LASER APPLICATIONS IN MEDICINE

Lasers have been investigated for possible use in medical applications ever since their discovery in the 1960s. Early applications of lasers in medicine were reported in ophthalmology (1–3), surgery (4), neurology (5,6), and dermatology (7). In recent years, numerous additional applications of lasers in medicine were the direct result of an improved understanding about how laser radiation interacts with biological tissues, the rapid progress in the manufacturing of laser sources at selective wavelengths that are absorbed by different biological tissues, and improved optical fiber and lens technologies for the efficient delivery of laser radiation.

Clinical applications of lasers can be divided into two major categories: therapeutic and diagnostic. Because of the many therapeutic uses of lasers in medicine, it is further possible to group the applications into surgical and nonsurgical procedures. Surgical applications involve direct removal of tissues. Nonsurgical applications include alternative methods to stimulate peripheral nerves (laser biostimulation) and to elevate local tissue temperature (hyperthermia), as well as photodynamic therapy.

LASER PHYSICS

The primary components of a laser (which is an acronym for Light Amplification by Stimulated Emission of Radiation) are (Fig. 1): (1) a lasing medium, which may be in a solid, liquid, or gas phase, capable of undergoing stimulated emission; (2) an excitation mechanism, which causes the atoms or molecules of the lasing medium to ionize and rise to a higher electronic energy state by absorbing either electrical, thermal, or optical energy (this process results in a condition known as a population inversion where more atoms have electrons at a higher energy state than at a lower energy level); and (3) a positive feedback system that consist of a highly reflective curved mirror and a partially transmitting flat mirror causing the spontaneous photon emission from the active medium to bounce back and forth between the two reflecting mirrors. The collision between the spontaneous emission and the atoms or molecules in the excited state stimulate additional emission ("stimulated emission") inside the active laser cavity or optical resonator. If the frequencies are properly chosen, the light will be amplified and emitted along the axis of the resonator as an intense narrow beam. The result of the stimulated emission is two electromagnetic waves of the same wavelength traveling parallel and in phase (spatial and temporal coherence) with one another. In contrast to gas-filled lasers, solid-state lasers, such as the Nd:YAG and ruby lasers, require an external optical light source as an excitation source to "pump" the atoms in the solid-state crystal.

Lasers produce a beam of nonionizing radiation (spot size on the order of 1 μm) that is highly coherent (directional), generally monochromatic (single wavelength) and collimated (the beam remains almost parallel along its trajectory with minimum loss of power due to divergence). In addition, a laser beam has a high power density, or irradiance, usually expressed in watts per square centimeters (W/cm^2). If the radiation is delivered as a pulse, the pulse duration becomes an additional factor in determining the effect on tissue because the energy applied during the exposure, which is expressed in Joules per square centimeter (J/cm^2), is equal to the power density times the pulse duration (also called the fluence).

When the laser is used as a cutting tool, the spot size must be very small in order to concentrate the power into a tiny spot. On the contrary, when a laser is used for coagulation, the beam is defocused to allow for an increased spot size to spread the laser beam over a large area (Fig. 2). Power densities above 1 kW/cm^2 tend to be used for incisions, whereas power densities below 500 mW/cm^2 are generally used for coagulation.

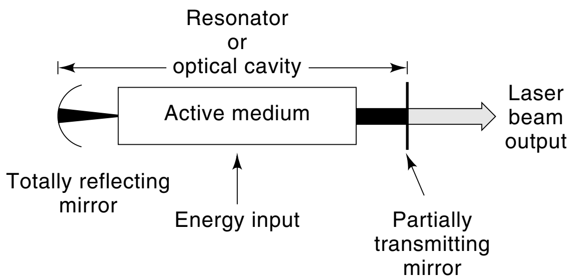

Figure 1. The common components of a laser system. Energy input can be supplied in the form of an electrical discharge current or from a flash lamp.

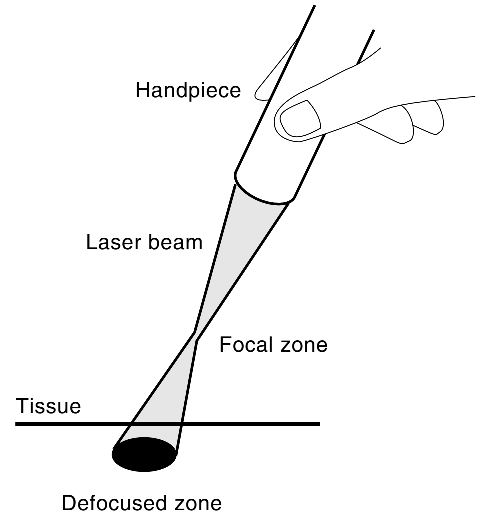

Figure 2. A laser beam can be used for cutting (vaporization) when the focal zone is near the surface of the tissue. For coagulation, the laser beam is defocused causing the energy to be distributed over a wider area.

