technology and its cardiovascular application may find the laser valuable in the cardiovascular system.

6.9. Lasers in neurosurgery

Since initial experimental studies on the effects of ruby, argon and CO_2 lasers on the central nervous system (CNS) of rats, dogs and pigs in the period 1965–1970 [239–242], dramatic progress has been made with respect to both technical and surgical applications in brain and nervous tissues. The major effect of a laser on neural tissue is thermal. Today, the CO_2 and Nd : YAG lasers, perhaps also new high power diode lasers, are effective in the treatment of CNS tumours and vascular malformations. Generally, laser-induced tissue vaporization is suited for resection of intracerebral, extra-axial, skull base and spinal tumours including acoustic neuromas, pituitary tumours, spinal cord neuromas, intracerebral gliomas and metastases; and also for dissection of intracranial, spinal cord and intra-orbital meningiomas; while laser-induced tissue coagulation is used for the resection of vascular malformations such as arteriovenous malformations and cavernomas. The benefits of such laser therapy are due to the accurate and non-contact instruments that can reduce surgical brain trauma.

It should be pointed out that normal and abnormal brain tissues may have very different optical properties. For example, most brain tumours (meningioma, neuromas, high-grade gliomas, metastases) are highly vascularised with a high haemoglobin level and thus demonstrate high absorption coefficients in the 400–800 nm wavelength band. This indicates that argon and diode lasers may be effective for these types of tumours [243].

Stereotactic techniques are more often used for neurosurgery because of their smaller openings, reduced brain injury, decreased morbidity and a shorter postoperative period [244, 245]. In fact, any fibreoptic-guided laser can be used for stereotactic neurosurgical procedures including imaging-guided (MRI, CT or angiography) resection of superficial and deep-seated tumours and vascular lesions or endoscopic resection of tumours and cysts in ventricles. Laser-induced interstitial thermotherapy (LITT) is also a minimally invasive neurosurgical approach to the stereotactic treatment of tumours in poorly accessible regions [246,247]. MRI serves as the most promising technique for on-line monitoring of LITT [248].

PDT is a relative new technique that has been used for the treatment of brain tumours with HPD, Photofrin or Foscan [249–252].

6.10. Lasers in orthopaedics

Patients suffering from herniated discs and unable to recover using physical therapy, can now be treated with lasers. Over 500 000 Americans undergo low-back pain treatment with a laser each year. Lasers can vaporize tissue in a disc, creating a vacuum. This causes the disc to shrink away from the pressed nerve, relieving pain. Such surgery eliminates the need for cutting, scarring, hospitalization, postoperative instability, immobility and even general anaesthesia.

7. Diagnostic applications of lasers

'Optical biopsy' or 'optical diagnostics' is a technique whereby light energy is used to obtain information on the structure and function of tissue without disrupting it. Today, this technique employs a number of spectroscopic and imaging methods including absorption, fluorescence, reflectance, elastic scattering and Raman scattering to distinguish malignant from benign tissue, monitor metabolic state and measure local blood flow as well as drug concentration.

The techniques of laser-induced fluorescence (LIF) spectroscopy and imaging are based on the findings that endogenous autofluorescence spectroscopic/imaging patterns differ between normal and premalignant or malignant tissues. For application of LIF to superficial lesions of internal hollow organs optical fibres are inserted through an endoscope, and tissue autofluorescence can be both laser-excited and captured for spectroscopic and imaging analyses [253–256]. For example, to view mucosal abnormalities or tumours in the trachea and bronchi, lung imaging fluorescence endoscopy (LIFE) uses a fibreoptic endoscope with a blue laser light source to stimulate the natural fluorescence of tissue. Normal and abnormal tissues respond to this illumination differently, so LIFE images reveal minor abnormalities that would otherwise remain invisible. LIFE can detect early lung cancers or precancerous lesions as small as one millimetre across before they grow into invasive lung cancers [257]. However, due to the complex structure of biological tissue, the low intensity of natural fluorescence signals and the artefacts from scattering and fluorescence reabsorption, photodetection and interpretation of the tissue autofluorescence may be complicated, particularly in the case of inflammatory conditions that may cause false-positive results. These optical diagnostic techniques may be significantly improved by exogenously administered fluorescence compounds or their precursors that selectively localize in specific lesions, such as those photosensitisers used for PDT [223, 224]. ALA- or its derivative-induced endogenously fluorescent PpIX has already shown the enhanced discriminating potential of fluorescence spectroscopy and imaging (figures 8 and 9). Furthermore, the endogenous PpIX can serve as a potent photosensitizing agent for PDT. Most importantly, as a result of rapid advances in methodology and technology of tissue fluorescence imaging and PDT, endoscopists will likely in the coming years have a new armamentarium of diagnostic and therapeutic tools for detection and treatment of superficial premalignancies and malignancies of internal hollow organs during a single procedure. A standard endoscope equipped with an imaging system and a therapeutic illumination system may meet such a requirement for initial photodetection and subsequent PDT of lesions within one treatment session after employing PpIX precursors or other photosensitizers. The combination of endoscopy with the techniques of photodetection and PDT may revolutionize endoscopic technology.

Confocal microscopy is a novel and non-invasive tool that allows for real-time imaging of tissue *in vivo* or fresh biopsies *ex vivo* without the fixing, sectioning and staining necessary for routine histopathology. A confocal microscope consists of a laser light source that illuminates a small spot in tissue. Reflected or fluorescent light from the illuminated spot of the tissue is then imaged through a small pinhole aperture, producing an image of the plane only in focus in the tissue. The confocal microscopy provides fast, high (axial) resolution and high contrast imaging of live tissue that has potential diagnostic applications for lesions.

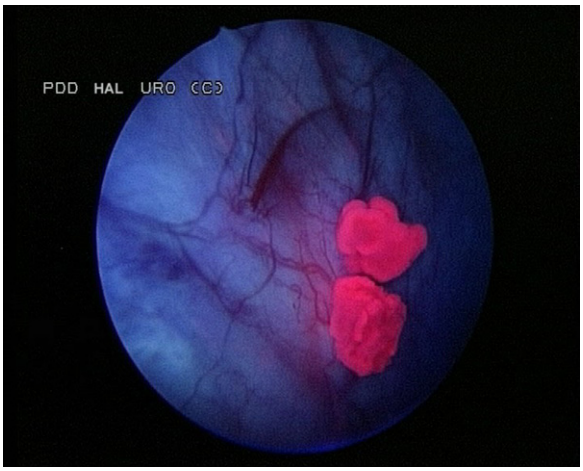

Figure 8. Highly selective ALA hexylester (Hexvix)-induced PpIX fluorescence in human bladder cancer (courtesy of Dr Dirt Zaak *et al*, Department of Urology, Klinikum Grosshadern, Ludwig-Maximilians-University of Munich, Munich).

Optical coherence tomography is a promising diagnostic method that uses low-coherence interferometry to produce a two-dimensional image of optical scattering from internal tissue microstructures in a way that is analogous to ultrasonic pulse-echo imaging. Cross-sectional images of tissue may be obtained *in vivo* with a better spatial resolution than confocal microscopy. This technique is potentially useful for non-invasive diagnosis of the retina and skin tumours with a penetration depth of 0.5–1.5 mm.

Laser Doppler velocimetry (LDV), also called laser Doppler flowmetry (LDF), is a simple and non-invasive method enabling the monitoring of microvascular blood flow, a very important marker of tissue health. In principle, a monochromatic laser beam is directed at the skin surface. Light that is reflected off stationary tissue undergoes no shift whilst light that is reflected off moving cells (like red blood cells) undergoes Doppler shift. The degree of Doppler shift increases with the velocity of the cells. This light is randomly reflected back from the tissue to a photodetector which calculates the average velocity of cells within the tissue.

As biotechnology evolves, a number of new techniques using a laser such as flow cytometry and mass spectrometry are more often applied to discover new biomarkers for detection of diseases as well as for evaluating the results of treatment.

8. Laser nanosurgery in cell biology

During the past 10 years the quality and availability of pulsed lasers have significantly improved. Very high light intensity can be delivered in an ultrashort period

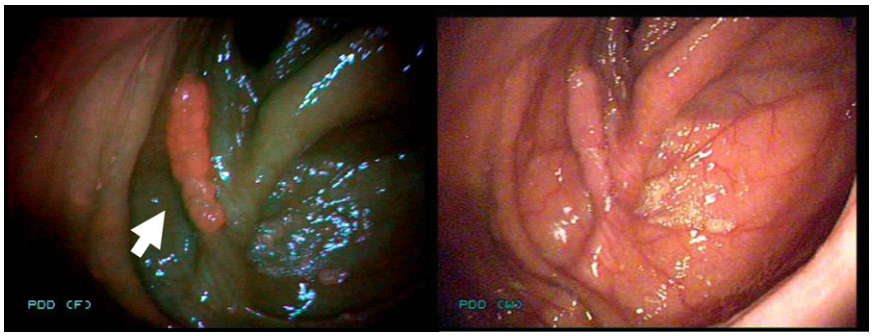

Figure 9. Highly selective ALA hexylester (Hexvix)-induced PpIX fluorescence (arrow in the left) in human rectal adenoma (courtesy of Dr Brigitte Mayinger *et al*, Department of Medicine II, Hospital Munich-Pasing, Munich).

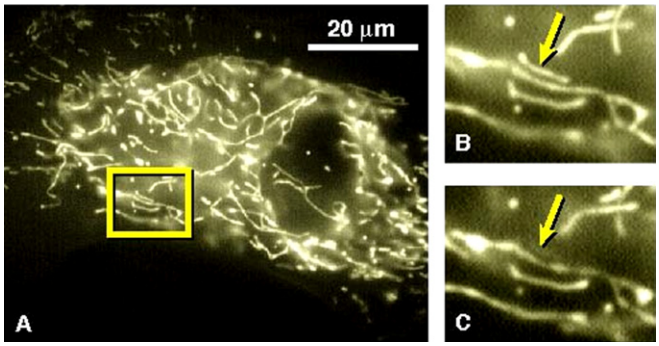

Figure 10. Ablation of single mitochondrion in a cell with a femtosecond pulsed laser. (*a*) Fluorescence image showing multiple mitochondria before the femtosecond pulsed laser application. Ablation of a single mitochondrion before ((*b*), arrow) and after ((*c*), arrow) laser pulses. Note that neighbouring mitochondria are unaffected (courtesy of Dr Eric Mazur, Department of Physics, Harvard University).

ranging from nanoseconds (10^{-9} s) to femtoseconds (10^{-15} s). By tightly focusing the femtosecond laser pulse with a microscope objective within an extremely small volume, it is possible to achieve ablation on the level of a single cell or a subcellular compartment with a precision in the range of hundreds of nanometres without damaging surrounding structures [258–260]. Since 1995 when Konig *et al* first demonstrated the dissection of isolated human chromosomes, picosecond UV and femtosecond IR pulsed lasers have increasingly been employed for cellular and subcellular surgery to ablate organelles without affecting cell viability [259]. Figure 10 shows, for example, the entire ablation of a single mitochondrion by a femtosecond laser with precision targeting [261]. Other subcellular targets include actin filaments and microtubules (figure 11) [261]. Femtosecond lasers have even improved transfection efficiency of DNA in cells for gene therapy [262]. In fact, femtosecond lasers can function as a pair of 'nanoscissors' in subcellular surgery and have potential applications in a single organelle or chromosome dissection, inactivation of specific genomic regions on individual chromosomes and highly localized gene and molecular transfer. The major advantage of pulsed laser nanosurgery is the well-controlled and non-invasive capability of severing subcellular structures with high accuracy in time and three-dimensional space.

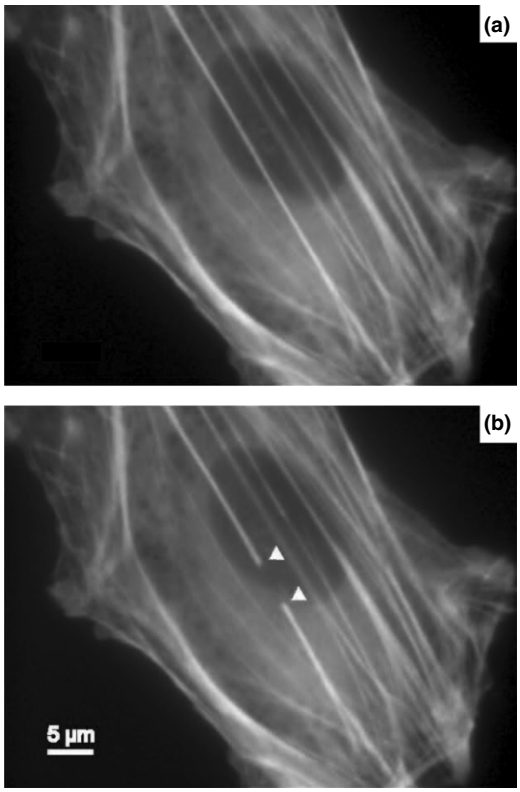

Figure 11. Ablation of actin filaments in a cell with a femtosecond pulsed laser. Fluorescence images of actin filaments before (*a*) and after (*b*) laser dissection (arrowheads) of an actin fibre (courtesy of Dr Eric Mazur, Department of Physics, Harvard University).

9. Future directions

The future development of medical lasers will largely depend upon the demands of patients and doctors for cost-effective methods. Although lasers have found their place in medical diagnosis and therapy (table 8) since their creation about half a century ago, they will find many more medical applications as the progress in optical technology and better understanding of the interactions between laser irradiation and tissue are made. A recent market study by Frost & Sullivan, a research firm in London, predicts that the European market for medical lasers will nearly triple by 2013 to $862 million from $329 million in 2006. The major driving force for the growth is the

Table 8. Common types of medical lasers and their major indications.

	Type of lasers	Major indications
Dermatology	Pulsed dye, ruby, KTP, diode, alexandrite, argon, CO_2, Nd : YAG, excimer	Vascular lesions Benign and malignant tumours infectious lesions Pigmented lesions and tattoos cosmetic conditions
Ophthalmology	Ruby, argon, Nd : YAG, diode, excimer	Diabetic retinopathy Age-related macular degeneration Glaucoma Corneal disorder
Dentistry	Argon, KTP, HeNe, diode, Nd : YAG, ErCr : YSGG, Er : YAG, CO_2	Caries Periodontitis Infected root canals Cavity preparation Soft tissue surgery Tooth whitening
Otolaryngology	CO_2, KTP, argon, Nd : YAG, Ho : YAG, diode	Polyps, nodules, cysts leukoplakia Subglottic stenosis Webs, capillary hemangiomas,
Gastroenterology	Nd : YAG, diode	Haemostasis Vascular lesions Dysplasia in Barrett's esophagus Cutting and debulking of tumours Fragmentation of gall stones
Urology	Pulsed dye, Ho : YAG, KTP, Nd : YAG, diode	Lithotripsy Benign prostate hyperplasia Prostate tumour Bladder tumour
Gynaecology	Nd : YAG, CO_2, KTP, dye, diode	Condyloma Leukoplakia CIN, VIN, VAIN Ectopic pregnancies Dysmenorrhea, endometriosis ovarian cysts Hysterectomies
Cardiovascular system	Argon, excimer, Ho : YAG, CO_2	Atherosclerotic lesions Thrombi and emboli Transmyocardial revascularization Percutaneous myocardial revascularization
Neurosurgery	CO_2, Nd : YAG, diode, argon	Meningiomas Acoustic neuromas Spinal tumours Tumour metastases Vascular malformations Stereotactic neurosurgery
Orthopaedics	Nd : YAG, Ho : YAG	Cutting and ablating soft/hard tissue Smoothing cartilage Knee surgery Lumbar disc decompression

ophthalmic, cardiovascular and urologic applications [263]. On the horizon, a number of newer types of lasers are under investigation for possible medical uses. Generally, new lasers are becoming smaller, more flexible and less expensive with specific applications. Femtosecond pulsed lasers with high power and low energy will allow surgeons to perform precise microsurgery without significant heating of the tissue. New fibre lasers with various wavelengths in a continuous or pulsed way will be developed without the need for a conventional resonant cavity. More powerful solid-state pumped lasers will have greater power and cover all the visible and near infrared regions. Mid-infrared semiconductor lasers with the capability of determining exact chemical specificity would likely enable optical characterization of a disease. Intense pulse light sources and LEDs will replace the laser in some applications. Perhaps the future of the laser will include multi-wave systems in a single or compact unit with multiple applications. In particular, multi-functional diagnostic laser facilities including *in vivo* spectroscopic and imaging systems can be combined with therapeutic laser procedures using an effective photosensitizer.