The transverse electromagnetic mode (TEM) is a term used to describe the power distribution of a laser beam over the spot area. For example, a TEM_{01} mode refers to a multimode distribution and indicates that the spot has a cool region in the center of the beam. A TEM_{00} mode, on the other hand, produces a uniform Gaussian power distribution with most of the power concentrated in the center of the beam and the rest decreasing in intensity toward the periphery of the beam.

Q-Switched Lasers

When a laser is Q-switched, the energy that is normally stored in the inverted atomic population is suddenly transferred to the oscillating laser cavity. The term Q is used to convey the fact that a laser cavity is essentially a resonator with a certain quality factor Q, similar to any conventional electronic resonant circuit. Normally, the two highly reflecting mirrors inside a conventional laser tube bounce the energy back and forth internally, thus leading to a high resonant Q factor. By inserting a lossy attenuator into the resonating laser cavity, it is possible to change the Q factor of the laser considerably to a point where the energy build-up is insufficiently high for laser oscillation to occur. Conversely, if the attenuation is suddenly switched off, the energy builds up inside the laser cavity so that the excess excitation can be released in a controllable manner as a very high burst of short-duration energy (usually nanoseconds).

Pulsed and CW Lasers

Depending on how the excitation energy inside the laser cavity is applied, the output beam could be either in the form of a continuous wave (CW) or a pulsed wave (PW). The output of PW lasers can vary widely depending on the duration, repetition rate, and energy of the individual pulses.

The effect of the laser on the tissue can be enhanced with PW rather than CW delivery lasers because pulsed radiation minimizes thermal diffusion of the energy deposited in the tissue away from the heated zone. Short pulses of intense laser radiation can produce nonlinear absorption effects such as optical breakdown and plasma formation. These effects can cause significant damage to optical components or optical fibers used to deliver the laser radiation.

INTERACTION OF ELECTROMAGNETIC RADIATION WITH BIOLOGICAL TISSUES

It is essential that the operator knows both the optical characteristics of the particular tissue being radiated and the properties of the laser used. Accordingly, different lasers must be used depending on the particular medical application. When a laser beam enters the tissue, it may be partially reflected from, transmitted through, scattered within, or absorbed by the tissue (Fig. 3). The interaction of laser radiation with biological tissue also depends on the incident angle of the beam, the wavelength of the laser, and tissue composition being treated.

Reflection

Light can be reflected from a target either by specular or by diffuse reflection. Specular reflection occurs from polished surfaces when the angle of reflection is equal to the angle of the incident beam. On the other hand, diffuse reflectance occurs from rough unpolished surfaces as a result of wide-angle backscattering of the light.

Scattering

Biological tissues are considered highly heterogeneous both at the microscopic and macroscopic scales. Therefore, electromagnetic radiation entering a biological medium will deviate from its incident direction mostly at the boundaries between regions having different indices of refraction. The scattering effect in turbid biological media depends on the size and shape of the scattering particles. When particle size is smaller than the wavelength of the incident light, we refer to this scattering as Rayleigh scattering. The result will be a homogeneous zone of light intensity surrounding the scattering particle. On the other hand, when the scattering particles are larger than the wavelength of radiation, the resulting radiation, also referred to as Mie scattering, generally continues in the forward orientation along the direction of the incident beam. Because scattering spreads the laser beam laterally where it is ultimately converted to heat, it can limit the precision with which certain tissue structures can be destroyed without causing damage to adjacent tissues. Therefore, potentially wide-spread tissue damage can result unless the target tissue has specific pigments that absorb the laser light before it reaches the surrounding tissue structures. From a practical point of view, obtaining a precise spot size for cutting or coagulation can sometimes be difficult because scattering in tissue also causes laser radiation to spread in different directions around the point of contact or below the tissue surface before it can be noticed by the surgeon.

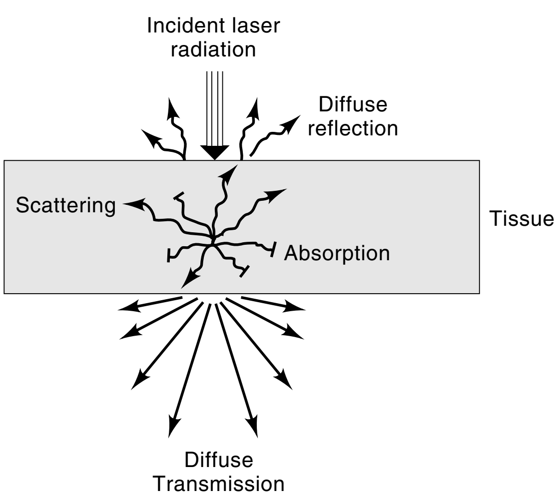

Figure 3. Laser–tissue interaction.

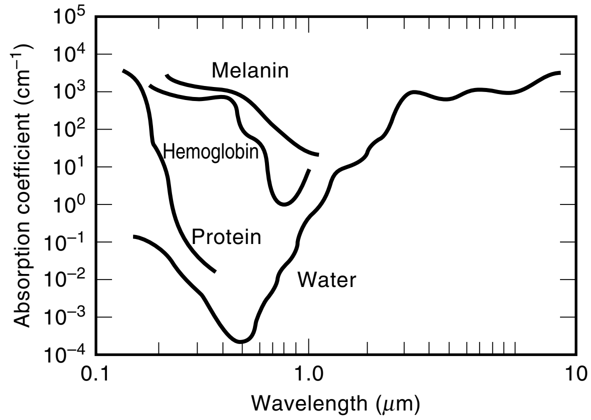

Figure 4. Laser absorption in biological tissue.

Absorption

For surgical applications, the monochromatic property of laser radiation is particular useful when tissue absorbs only certain wavelengths. In order for the laser light to affect a biological medium, it must be absorbed by the tissue and either converted to heat or, in the case of ultraviolet (UV) radiation, initiating a photochemical decomposition process without generating heat.

The absorption of electromagnetic radiation by biological tissues arises from the wavelength-dependent resonant absorption by the tissue components (Fig. 4). For example, hemoglobin and red blood cells reflect the red light produced by a ruby laser but absorb the blue/green light from an argon laser. Likewise, melanosomes, the granular pigments in the skin, act as absorbing chromophores for wavelengths in the UV and visible range.

In the absence of scattering, absorption results in an exponential decrease in light intensity according to Lambert-Beer's Law. With appreciable scattering, this decrease in incident intensity is not monotonic. The relative contributions of absorption and scattering will stipulate the depth in a given biological tissue at which the resulting tissue effects will be present.

EFFECT OF LASER RADIATION ON BIOLOGICAL TISSUES

The effect of laser radiation on biological tissues depends on the wavelength of the beam, the power density, the duration

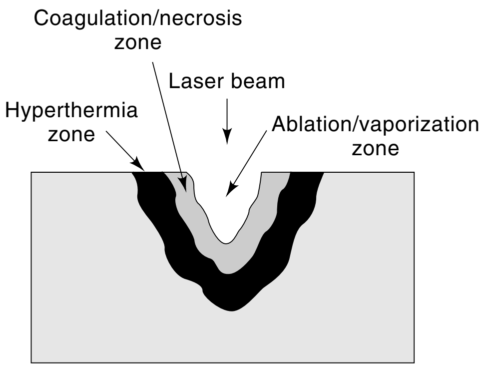

Figure 5. Thermal zones inside biological tissue.

of the exposure, and the amount of energy absorbed and then released by the tissue. The common way to control power density during surgery is by adjusting the spot size of the laser beam. Spot size can be varied by adjusting the distance between the focusing lens in the hand piece and the treated tissue. A 2-fold decrease in the spot size will produce a 4-fold decrease in the power density.

Energy release from water, hemoglobin, and melanin pigments in tissue is by molecular vibrations resulting in a local temperature increase. Between 50 and 100°C, this heating energy causes proteins, enzymes, and collagens to denature or coagulate within a few seconds. Above 100°C, photothermal vaporization or ablation takes place. At this temperature, water boiling and evaporation generates gaseous decomposition products, followed by carbonization of the dry tissue. Tissue evaporation can take place when sufficient energy is generated either to disrupt carbon bonding or when the local temperature causes the water in tissue to reach a boiling point leading to localized micro explosions and consequently rupturing of the fine tissue structure. Because tissue rupturing and protein coagulation occur simultaneously, the tissue can be cut and coagulated at the same time leading to nearly blood-free dissections (Fig. 5). When diseased tissue is destroyed and removed, the surrounding tissues remain unaffected. Bleeding is minimized because the laser beam seals off the small blood vessels in the surrounding tissues. In addition, microorganisms are destroyed by the intense laser radiation, so the risk of postoperative infections is minimized considerably.

The penetration depth of laser radiation in biological tissues depends on the incident wavelength. For wavelengths in the mid-infrared (IR) region above 2 μm, most of the energy is absorbed within a very short distance from the tissue surface; therefore, scattering becomes insignificant. For example, 10.6 μm IR radiation produced by a CO_2 laser passes only a short distance of about 0.1 mm before it is completely absorbed by soft tissues and converted to heat. Because this radiation is concentrated in a relatively small tissue volume near the point of impact, the CO_2 laser is widely used to produce sharp and rapid incisions.

Near-IR and visible range laser radiation penetrate deeper into soft tissue compared to mid-IR radiation. For comparison, radiation produced by an argon laser, which is heavily absorbed by the hemoglobin in blood, typically penetrates an average distance of about 0.5 mm. Energy from a Nd:YAG laser, on the other hand, can readily penetrate into deeper structures in tissues, typically to an average depth of about 2 to 5 mm. Therefore, it is able to coagulate a larger volume of blood vessels at the vicinity of an incision, thereby providing better homeostasis.