10. Conclusions

The medical applications of the laser started about half a century ago, shortly after the invention of the laser. Today, lasers are applied to almost all fields of medicine, providing considerable benefits to both doctors and patients for both diagnostic and therapeutic purposes. Laser therapy consists mainly of photothermal therapy and PDT, the latter is a

combination of a lesion-localizing photosensitizer with non-thermal laser irradiation. In thermal laser therapy, the major advantages are precision, haemostasis, sterilized treated site, reduced oedema, less scarring, less pain and short recovery period. Being complicated to use thus requiring proper training may be the main disadvantage. The benefits of PDT include high selectivity and no toxicity of a photosensitizer, usefulness of both diagnosis and therapy and possible repetition if necessary; although it has a limited light penetration into tissue and may cause skin photosensitization to light. Successful laser treatment depends on the understanding of interactions between optical irradiation and biological tissue and on the appropriate laser being used for a particular disease by a fully trained doctor in a safe manner. In addition, an effective photosensitizer is essential for PDT treatment. It should, however, be pointed out that lasers should only be used when they can offer clear advantage over conventional modalities.

References

[1] Einstein A 1905 Über einen die Erzeugung und Verwandlung des Lichtes betreffenden heuristischen Gesichtspunkt *Ann. Phys.* **17** 132

[2] Bose S N 1924 Plancks Gesetz und Lichtquantenhypothese *Z. Phys.* **26** 178

[3] Einstein A 1924 Quantentheorie des einatomigen idealen Gases *Sitz. Preussischen Akad. Wiss.* **22** 261

[4] Einstein A 1925 Quantentheorie des einatomigen idealen Gases, Zweite Abhandlung *Sitz. Preussischen Akad. Wiss.* **8** 3

[5] Basov N G and Prochorov A M 1954 Application of molecular beams for the radiospectroscopic study of rotational molecular spectra *J. Exp. Theor. Phys.* **27** 431

[6] Gordon J P, Zeiger H J and Townes C H 1954 Molecular microwave oscillator and new hyperfine structure in the microwave spectrum of NH_3 *Phys. Rev.* **95** 282

[7] Schawlow A L and Townes C H 1958 Infrared and optical masers *Phys. Rev.* **112** 1940

[8] Maiman T H 1960 Simulated optical radiation in ruby *Nature* **187** 493

[9] Javan A, Bennett W R and Herriott D R 1961 Population inversion and continuous optical maser oscillation in a gas discharge containing a He–Ne mixture *Phys. Rev. Lett.* **6** 106

[10] Johnson L F 1961 Optical maser characteristics of rare-earth ions in crystals *J. Appl. Physiol.* **34** 897

[11] Bennett W R, Faust W L, McFarlane R A and Patel C K N 1962 Dissociative excitation transfer and optical maser oscillation in Ne–O_2 and Ar–O_2 rf discharges *Phys. Rev. Lett.* **8** 470

[12] Patel C K N 1964 Selective excitation through vibrational energy transfer and optical maser action in N_2–CO_2 *Phys. Rev. Lett.* **13** 617

[13] Choy D S 1988 History of lasers in medicine *Thorac. Cardiovasc. Surg.* **36** (Suppl.) 114

[14] Kirschner R A and Unger M 1984 Introduction to laser surgery *Surg. Clin. North Am.* **64** 839

[15] van Gemert, M J C and Welch A J 1989 Clinical use of laser-tissue interactions *IEEE Eng. Med. Biol. Mag.* **8** 10

[16] Knappe V, Frank F and Rohde E 2004 Principles of lasers and biophotonic effects *Photomed. Laser Surg.* **22** 411

[17] McKenzie A L and Carruth J A 1984 Lasers in surgery and medicine *Phys. Med. Biol.* **29** 619

[18] Eichler J and Gonçalves O 2002 A review of different lasers in endonasal surgery: Ar-, KTP-, dye-, diode-, Nd-, Ho- and CO_2-laser *Med. Laser Appl.* **17** 190

[19] Fitzpatrick R E and Goldman M P 1995 Advances in carbon dioxide laser surgery *Clin. Dermatol.* **13** 35

[20] Rodrigues L K, dos Santos M N, Pereira D, Assaf A V and Pardi V 2004 Carbon dioxide laser in dental caries prevention *J. Dent.* **32** 531

[21] Hamilton M M 2004 Carbon dioxide laser resurfacing *Facial Plast. Surg. Clin. North Am.* **12** 289

[22] Weinstein C and Scheflan M 2000 Simultaneously combined ER : YAG and carbon dioxide laser (derma K) for skin resurfacing *Clin. Plast. Surg.* **27** 273

[23] Jacobson D, Bass L S, VanderKam V and Achauer B M 2000 Carbon dioxide and ER : YAG laser resurfacing: results *Clin. Plast. Surg.* **27** 241

[24] Miyamoto A, Sakurada M, Arai T, Mizuno K, Kurita A, Nakamura H and Kikuchi M 1993 Efficacy of carbon monoxide laser in selectively intimal thermal welding-implications for laser balloon angioplasty *Japan. Circ. J.* **57** 825

[25] Katzir A 1993 *Lasers and Optical Fibers in Medicine* (San Diego: Academic)

[26] Walbarsht M L 1984 Laser surgery CO_2 or HF? *IEEE J. Quantum Electron.* **20** 1427

[27] Basov N G, Danilychev V A and Popov Yu M 1971 Stimulated emission in the vacuum ultraviolet region *Sov. J. Quantum Electron.* **1** 18

[28] Shortt A J and Allan B D 2006 Photorefractive keratectomy (PRK) versus laser-assisted in-situ keratomileusis (LASIK) for myopia *Cochrane Database Syst. Rev.* CD005135

[29] Bansal A K and Veenashree M P 2001 Laser refractive surgery: technological advance and tissue response *Biosci. Rep.* **21** 491

[30] Spencer J M and Hadi S M 2004 The excimer lasers *J. Drugs Dermatol.* **3** 522

[31] Wong B J, Dickinson M R, Berns M W and Neev J 1996 Identification of photoacoustic transients during pulsed laser ablation of the human temporal bone: an experimental model *J. Clin. Laser Med. Surg.* **14** 385

[32] Maiman T H 1960 Optical and microwave-optical experiments in ruby *Phys. Rev. Lett.* **4** 564

[33] Goldman L, Blanet D J, Kindet D J Jr, Richfield D and Franke E K 1963 Pathology of the effect of the laser beam on the skin *Nature* **197** 912

[34] McGuff P E, Deterling R A Jr, Gottlier L S, Fahimi H D, Bushnell D and Roeber F 1964 The laser treatment of experimental malignant tumours *Can. Med. Assoc. J.* **91** 1089

[35] McGuff P E, Bushnell D, Soroff H S and Deterling R A Jr 1963 Studies of the surgical applications of laser (light amplification by stimulated emission of radiation) *Surg. Forum* **14** 143

[36] McGuff P E, Deterling R A Jr, Gottlieb L S, Fahimi H D and Bushnell D 1964 Surgical applications of laser *Ann. Surg.* **160** 765

[37] Campbell C J, Koester C J, Curtice V, Noyori K S and Rittler M C 1965 Clinical studies in laser photocoagulation *Arch. Ophthalmol.* **74** 57

[38] Nanni C A and Alster T S 1998 A practical review of laser-assisted hair removal using the Q-switched Nd : YAG, long-pulsed ruby, and long-pulsed alexandrite lasers *Dermatol. Surg.* **24** 1399

[39] Bernstein E F 2006 Laser treatment of tattoos *Clin. Dermatol.* **24** 43

[40] Kuperman-Beade M, Levine V J and Ashinoff R 2001 Laser removal of tattoos *Am. J. Clin. Dermatol.* **2** 21

[41] Raulin C, Schonermark M P, Greve B and Werner S 1998 Q-switched ruby laser treatment of tattoos and benign pigmented skin lesions: a critical review *Ann. Plast. Surg.* **41** 555

[42] Adrian R M and Griffin L 2000 Laser tattoo removal *Clin. Plast. Surg.* **27** 181

[43] Bradley P F 1997 A review of the use of the neodymium YAG laser in oral and maxillofacial surgery *Br. J. Oral Maxillofac. Surg.* **35** 26

[44] Myers T D and McDaniel J D 1991 The pulsed Nd : YAG dental laser: review of clinical applications *J. Calif. Dent. Assoc.* **19** 25

[45] Fankhauser F and Kwasniewska S 2003 Clinical effects of the Nd : YAG laser operating in the photodisruptive and thermal modes: a review *Ophthalmologica* **217** 1

[46] Gossner L, May A, Stolte M, Seitz G, Hahn E G and Ell C 1999 KTP laser destruction of dysplasia and early cancer in columnar-lined Barrett's esophagus *Gastrointest. Endosc.* **49** 8

[47] Smith J A Jr and Landau S 1989 Neodymium: YAG laser specifications for safe intravesical therapy *J. Urol.* **141** 1238

[48] Bhatta K M 1995 Lasers in urology *Lasers Surg. Med.* **16** 312

[49] Mackety C J 1990 Lasers in urology *Nurs. Clin. North Am.* **25** 697

[50] Sacknoff E J 1993 Laser advances in urology *J. Clin. Laser Med. Surg.* **11** 173

[51] Kulpati D D and Kumar V 1991 Lasers in pulmonology *J. Assoc. Physicians India* **39** 630

[52] Absten G T 1991 Physics of light and lasers *Obstet. Gynecol. Clin. North Am.* **18** 407

[53] Ito Y and Kasugai T 1987 Use of endoscopic laser in gastroenterology *Ann. Acad. Med. Singapore* **16** 290

[54] Sohajda Z, Bekesi L and Berta A 1997 In ophthalmology new possibilities for the use Nd : YAG laser *Acta Chir Hung.* **36** 331

[55] Caniglia R J 2004 Erbium : YAG laser skin resurfacing *Facial Plast. Surg. Clin. North Am.* **12** 373

[56] Papadavid E and Katsambas A 2003 Lasers for facial rejuvenation: a review *Int. J. Dermatol.* **42** 480

[57] Kohnen T, Koch D D, McDonnell P J, Menefee R F and Berry M J 1997 Noncontact holmium : YAG laser thermal keratoplasty to correct hyperopia: 18-month follow-up *Ophthalmologica* **211** 274

[58] Papadopoulos N T, Balidis M, Brazitikos P D, Androudi S, Fotiadis K, Kalinderis K A and Stangos N T 2005 Non-contact holmium : YAG laser thermal keratoplasty for hyperopia: two-year follow-up *J. Refract. Surg.* **21** 82

[59] Rocha G, Castillo J M, Sanchez-Thorin J C, Johnston J and Cartagena R G 2003 Two-year follow-up of noncontact holmium laser thermokeratoplasty for the correction of low hyperopia *Can. J. Ophthalmol.* **38** 385

[60] Moulton P F 1986 Spectroscopic and laser characteristics of Ti : Al_2O_3 *J. Opt. Soc. Am.* B **3** 125

[61] Haedersdal M and Wulf H C 2006 Evidence-based review of hair removal using lasers and light sources *J. Eur. Acad. Dermatol. Venereol.* **20** 9

[62] Lask G, Eckhouse S, Slatkine M, Waldman A, Kreindel M and Gottfried V 1999 The role of laser and intense light sources in photo-epilation: a comparative evaluation *J. Cutan. Laser Ther.* **1** 3

[63] Liew S H 2002 Laser hair removal: guidelines for management *Am. J. Clin. Dermatol.* **3** 107

[64] Sanchez L A, Perez M and Azziz R 2002 Laser hair reduction in the hirsute patient: a critical assessment *Hum. Reprod. Update* **8** 169

[65] Wanner M 2005 Laser hair removal *Dermatol. Ther.* **18** 209

[66] Pearle M S, Sech S M, Cobb C G, Riley J R, Clark P J, Preminger G M, Drach G W and Roehrborn C G 1998 Safety and efficacy of the alexandrite laser for the treatment of renal and ureteral calculi *Urology* **51** 33

[67] Pertusa C, Albisu A, Acha M, Blasco M, Llarena R and Arregui P 1991 Lithotripsy with the alexandrite laser: our initial 100 clinical cases *Eur. Urol.* **20** 269

[68] Nair L G 1982 Dye lasers *Prog. Quantum Electron.* **7** 153

[69] Alexiades-Armenakas M 2006 Laser-mediated photodynamic therapy *Clin. Dermatol.* **24** 16

[70] Kauvar A N and Khrom T 2005 Laser treatment of leg veins *Semin. Cutan. Med. Surg.* **24** 184

[71] Kelly K M, Choi B, McFarlane S, Motosue A, Jung B, Khan M H, Ramirez-San-Juan J C and Nelson J S 2005 Description and analysis of treatments for port-wine stain birthmarks *Arch. Facial Plast. Surg.* **7** 287

[72] Nouri K and Ballard C J 2006 Laser therapy for acne *Clin. Dermatol.* **24** 26

[73] Rokhsar C K, Lee S and Fitzpatrick R E 2005 Review of photorejuvenation: devices, cosmeceuticals, or both? *Dermatol. Surg.* **31** 1166

[74] Gevargez A, Groenemeyer D W and Czerwinski F 2000 C T-guided percutaneous laser disc decompression with Ceralas D, a diode laser with 980-nm wavelength and 200-microm fiber optics *Eur. Radiol.* **10** 1239

[75] Hammer-Wilson M J, Sun C H, Ghahramanlou M and Berns M W 1998 In vitro and in vivo comparison of argon-pumped and diode lasers for photodynamic therapy using second-generation photosensitizers *Lasers Surg. Med.* **23** 274

[76] Spitzer M and Krumholz B A 1991 Photodynamic therapy in gynecology *Obstet. Gynecol. Clin. North Am.* **18** 649

[77] O'Shea P G and Freund H P 2001 Free-electron lasers: status and applications *Science* **292** 1853

[78] Niemz M H 2003 *Laser-Tissue Interactions: Fundamentals and Applications* (Berlin: Springer)

[79] Pogue B W, Lilge L, Patterson M S, Wilson B C and Hasan T 1997 Absorbed photodynamic dose from pulsed versus continuous wave light examined with tissue-simulating dosimeters *Appl. Opt.* **36** 7257

[80] Sterenborg H J and van Gemert M J 1996 Photodynamic therapy with pulsed light sources: a theoretical analysis *Phys. Med. Biol.* **41** 835

[81] Lui H *et al* 2004 Photodynamic therapy of multiple nonmelanoma skin cancers with verteporfin and red light-emitting diodes: two-year results evaluating tumor response and cosmetic outcomes *Arch. Dermatol.* **140** 26

[82] Babilas P, Kohl E, Maisch T, Backer H, Gross B, Branzan A L, Baumler W, Landthaler M, Karrer S and Szeimies R M 2006 In vitro and in vivo comparison of two different light sources for topical photodynamic therapy *Br. J. Dermatol.* **154** 712

[83] Babilas P, Travnik R, Werner A, Landthaler M and Szeimies R M 2008 Split-face-study using two different light sources for topical PDT of actinic keratoses : non-inferiority of the LED system *J. Dtsch. Dermatol. Ges.* **6** 25

[84] Whelan H T *et al* 2001 Effect of NASA light-emitting diode irradiation on wound healing *J. Clin. Laser Med. Surg.* **19** 305

[85] Al-Watban F A and Andres B L 2003 Polychromatic LED therapy in burn healing of non-diabetic and diabetic rats *J. Clin. Laser Med. Surg.* **21** 249

[86] Whelan H T *et al* 2003 Effect of NASA light-emitting diode irradiation on molecular changes for wound healing in diabetic mice *J. Clin. Laser Med. Surg.* **21** 67

[87] Vladimirov Y A, Osipov A N and Klebanov G I 2004 Photobiological principles of therapeutic applications of laser radiation *Biochemistry (Moscow)* **69** 81