LASER DELIVERY SYSTEMS

The most common methods to guide a laser beam to the biological target site typically fall into three categories: (1) a fixed optical delivery system, (2) a flexible fiber optic-based delivery system, and (3) a semirigid mechanical system based on an articulated arm (Fig. 6).

Fixed Delivery Systems

Fixed laser delivery systems are used to deliver the energy to the target by a joystick or similar control mechanism over a relatively limited movement range. They are typically found in ophthalmic laser systems that are connected to a slit lamp to permit the surgeon a clear view of the operating site.

Fiber Optics Delivery Systems

The energy generated by a laser can be delivered to the operating site via a flexible fiber optic cable. The laser beam is

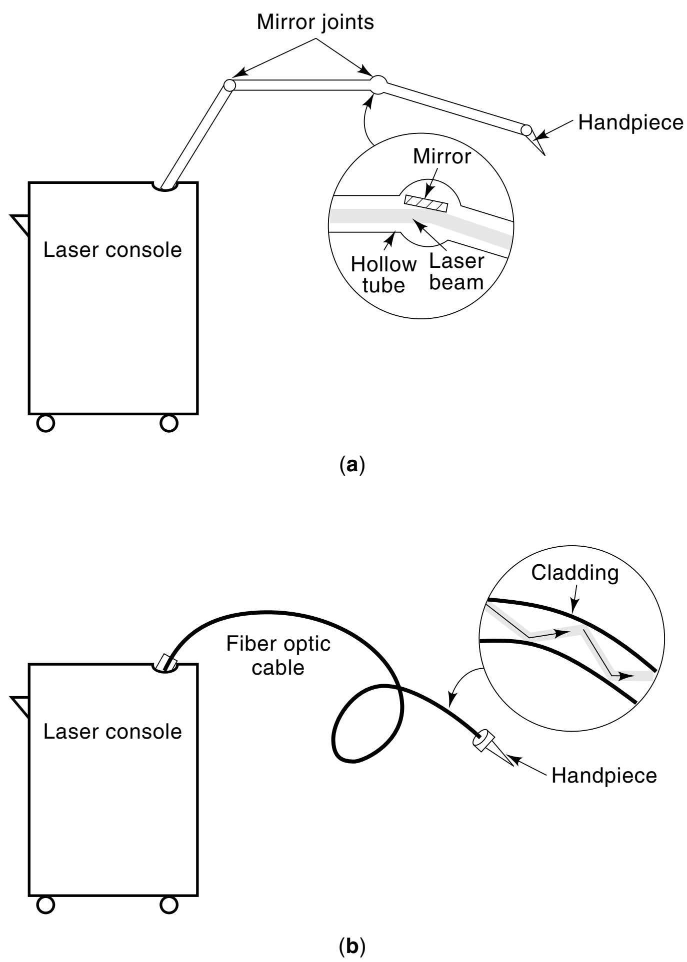

Figure 6. Typical medical laser delivery systems. (a) Articulated arm. (b) Fiber optic coupling.

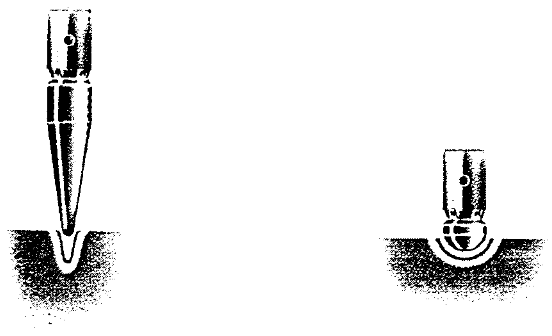

Figure 7. Different laser probe geometries can generate different power densities. (a) A general-purpose elongated tip can be used for precise cutting with maximal lateral coagulation. (b) A round probe is used for wider vaporization including coagulation.

introduced into the proximal end of the fiber and is transmitted along the fiber length through a process known as total internal reflection. Flexible fiber optic guides for laser beam delivery are usually made of silica (SiO_2) glass and some additives. These fibers are commonly used for visible wavelengths as well as near-infrared wavelengths below 2.1 μm and can deliver a relatively low output power. For example, argon and YAG laser energy can be transmitted through glass optical fibers with very little loss. Wavelengths above 2.1 μm are usually absorbed by the fused silica or by water impurities inside the fiber core. High-power UV radiation produced for example by excimer lasers is difficult to transmit by optical glass fibers. Therefore, regular glass fibers are used only for light transmission in the visible region of the spectrum.