[88] Vreman H J, Wong R J, Stevenson D K, Route R K, Reader S D, Fejer M M, Gale R and Seidman D S 1998

Light-emitting diodes: a novel light source for phototherapy *Pediatr. Res.* **44** 804

[89] Seidman D S, Moise J, Ergaz Z, Laor A, Vreman H J, Stevenson D K and Gale R 2000 A new blue light-emitting phototherapy device: a prospective randomized controlled study *J. Pediatr.* **136** 771

[90] Lee S Y, Park K H, Choi J W, Kwon J K, Lee D R, Shin M S, Lee J S, You C E and Park M Y 2007 A prospective, randomized, placebo-controlled, double-blinded, and split-face clinical study on LED phototherapy for skin rejuvenation: clinical, profilometric, histologic, ultrastructural, and biochemical evaluations and comparison of three different treatment settings *J. Photochem. Photobiol.* B **88** 51

[91] Corazza A V, Jorge J, Kurachi C and Bagnato V S 2007 Photobiomodulation on the angiogenesis of skin wounds in rats using different light sources *Photomed. Laser Surg.* **25** 102

[92] Weiss R A, Weiss M A, Geronemus R G and McDaniel D H 2004 A novel non-thermal non-ablative full panel LED photomodulation device for reversal of photoaging: digital microscopic and clinical results in various skin types *J. Drugs Dermatol.* **3** 605

[93] Weiss R A, McDaniel D H, Geronemus R G and Weiss M A 2005 Clinical trial of a novel non-thermal LED array for reversal of photoaging: clinical, histologic, and surface profilometric results *Lasers Surg. Med.* **36** 85

[94] Karu T 1998 *Science of Low Power Laser Therapy* (London: Taylor & Francis)

[95] Boulnois J L 1986 Photophysical processes in recent medical laser developments: a review *Laser Med. Sci.* **1** 47

[96] Fradin D W, Bloembergen N and Letellier J P 1973 Dependence of laser-induced breakdown field strength on pulse duration *Appl. Phys. Lett.* **22** 635

[97] Geerling G, Roider J, Schmidt-Erfurt U, Nahen K, El-Hifnawi E, Laqua H and Vogel A 1998 Initial clinical experience with the picosecond Nd : YLF laser for intraocular therapeutic applications *Br. J. Ophthalmol.* **82** 504

[98] Krause M H and D'Amico D J 2003 Ablation of vitreous tissue with a high repetition rate erbium : YAG laser *Eur. J. Ophthalmol.* **13** 424

[99] Krause M, Steeb D, Foth H J, Weindler J and Ruprecht K W 1999 Ablation of vitreous tissue with erbium : YAG laser *Invest Ophthalmol. Vis. Sci.* **40** 1025

[100] Thompson K P, Ren Q S and Parel J M 1992 Therapeutic and diagnostic application of lasers in ophthalmology *Proc. IEEE* **80** 838

[101] Srinivasan R, Dyer P E and Braren B 1987 Far-ultraviolet laser ablation of the cornea: photoacoustic studies *Lasers Surg. Med.* **6** 514

[102] Grosvenor T 1995 How predictable are the results of excimer laser photorefractive keratectomy? A review *Optom. Vis. Sci.* **72** 698

[103] Klyce S D and Smolek M K 1993 Corneal topography of excimer laser photorefractive keratectomy *J. Cataract Refract. Surg.* **19** (Suppl) 122

[104] Leccisotti A 2006 Bioptics: where do things stand? *Curr. Opin. Ophthalmol.* **17** 399

[105] Kohlhaas M 1998 Corneal sensation after cataract and refractive surgery *J. Cataract Refract. Surg.* **24** 1399

[106] Gilmour M A 2003 Laser applications for corneal disease *Clin. Tech. Small Animal Pract.* **18** 199

[107] Pallikaris I G, Katsanevaki V J, Kalyvianaki M I and Naoumidi I I 2003 Advances in subepithelial excimer refractive surgery techniques: Epi-LASIK *Curr. Opin. Ophthalmol.* **14** 207

[108] Raunest J and Lohnert J 1990 Arthroscopic cartilage debridement by excimer laser in chondromalacia of the knee joint. A prospective randomized clinical study *Arch. Orthop. Trauma Surg.* **109** 155

[109] Koster R, Kahler J, Brockhoff C, Munzel T and Meinertz T 2002 Laser coronary angioplasty: history, present and future *Am. J. Cardiovasc. Drugs* **2** 197

[110] Dahm J B 2001 Excimer laser coronary angioplasty (ELCA) for diffuse in-stent restenosis: beneficial long-term results after sufficient debulking with a lesion-specific approach using various laser catheters *Lasers Med. Sci.* **16** 84

[111] Tcheng J E and Volkert-Noethen A A 2001 Current multicentre studies with the excimer laser: design and aims *Lasers Med. Sci.* **16** 122

[112] Welch A J, Kang H W, Lee H and Teichman J M 2004 Calculus fragmentation in laser lithotripsy *Minerva Urol. Nefrol.* **56** 49

[113] Svaasand L O 1989 Dosimetry for laser induced hyperthermia *Laser Med. Sci.* **4** 309

[114] Svaasand L O, Gomer C J and Morinelli E 1990 On the physical rationale of laser induced hyperthermia *Laser Med. Sci.* **5** 121

[115] Jori G and Spikes J D 1990 Photothermal sensitizers: possible use in tumour therapy *J. Photochem. Photobiol.* B **6** 93

[116] Chen W R, Adams R L, Bartels K E and Nordquist R E 1995 Chromophore-enhanced in vivo tumour cell destruction using an 808-nm diode laser *Cancer Lett.* **94** 125

[117] Chen W R, Adams R L, Heaton S, Dickey D T, Bartels K E and Nordquist R E 1995 Chromophore-enhanced laser-tumour tissue photothermal interaction using an 808-nm diode laser *Cancer Lett.* **88** 15

[118] Chen W R, Adams R L, Higgins A K, Bartels K E and Nordquist R E 1996 Photothermal effects on murine mammary tumours using indocyanine green and an 808-nm diode laser: an in vivo efficacy study *Cancer Lett.* **98** 169

[119] Camerin M, Rodgers M A, Kenney M E and Jori G 2005 Photothermal sensitisation: evidence for the lack of oxygen effect on the photosensitising activity *Photochem. Photobiol. Sci.* **4** 251

[120] Busetti A, Soncin M, Reddi E, Rodgers M A, Kenney M E and Jori G 1999 Photothermal sensitization of amelanotic melanoma cells by Ni(II)-octabutoxy-naphthalocyanine *J. Photochem. Photobiol.* B **53** 103

[121] Zharov V P, Letfullin R R and Galitovskaya E N 2005 Microbubbles-overlapping mode for laser killing of cancer cells with absorbing nanoparticle clusters *J. Phys. D: Appl. Phys.* **38** 2571

[122] Leszczynski D, Pitsillides C M, Pastila R K, Rox A R and Lin C P 2001 Laser-beam-triggered microcavitation: a novel method for selective cell destruction *Radiat. Res.* **156** 399

[123] Pitsillides C M, Joe E K, Wei X, Anderson R R and Lin C P 2003 Selective cell targeting with light-absorbing microparticles and nanoparticles *Biophys. J.* **84** 4023

[124] Lapotko D O 2006 Laser-induced bubbles in living cells *Lasers Surg. Med.* **38** 240

[125] Huang X, Jain P K, El-Sayed I H and El-Sayed M A 2006 Determination of the minimum temperature required for selective photothermal destruction of cancer cells with the use of immunotargeted gold nanoparticles *Photochem. Photobiol.* **82** 412

[126] Chen W R, Carubelli R, Liu H and Nordquist R E 2003 Laser immunotherapy: a novel treatment modality for metastatic tumours *Mol. Biotechnol.* **25** 37

[127] Chen W R, Singhal A K, Liu H and Nordquist R E 2001 Antitumour immunity induced by laser immunotherapy and its adoptive transfer *Cancer Res.* **61** 459

[128] Chen W R, Liu H, Ritchey J W, Bartels K E, Lucroy M D and Nordquist R E 2002 Effect of different components of laser immunotherapy in treatment of metastatic tumours in rats *Cancer Res.* **62** 4295
[129] Chen W R, Carubelli R, Liu H and Nordquist R E 2003 Detection of anti-tumour immunity induced by laser immunotherapy *Mol. Biotechnol.* **25** 45
[130] Chen W R, Korbelik M, Bartels K E, Liu H, Sun J and Nordquist R E 2005 Enhancement of laser cancer treatment by a chitosan-derived immunoadjuvant *Photochem. Photobiol.* **81** 190
[131] Halliwell B 1991 Reactive oxygen species in living systems: source, biochemistry, and role in human disease *Am. J. Med.* **91** 14S
[132] Bayir H 2005 Reactive oxygen species *Crit. Care Med.* **33** S498–501
[133] Devasagayam T P and Kamat J P 2002 Biological significance of singlet oxygen *Indian J. Exp. Biol.* **40** 680
[134] Weishaupt K R, Gomer C J and Dougherty T J 1976 Identification of singlet oxygen as the cytotoxic agent in photoinactivation of a murine tumour *Cancer Res.* **36** 2326
[135] Moan J, Peng Q, Sorensen R, Iani V and Nesland J M 1998 The biophysical foundations of photodynamic therapy *Endoscopy* **30** 387
[136] Anderson R R and Parrish J A 1981 The optics of human skin *J. Invest. Dermatol.* **77** 13
[137] Brancaleon L and Moseley H 2002 Laser and non-laser light sources for photodynamic therapy *Lasers Med. Sci.* **17** 173
[138] Kelty C J, Brown N J, Reed M W and Ackroyd R 2002 The use of 5-aminolaevulinic acid as a photosensitiser in photodynamic therapy and photodiagnosis *Photochem. Photobiol. Sci.* **1** 158
[139] Morton C A 2002 The emerging role of 5-ALA-PDT in dermatology: is PDT superior to standard treatments? *J. Dermatol. Treat.* **13** (Suppl) S25–9
[140] Szeimies R M, Landthaler M and Karrer S 2002 Non-oncologic indications for ALA-PDT *J. Dermatol. Treat.* **13** (Suppl) S13–8
[141] Peng Q, Warloe T, Berg K, Moan J, Kongshaug M, Giercksky K E and Nesland J M 1997 5-Aminolevulinic acid-based photodynamic therapy: clinical research and future challenges *Cancer* **79** 2282
[142] Moan J, van den Akker J T H M, Juzenas P and Ma L-W 2001 On the basis for tumour selectivity in the 5-aminolevulinic acid-induced synthesis of protoporphyrin IX *J. Porphyrins Phthalocyanines* **5** 170
[143] Collaud S, Juzeniene A, Moan J and Lange N 2004 On the selectivity of 5-aminolevulinic acid-induced protoporphyrin IX formation *Curr. Med. Chem. Anticancer Agents* **4** 301
[144] Chen B, Xu Y, Agostinis P and de Witte P A 2001 Synergistic effect of photodynamic therapy with hypericin in combination with hyperthermia on loss of clonogenicity of RIF-1 cells *Int. J. Oncol.* **18** 1279
[145] Chen B, Roskams T and de Witte P A 2002 Enhancing the antitumoural effect of hypericin-mediated photodynamic therapy by hyperthermia *Lasers Surg. Med.* **31** 158
[146] Christensen T, Wahl A and Smedshammer L 1984 Effects of haematoporphyrin derivative and light in combination with hyperthermia on cells in culture *Br. J. Cancer* **50** 85
[147] Mang T S 1990 Combination studies of hyperthermia induced by the neodymium: yttrium-aluminum-garnet (Nd : YAG) laser as an adjuvant to photodynamic therapy *Lasers Surg. Med.* **10** 173
[148] Rasch M H, Tijssen K, VanSteveninck J and Dubbelman T M 1996 Synergistic interaction of photodynamic treatment with the sensitizer aluminum phthalocyanine and hyperthermia on loss of clonogenicity of CHO cells *Photochem. Photobiol.* **64** 586
[149] Yanase S, Nomura J, Matsumura Y, Nagai K, Kinoshita M, Nakanishi H, Ohnishi Y, Tokuda T and Tagawa T 2005 Enhancement of the effect of 5-aminolevulinic acid-based photodynamic therapy by simultaneous hyperthermia *Int. J. Oncol.* **27** 193
[150] Yanase S, Nomura J, Matsumura Y, Nagata T, Fujii T and Tagawa T 2006 Synergistic interaction of 5-aminolevulinic acid-based photodynamic therapy with simultaneous hyperthermia in an osteosarcoma tumour model *Int. J. Oncol.* **29** 365
[151] Moan J and Berg K 1991 The photodegradation of porphyrins in cells can be used to estimate the lifetime of singlet oxygen *Photochem. Photobiol.* **53** 549
[152] Peng Q, Moan J and Nesland J M 1996 Correlation of subcellular and intratumoural photosensitizer localization with ultrastructural features after photodynamic therapy *Ultrastruct. Pathol.* **20** 109
[153] Moan J, Cunderlikova B, Juzeniene A, Juzenas P, Ma L-W and Iani V 2003 Tumour selectivity of photodynamic therapy Targeted Cancer Therapies—An Odyssey ed Q S Bruland and T Flægstad *Proc. Tromsø Symp.* 2003 (Tromsø: Ravnetrykk) pp 208–13
[154] Strauss W S, Sailer R, Schneckenburger H, Akgun N, Gottfried V, Chetwer L and Kimel S 1997 Photodynamic efficacy of naturally occurring porphyrins in endothelial cells in vitro and microvasculature in vivo *J. Photochem. Photobiol.* B **39** 176
[155] Peng Q and Nesland J M 2004 Effects of photodynamic therapy on tumour stroma *Ultrastruct. Pathol.* **28** 333
[156] Canti G, De S A and Korbelik M 2002 Photodynamic therapy and the immune system in experimental oncology *Photochem. Photobiol. Sci.* **1** 79
[157] Canti G, Lattuada D, Nicolin A, Taroni P, Valentini G and Cubeddu R 1994 Antitumour immunity induced by photodynamic therapy with aluminum disulfonated phthalocyanines and laser light *Anticancer Drugs* **5** 443
[158] Schreiber S, Gross S, Brandis A, Harmelin A, Rosenbach-Belkin V, Scherz A and Salomon Y 2002 Local photodynamic therapy (PDT) of rat C6 glioma xenografts with Pd-bacteriopheophorbide leads to decreased metastases and increase of animal cure compared with surgery *Int. J. Cancer* **99** 279
[159] Moshkovska T and Mayberry J 2005 It is time to test low level laser therapy in Great Britain *Postgrad. Med. J.* **81** 436
[160] Chow R T and Barnsley L 2005 Systematic review of the literature of low-level laser therapy (LLLT) in the management of neck pain *Lasers Surg. Med.* **37** 46
[161] Posten W, Wrone D A, Dover J S, Arndt K A, Silapunt S and Alam M 2005 Low-level laser therapy for wound healing: mechanism and efficacy *Dermatol. Surg.* **31** 334
[162] Sun G and Tuner J 2004 Low-level laser therapy in dentistry *Dent. Clin. North Am.* **48** 1061
[163] Lucas C, Criens-Poublon L J, Cockrell C T and de Haan R J 2002 Wound healing in cell studies and animal model experiments by low level laser therapy; were clinical studies justified? a systematic review *Lasers Med. Sci.* **17** 110
[164] Conlan M J, Rapley J W and Cobb C M 1996 Biostimulation of wound healing by low-energy laser irradiation: a review *J. Clin. Periodontol.* **23** 492
[165] Navratil L and Kymplova J 2002 Contraindications in noninvasive laser therapy: truth and fiction *J. Clin. Laser Med. Surg.* **20** 341