The advantages of fiber optic guides, compared to the more traditional articulating arms or fixed delivery systems, is their small size, flexibility, improved manipulation, low weight, and reduced cost. The ability to launch high optical power into small optical fibers extends the clinical application of lasers considerably. It permits precisely controlled energy delivery through flexible endoscopes to remote intravascular or intracavitary regions of the body where conventional surgical procedures would otherwise be very invasive to perform.

Recently, new polycrystalline fiber optic materials are being evaluated for short-length delivery of the longer IR wavelengths. Examples include Al_2O_3 fibers for transmission of CO_2 laser energy and silver halide fibers for use with Er:YAG lasers.

Fiber optic systems used to deliver laser light culminate in either “hot tip” (contact) interaction or “free beam” (noncontact) interaction, depending on what happens to the beam at the end of the fiber. If the beam is absorbed by the fiber tip or a tip affixed to the fiber distal end, it is called a hot tip; if the beam is directed out of the fiber tip and travels a short distance before it interacts with the tissue, it is considered a free beam. Tips come in a wide variety of designs. Some tips are intended to focus the beam, other are shaped to spread the beam over a wider area (Fig. 7).

Articulated Arms

The multisegmented adjustable articulated arm, coupled to a detachable lensed handpiece or endoscope, is the most widely used technique to deliver the radiation and position the laser beam onto the desired tissue spot. Efficient coupling and direction of the energy from the laser source to the distal end is accomplished by high reflectivity multilayered mirrors and lenses that are positioned near the distal end of the arm to concentrate the beam into a small spot. These mirrors are mounted inside tubular sections and are precisely aligned to help guide the laser beam during the manipulation of the arm by the surgeon. Some articulated arms can also be attached to operating microscopes that are used to visualize the operating field in delicate surgical procedures.

Articulated arms are used for wavelengths above 2.1 μm and for high laser output powers capable of damaging delicate optical fibers. A He–Ne laser beam is usually used as a coaxial aiming (aligning) guide alongside an invisible beam (e.g., from a CO_2 laser) to direct IR radiation to the target tissue.

TYPES OF LASERS USED IN MEDICAL APPLICATIONS

Many specialities in medicine are using or exploring the use of lasers as alternative treatments to conventional surgical procedures. The use of each laser depends on the specific medical application. Some widely used methods to classify medical lasers are based on their active medium, emission wavelength, or intended applications (Table 1).

Gas Lasers

Gas lasers are available from the far UV (excimer) through the visible (He–Ne) to the infrared (CO_2). The basic types of gas mixtures used in lasers include He–Ne, Ar, Kr, CO_2, and the rare-gas excimer lasers. Gas lasers are relatively inexpensive but are bulky and can be fragile.

Table 1. Classification Criteria for Medical Lasers

Laser	Wavelength (nm)	Color
Excimer:		
Arf	193	Ultraviolet
KrCl	222	Ultraviolet
KrF	248	Ultraviolet
XeCl	308	Ultraviolet
XeF	351	Ultraviolet
Helium–cadmium	325	Ultraviolet
Argon	488	Blue
	514	Green
Copper vapor	511	Green
	578	Yellow
Gold vapor	627	Red
Helium–neon	633	Red
Krypton	531	Green
	568	Yellow
	647	Red
Ruby	694	Red
Alexandrite	720–800	Near-IR
Diode	660–1500	Near-IR
Thulium : YAG	2010	Near-IR
Holmium : YAG	2120	Near-IR
Erbium/YAG	2940	Near-IR
Neodimium : YAG	1064	Near-IR
	1318	Near-IR
Carbon dioxide	10,600	Mid-IR

Dye Lasers

Dye lasers are more complex than gas lasers and require optical pumping either by an intense flash lamp or by another laser because the laser action is not very efficient. They typically use flowing organic dyes and operate in the visible optical spectrum. Dye lasers operate over a broad wavelength range and have relatively low efficiency. Dye lasers are useful mostly in photodynamic therapy (PDT) and in retinal photocoagulation.

Carbon Dioxide Lasers

Carbon dioxide (CO_2) gas-filled infrared lasers, introduced by Patel et al. in 1964 (8), produce radiation at 10.6 μm. This radiation is highly absorbed by water, making it useful for precise surface ablation in soft tissue applications. The CO_2 laser is the most common type of laser and can be found in almost every medical specialty except ophthalmology and PDT. It is used extensively in general surgery to remove polyps, warts, cysts, and tumors and to cut through heavily vascularized tissues where fast coagulation is desired.

Helium-Neon Lasers

Helium-neon (He–Ne) lasers, first developed in 1961 (9), produce a dominant spectral line at a red wavelength of 632.8 nm. Standard He–Ne lasers offer powers between 1 and 50 mW. He–Ne lasers are used primarily for positioning patients in radiation therapy, for aiming invisible IR laser beams in surgery, and in laser Doppler flowmetry.

Argon Lasers

Argon (Ar) ion gas-filled lasers, introduced by Bennett in 1962 (10), produce wavelengths in the 476.5 nm (blue) to 514.5 nm (green) region of the spectrum. Ar lasers are used in gynecological applications for ablation of pigmented vascular tissues, in otolaryngology for coagulation of vascular lesions in dermatologic applications, and in ophthalmology for retinal coagulation.

Erbium-Yttrium-Aluminum-Garnet Lasers

Erbium (Er) has been used to dope a yttrium-aluminum-garnet (a crystal composed of aluminum and yttrium oxides) and form a Er:YAG laser. This solid-state laser emits a 2.94 μm and can be used for ablation of tooth enamel and dentin, for corneal ablation, and more recently also in cosmetic skin resurfacing surgery.

Holmium-Doped Lasers

Holmium (a rare earth element)-doped YAG (Ho:YAG) lasers emit pulses of 2.1 μm wavelength typically with energies below 4 J. They are being used by orthopedic surgeons for soft tissue ablation in arthroscopic joint surgery and in some urologic applications because it can be used in fluid environments.

Ruby Lasers

Q-switched ruby ($Cr{:}Al_2O_3$) lasers, which emit pulses of 694.3 nm (red) wavelength and can deliver up to 2 J in energy, are used in dermatological applications to disperse different tattoo pigments and various nonmalignant pigmented lesions.

Neodymium-Doped Lasers

Neodymium-doped YAG (Nd:YAG) solid-state lasers, introduced in 1961 (11), produce 1.064 and 1.32 μm (near infrared) radiation. These lasers are widely employed when heavy coagulation is desired or when the use of a fiber optic-based delivery system is preferred.

Excimer Lasers

Excimer lasers are based on the ionization of inert gas molecules, such as xenon, argon, or krypton combined with halogen molecules, such as fluorine or chlorine, to generate a source of high-power UV radiation. Examples of excimer lasers include XeF, which provides a source of 351 nm radiation; XeCl, which is lasing at 308 nm; KrF, which lases at 248 nm; and ArF, which is lasing at 193 nm. These lasers have a relatively shallow depth of penetration into soft tissues, making them available for very delicate surgical procedures like the removal of occluding atherosclerotic plaques (thrombus) inside the vascular system.

An excimer argon fluoride (ArF) laser produces radiation at 193 nm. This radiation predominantly causes tissue ablation by a photochemical process because short wavelength radiation have sufficient energy to break molecular bonds. Pulsed ArF lasers enable the removal of approximately 0.2 μm-thick tissue layers and are therefore useful in ophthalmology for the correction of near-sighted vision.

MEDICAL APPLICATIONS OF LASERS

Therapeutic Applications

Ophthalmology. The application of lasers in ophthalmology was among the earliest uses of lasers in surgery. The main application was as photocoagulating devices that replaced the more traditional and difficult to use xenon-arc light sources. For example, argon lasers are widely used to treat glaucoma (a disease leading to elevated intraocular pressure) by drilling tiny holes around the trabecular network at the corners of the eye (a procedure known as trabeculoplasty) to allow drainage of the aqueous fluid (12). Likewise, argon and Nd:YAG lasers are widely used for coagulation of the retina in diabetic retinopathy and the treatment of chronic simple glaucoma because the radiation can pass through the semitransparent medium of the eye with little attenuation (13).

The cornea at the front of the eye absorbs both far UV (200 to 300 nm) and far IR (above 1.4 μm) radiation. Near-UV (300 to 400 nm) radiation, on the other hand, will penetrate through the cornea and will be almost totally absorbed by the normal crystalline lens. Visible (400 to 700 nm) and near-IR (700 nm to 1.4 μm) radiation will penetrate all the way to the back of the eye where the retina is located. This unique property makes the retina in the eye available for treatment but, at the same time, poses a safety concern because it is also highly vulnerable to damage from sufficiently intense laser radiation (Fig. 8).

Other uses of lasers in ophthalmology involve reshaping the corneal surface to correct refractive abnormalities and treatment of dry eyes, which is a condition of inadequate production of tears to moisten the cornea. Excimer lasers are also being used to correct mild to moderate near-sightness (myopia) in patients with minimal astigmatism. In this surgical