[166] Karu T 1989 Photobiology of low-power laser effects *Health Phys.* **56** 691
[167] Greguss P 1984 Low-level laser therapy—reality or myth? *Opt. Laser Technol.* **16** 81
[168] Nemeth A J 1993 Lasers and wound healing *Dermatol. Clin.* **11** 783
[169] Steiner H 2003 Interactions of laser radiation with biological tissue *Applied Laser Medicine* ed H P Berlien and G J Muller (Berlin: Springer) p 101
[170] Allison S W, Gillies G T, Magnuson D W and Pagano T S 1985 Pulsed laser damage to optical fibers *Appl. Opt.* **24** 3140
[171] Thomas R J, Rockwell B A, Marshall W J, Aldrich R C, Gorschboth M F, Zimmerman S A and Rockwell R J 2007 Procedure for the computation of hazards from diffusely scattering surfaces under the Z136.1-2000 American National Standard for Safe Use of Lasers *J. Laser Appl.* **19** 46
[172] Lumbert S 2007 Seven-year update drives national laser safety standard forward *Photonics Spectra* **41** 60
[173] Parker S 2007 Laser regulation and safety in general dental practice *Br. Dent. J.* **202** 523
[174] Teirlinck C J P M and Vaartjes S R 2001 Dutch Committee on Laser Safety in Health Care *Laser Safety in Health Care Proc. SPIE* **4156** 102
[175] Gabay S 2003 Laser safety aspects for medical applications *Proc. SPIE* **5287** 1
[176] Zuclich J A, Lund D J and Stuck B E 2007 Wavelength dependence of ocular damage thresholds in the near-IR to far-IR transition region: proposed revisions to MPEs *Health Phys.* **92** 15
[177] Anderson R R and Parrish J A 1983 Selective photothermolysis: precise microsurgery by selective absorption of pulsed radiation *Science* **220** 524
[178] Wheeland R G 1995 Clinical uses of lasers in dermatology *Lasers Surg. Med.* **16** 2
[179] Reinisch L 1996 Laser physics and tissue interactions *Otolaryngol. Clin. North Am.* **29** 893
[180] Tanzi E L, Lupton J R and Alster T S 2003 Lasers in dermatology: four decades of progress *J. Am. Acad. Dermatol.* **49** 1
[181] Peng Q, Berg K, Moan J, Kongshaug M and Nesland J M 1997 Review: 5-aminolevulinic acid-based photodynamic therapy: principle and experimental research *Photochem. Photobiol.* **65** 235
[182] Fritsch C and Ruzicka T 2006 Fluorescence diagnosis and photodynamic therapy in dermatology from experimental state to clinic standard methods *J. Environ. Pathol. Toxicol. Oncol.* **25** 425
[183] Anderson R R 2000 Lasers in dermatology—a critical update *J. Dermatol.* **27** 700
[184] Meyer-Schwickerath G 1949 Koagulation der Netzhaut mit Sonnenlicht *Ber. Dtsch Ophth. Ges.* **55** 256
[185] Burt B A and Eklund S A 1999 *Dentistry, Dental Practice, and the Community* (Philadelphia: W B Saunders Co.)
[186] Wilson M, Dobson J and Harvey W 1992 Sensitisation of oral bacteria to killing by low-power laser radiation *Curr. Microbiol.* **25** 77
[187] Burns T, Wilson M and Pearson G J 1993 Sensitisation of cariogenic bacteria to killing by light from a helium/neon laser *J. Med. Microbiol.* **38** 401
[188] Burns T, Wilson M and Pearson G J 1994 Killing of variogenic bacteria by light from a gallium arsenide diode laser *J. Dent.* **22** 273
[189] Wilson M, Burns T, Pratten J and Pearson G J 1995 Bacteria in supragingival plaque samples can be killed by low-power laser light in the presence of a photosensitiser *J. Appl. Bacteriol.* **78** 569
[190] Wood S *et al* 1999 An in vitro study of the use of photodynamic therapy for the treatment of natural oral plaque biofilm formed in vivo *J. Photochem. Photobiol.* B **50** 1
[191] Wilson M 1993 Photolysis of oral bacteria and its potential use in the treatment of caries and periodontal disease: a review *J. Appl. Bacteriol.* **75** 299
[192] Wilson M, Dobson J and Sarkar S 1993 Lethal photosensitization of oral anaerobic bacteria *Oral Microbiol. Immunol.* **8** 182
[193] Sarkar S and Wilson M 1993 Lethal photosensitisation of bacteria in subgingival plaque samples from patients with chronic periodontitis *J. Periodont. Res.* **28** 204
[194] Rovaldi C R *et al* 2000 Photoactive porphyrin derivative with broad-spectrum activity against oral pathogens in vitro *Antimicrob. Agents Chemother.* **44** 3364
[195] Wilson M, Sarkar S and Bulman J 1994 Effect of blood on the lethal photosensitisation of bacteria in subgingival plaque from patients with chronic periodontitis *Lasers Med. Sci.* **8** 297
[196] Shi X Q *et al* 2000 Occlusal caries detection with KaVo DIAGNOdent and radiography: an in vitro comparison *Caries Res.* **34** 151
[197] Lussi A *et al* 2001 Clinical performance of a laser fluorescence device for detection of occlusal caries lesions *Eur. J. Oral Sci.* **109** 14
[198] Angmar-Månsson B, al-Khateeb S and Tranaeus S 1996 Monitoring the caries process. Optical methods for clinical diagnosis and quantification of enamel caries *Eur. J. Oral Sci.* **104** 480
[199] Al-Khateeb S *et al* 1998 A longitudinal laser fluorescence study of white spot lesions in orthodontic patients *Am. J. Orthod. Dentofacial. Orthop.* **113** 595
[200] Hibst R and Keller U 1989 Experimental studies of the application of the Er : YAG laser on dental hard substances: I. Measurement of the ablation rate *Lasers Surg. Med.* **9** 338
[201] Hibst R and Keller U 1989 Experimental studies of the application of the Er : YAG laser on dental hard substances: II. Light microscopic and SEM investigations *Lasers Surg. Med.* **9** 327
[202] Walsh J T, Flotte T J and Deutsch T E 1989 Er : YAG laser ablation of tissue: effect of pulse duration and tissue type on thermal damage *Lasers Surg. Med.* **9** 314
[203] Walsh L J 1992 Soft tissue management in periodontics using a carbon dioxide surgical laser *Periodontology* **13** 13
[204] Walsh L J 1992 The use of lasers in implantology: an overview *J. Oral Implantol.* **18** 335
[205] Walsh L J 1996 The clinical challenge of laser use in periodontics *Periodontology* **17** 66
[206] Lin L C, Pitts D L and Burgess L W 1988 An investigation into the feasibility of photobleaching tetracycline-stained teeth *J. Endodont.* **14** 293
[207] Shapshay S M, Rebeiz E E, Bohigian R K and Hybels R L 1990 Benign lesions of the larynx: should the laser be used? *Laryngoscope* **100** 953
[208] Remacle M, Bodart E, Lawson G and Minet M 1996 Use of the CO_2-laser micropoint micromanipulator for the treatment of laryngomalacia *Eur. Arch. Otorhinolaryngol.* **253** 401
[209] Remacle M, Declaye X and Mayne A 1989 Subglottic haemangioma in the infant: contribution by CO_2 laser *J. Laryngol. Otol.* **103** 930
[210] Remacle M, Lawson G, Degols J C, Evrard I and Jamart J 2000 Microsurgery of sulcus vergeture with carbon dioxide laser and injectable collagen *Ann. Otol. Rhinol. Laryngol.* **109** 141
[211] Nishloka N S 1995 Application of lasers in gastroenterology *Lasers Surg. Med.* **16** 205