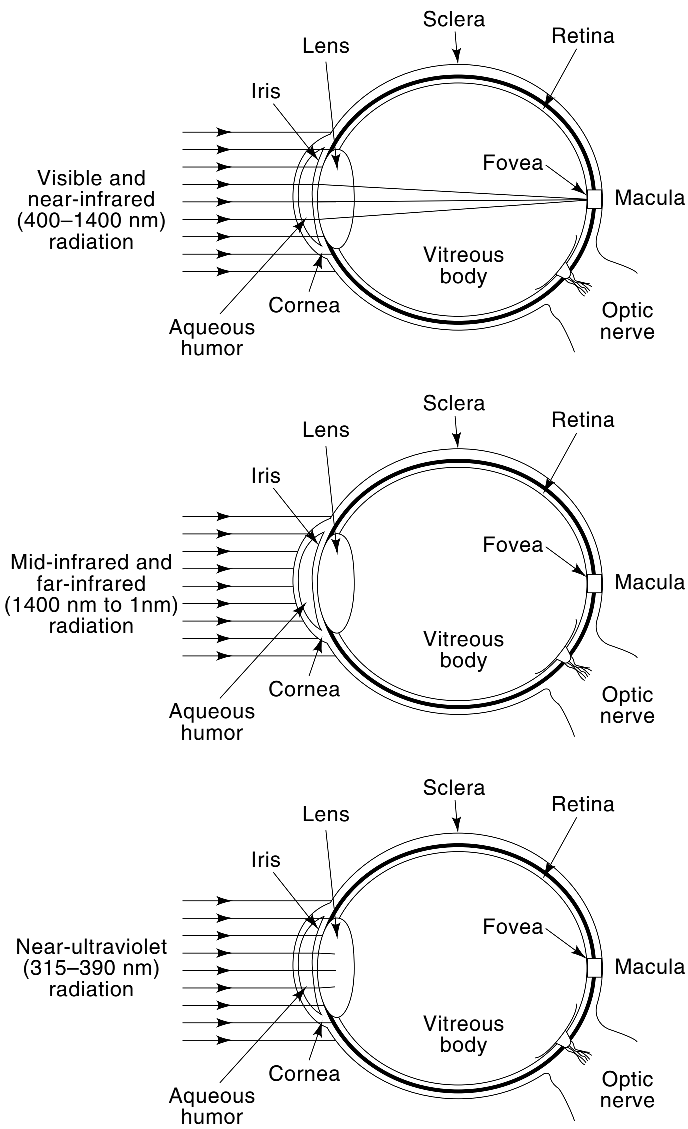

Figure 8. Laser absorption and penetration in different parts of the human eye.

procedure, termed photorefractive keratectomy (PRK), the laster ablates a predetermined curvature in the cornea and thus alters the refraction of the eye. Directing laser light into the eye requires delicate delivery devices that must provide a means for illuminating and visualizing the treatment site and protecting the surgeon from potential harmful reflected laser light. Modified slit-lamps equipped with micromanipulator positioners are commonly used in laser ophthalmology because they provide improved illumination and more stable aiming of the laser beam.

Ophthalmologists have focused the radiation from Q-switched YAG lasers onto the posterior part of the lens in the eye and cut away the thin membrane coating of the lens, which becomes cloudy with age and can cause partial obstruction of vision.

HeNe lasers have also found diagnostic values in ophthalmic applications. One application of this laser is as a computerized scanning ophthalmoscope to produce very rapid images of the retina.

Urology. Nd:YAG, CO_2, Ho:YAG, and Ar lasers have been used successfully in urological applications to remove bladder tumors and to treat urethral strictures. Other applications of lasers beyond the more traditional uses—cutting, coagulation, and vaporization—include fragmenting certain urinary stones (calculi) either through a small diameter flexible or semirigid ureteroscope (14,15). In this procedure, also called intracorporeal lasertripsy, the photoacoustic effect of the ultrashort (1 to 2 μs duration at 10 Hz) bursts of laser energy first causes a portion of the stone surface to heat up and then creates a plasma (a microscopic cloud of rapidly expanding electrons) that expands and collapses, generating a mechanical shock wave to fragment the yellow stones without damaging the surrounding mucosal walls of inside the ureter. Some of the small stone fragments are passed spontaneously through the urine.

Another common surgical laser procedure involves the treatment of bilateral prostatic hypertrophy (BPH), a condition causing the prostate gland that encircles the neck of the bladder and proximal urethral outflow tract to enlarge leading to voiding dysfunction in men. The laser procedure to treat BPH usually involves the use of a noncontact flexible fiber or a specially designed side-firing (normally a right-angled) optical fiber introduced through a cystoscope that delivers the laser energy to the hypertrophied prostate gland.

Gynecology. The CO_2 gas lasers were among the first lasers used in a number of gynecological procedures. The laser may be hand-held or used in combination with a hysteroscope, colposcope, or laparoscope. Example applications include the treatment of gynecological conditions such as cervical intraepithelial neoplasia (CIN), which is an abnormal growth of cells in the epithelium of the cervix; vaginal and vulval intraepithelial neoplasia (VAIN and VIN) to superficially ablate diseased areas of vaginal and vulvar tissues; and endometriosis (bleeding from the endometrium), a painful condition common in young women especially during menstruation (16,17).

Dermatology. Dermatologists have been using different types of lasers to treat a number of skin conditions including the irradiation of disfiguring birthmarks, the removal of tattoos, and the treatment of skin cancer (18). Among the most common types of lasers used in dermatology are the argon and ND:YAG lasers.