[212] Fleischer D, Kesseler F and Haye O 1982 Endoscopic Nd : YAG laser therapy for carcinoma of the esophagus: a new palliative approach *Am. J. Surg.* **143** 280
[213] Bown S G 1991 Palliation of malignant dysphagia-surgery, radiotherapy, laser, intubation alone or in combination *Gut* **32** 841
[214] Amin Z, Donald J J, Masters A, Kant R, Steger A C and Bown S G 1993 Hepatic metastases interstitial laser photocoagulation with real-time US monitoring and dynamic C T evaluation of treatment *Radiology* **187** 339
[215] Marks A J and Teichman J M 2007 Lasers in clinical urology: state of the art and new horizons *World J. Urol.* **25** 227
[216] Ravi H A and Denstedt J D 1996 Lasers in urology *Contemp. Urol.* **8** 32
[217] Floratos D L and de la Rosette J J 1999 Lasers in urology *BJU Int.* **84** 204
[218] Chan K F, Pfefer T J, Teichman J M H and Welch A J 2001 A perspective on laser lithotripsy: the fragmentation process *J. Endourol.* **15** 257
[219] Chan K F *et al* 1999 Holmium : YAG laser lithotripsy: a dominant photothermal ablative mechanism with chemical decomposition of urinary calculi *Lasers Surg. Med.* **25** 22
[220] Syed H A,Biyani C S, Bryan N, Brough S J and Powell C S 2001 Holmium : YAG laser treatment of recurrent superficial bladder carcinoma : initial clinical experience *J. Endourol.* **15** 625
[221] Van Bezooijen B P, Horenblas S, Meinhard W and Newling D W 2001 Laser therapy for carcinoma in situ of the penis *J. Urol.* **166** 1670
[222] Gupta N P, Ansart M S and Singh I 2001 Laser endoscopic incision: a viable alternative to treat adult ureterocele *Int. Urol. Nephrol.* **33** 325
[223] Dougherty T J, Gomer C J, Henderson B W, Jori G, Kessel D, Korbelik M, Moan J and Peng Q 1998 Photodynamic therapy *J. Natl Cancer Inst.* **90** 889
[224] Peng Q 2006 Photodynamic therapy and detection *J. Environ. Pathol. Toxicol. Oncol.* **25** 1
[225] Reid R *et al* 1990 Superficial laser vulvectomy. IV. Extended laser vaporization and adjuvant 5-fluorouracil therapy of human papillomavirus associated vulvar diseases *Obstet. Gynecol.* **76** 439
[226] Jones R W and Mclean M R 1986 Carcinoma in situ of the vulva: a review of 31 treated and five untreated cases *Obstet. Gynecol.* **68** 499
[227] Campion M J and Singer A 1987 Vulvar intraepithelial neoplasis: a clinical review *Genitourin. Med.* **63** 147
[228] Chafee W, Ferguson K and Wilkinson E J 1988 Vulvar intraepithelial neoplasia (VIN): principles of surgical therapy *Colposc. Gynecol. Laser Surg.* **4** 125
[229] Choy D S J *et al* 1984 Human coronary laser recanalization *Clin. Cardiol.* **7** 377
[230] Margolis J R and Mehta S 1992 Excimer laser coronary angioplasty *Am. J. Cardiol.* **69** 3F
[231] Bittl J A and Sanborn T A 1992 Excimer laser-facilitated coronary angioplasty *Circulation* **86** 71
[232] Holmes D R *et al* 1994 Coronary perforation after excimer laser coronary angioplasty: the excimer laser coronary angioplasty registry experience *J. Am. Coll. Cardiol.* **23** 330
[233] Bittl J A *et al* 1992 Clinical success, complications and restenosis rates with excimer laser coronary angioplasty *Am. J. Cardiol.* **70** 1553
[234] Lamuraglia G M *et al* 1988 Selective laser ablation of venous thrombus: implications for a new approach in the treatment of pulmonary embolus *Lasers Surg. Med.* **8** 486
[235] Gregory K W *et al* 1993 Laser thrombolysis in acute myocardial infaraction *Lasers Surg. Med.* **5** (Suppl.) 13
[236] Tasse J and Arora R 2007 Transmyocardial revascularization: peril and potential *J. Cardiovasc. Pharmacol. Ther.* **12** 44
[237] Saksena S *et al* 1987 Intraoperative mapping-guided argon laser ablation of malignant ventricular tachycardia *Am. J. Cardiol.* **59** 78
[238] Isner J M *et al* 1987 Laser-assisted endocardiectomy for refractory ventricular tachyarrhythmias: preliminary operative experience *Clin. Cardiol.* **10** 201
[239] Earle K M, Carpentier S, Roessmann U, Hayes J R and Zeitler E 1965 Central nervous system effect of laser radiation *Fed. Proc.* **24** 129
[240] Stellar S 1965 Effects of laser energy on brain and nervous tissue *Laser Focus* **1** 3
[241] Brown T E, True C, McLauria R L, Hornby P and Rockwell R J 1966 Laser radiation: acute effects on cerebral cortex *Neurology* **17** 789
[242] Stellar S 1970 Experimental studies wit the carbon dioxide laser as a neurosurgical instrument *Med. Biol. Eng.* **8** 549
[243] Fassano V A 1982 The use of laser in neurosurgery *J. Neurosurg. Sci.* **26** 245
[244] Kelly P J and Alker G J Jr 1981 A sterotactic approach to deep-seated CNS neoplasm using the carbon dioxide laser *Surg. Neurol.* **15** 331
[245] Kelly P J, Alker G J Jr, Kall B and Goerss S 1983 Precision resection of intra-axial CNS lesions by CT-based stereotactic craniotomy and computer monitored CO_2 laser *Acta Neurochir. (Wien)* **68** 1
[246] Kahn T, Bettag M, Ulrich F, Schwarzmaier H J, Schober R, Furst G and Modder U 1994 MRI-guided laser-induced interstitial thermotherapy of cerebral neoplasm *J. Comput. Assist. Tomogr.* **18** 519
[247] Schwarzmaier H J, Yaroslavsky I, Yaroslavsky A, Fiedler V, Ulrich F and Kahn T 1998 Treatment planning for MRI-guided laser-induced interstitial thermotherapy of brain tumours—the role of blood perfusion *J. Magn. Reson. Imaging* **8** 121
[248] Schulze P C, Kahn T, Harth T, Schwarzmaier H J, Schober R and Schulze C P 1998 Correlation of neuropathologic findings and phase-based MRI temperature maps in experimental laser-induced interstitial thermotherapy *J. Magn. Reson. Imaging* **8** 115
[249] Stylli S S, Howes M, MacGregor L, Rajendra P and Kaye A H 2004 Photodynamic therapy of brain tumours: evaluation of porphyrin uptake versus clinical outcome *J. Clin. Neurosci.* **11** 584
[250] Muller P, Wilson B, Lilge L, Yang V, Hetzel F, Chen Q, Fullager T, Fenstermaker R, Selker R and Abrams J 2001 Photofrin-photodynamic therapy for malignant brain tumours *Proc. SPIE* **4248** 34
[251] Kostron H, Obwegeser A and Jakober R 1996 Photodynamic therapy in neurosurgery: a review *J. Photochem. Photobiol.* B **36** 157
[252] Madsen S J and Hirschberg H 2006 Photodynamic therapy and detection of high-grade gliomas *J. Environ. Pathol. Toxicol. Oncol.* **25** 453
[253] Alfano R R *et al* 1984 Laser induced fluorescence spectroscopy from native cancerous and normal tissue *IEEE J. Quantum Electron.* **QE-20** 1507
[254] Nishioka N S 1994 Laser-induced fluorescence spectroscopy *Gastrointestinal Endoscopy Clin.* **4** 313
[255] Andersson-Engels S, Klinteberg C, Svanber K and Svanberg S 1997 In vivo fluorescence imaging for tissue diagnosis *Phys. Med. Biol.* **42** 815
[256] Lovat L B and Bown S G 2001 Lasers in gastroenterology *World J. Gastroenterol.* **7** 317
[257] Lam S, MacAulay C, LeRiche J C and Palcic B 2000 Detection and localization of early lung cancer by fluorescence bronchoscopy *Cancer* **89** (Suppl) 2468

[258] Huttmann G, Yao C and Endl E 2005 New concepts in laser medicine: towards a laser surgery with cellular precision *Med. Laser Appl.* **20** 135
[259] Konig K, Riemann I, Fischer P and Halbhuber K J 1995 Intracellular nanosurgery with near infrared femtosecond laser pulses *Cell Mol. Biol.* **45** 195
[260] Vogel A and Venugopalan V 2003 Mechanisms of pulsed laser ablation of biological tissues *Chem. Rev.* **103** 577
[261] Shen N, Datta D, Schaffer C B, LeDuc P, Ingber D E and Mazur E 2005 Ablation of cytoskeletal filaments and mitochondria in cells using a femtosecond laser nanoscissor *Mech. Chem. Biosys.* **2** 17
[262] Tirlapur U K and Konig K 2002 Targeted transfection by femtosecond laser *Nature* **418** 290
[263] Fischer A L 2007 Medical laser market on the rise *Biophotonics Int.* **14** 40