One application of laser radiation involves the removal of port-wine spots, a red-purple skin mark that often occurs on the face due to abnormal skin vasculature. A large area of stains can be treated at a time with very little pain (19). Another application includes the effective removal of tattoos and other pigmented lesions in the skin using a Q-switched ruby laser operating at 694.3 nm.

Endoscopic Applications. Endoscopic applications of lasers is common in surgery of the larynx and the gastrointestinal tract (20,21). The two most common types of endoscopic lasers are the argon and the Nd:YAG lasers because the wavelengths generated by these lasers can be readily transmitted through flexible fiber optic endoscopes. Among the uses of lasers in gastrointestinal applications is to control bleeding ulcers in the stomach, colon, and esophagus.

Photodynamic Therapy. Photodynamic therapy is a photochemotherapy technique of photoactivation exogenous photosensitized drugs at specific target sites and the subsequent selective destruction of certain tumors. Typically, a photosensitizing dye (e.g., hematoporphyrin derivative, or HpD) is first introduced into malignant cells, which retain the dye, perhaps because of impaired lymphatic drainage or abnormal tumor vasculature. The tissue is then exposed to the incident laser radiation. Dye lasers in the 630 nm range (e.g., argon) are generally employed in PDT because this wavelength is most effective in activating the photosensitizing dye. Even though the exact mechanism involved in this process is not fully understood, it is generally believed that this photosensitizer produces a side effect in the target cells that arises from the highly toxic level of oxygen-free radicals that damage intracellular organelles in the malignant cells, leading to cell death. The technique has been used mostly to treat superficial tumors in the skin (22,23). Among the side effects of PDT is excessive skin photosensitivity, which requires that patients avoid direct exposure to sunlight for several weeks thereby preventing potential sunburns.

Diagnostic Applications

Laser Doppler Velocimetry

Basic Principle. Laser Doppler velocimetry (LDV) is a relatively new clinical method for assessing cutaneous blood flow. This real-time measurement technique is based on the Doppler shift of light backscattered from moving red blood cells and is used to provide a continuous measurement of blood flow through the microcirculation in the skin. Although LDV provides a relative rather than an absolute measure of blood flow, empirical observations have shown good correlation between this technique and other independent methods to measure skin blood flow.

According to the fundamental Doppler principle, the frequency of sound, or any other type of monochromatic and coherent electromagnetic radiation such as laser light, that is emitted by a moving object is shifted in proportion to the velocity of the moving object relative to a stationary observer. Accordingly, when the object is moving away from an observer, the observer will detect a lower wave frequency. Likewise, when the object moves toward the observer, the frequency of the wave will appear higher. By knowing the difference between the frequencies of both the emitted and the detected waves, the Doppler shift, it is possible to calculate the velocity of the moving object according to the following equation:

$$f = 2\upsilon_0^f \cos\theta / c \tag{1}$$

where f is the Doppler shift frequency, θ is the mean angle that the incident light makes with the moving red blood cells, c is the speed of light, f_0 is the frequency of the incident light, and υ is the average velocity of the moving red blood cells. Because the red blood cells do not move through the microcirculation at a constant velocity and light scattering leads to a wide distribution of angles θ, the Doppler-shifted light contains a spectrum of different frequency components.

The Doppler shift of laser light caused by the average blood velocity in the capillaries (around 10^{-3} m/s) is very small and difficult to measure directly. Therefore, the frequency shifted and unshifted backscattered light components from the skin are mixed on the surface of a nonlinear photodiode. The output from the photodiode, an average dc offset voltage and a small superimposed ac component, is amplified and band pass filtered to eliminate low-frequency components in the range between 10 and 50 Hz. These frequencies are attributed to noise resulting from motion artifact and high-frequency noise components (typically in the kilohertz range) resulting from nonbiological noise. As the average red blood cells (RBC) velocity is increased, the frequency content of the ac signal changes proportionally.

Assuming a constant blood flow geometry, Stern (24) proposed the following empirical relationship between the amplitude of the Doppler-shifted spectrum and the velocity of the blood flow:

$$F = \sqrt{\int_0^\infty \omega^2 P(\omega)\, d\omega} \tag{2}$$

where F is the root-mean-square (rms) bandwidth of the Doppler power spectrum signal, ω is the angular frequency, and $P(\omega)$ is the power spectral density of the Doppler signal. To compensate for laser light intensity, skin pigmentation, and numerous other factors that affect the total amount of light backscattered from the skin, the flow parameter is usually calculated by multiplying the percentage of light reflected from the moving RBCs by the mean photodiode current, which is a function of the average backscattered light intensity.

Instrumentation. The original light source used in LDV was a HeNe laser (25,26). Newer systems use a much smaller and less expensive single-mode semiconductor laser diode in the near-infrared region around 750 to 850 nm as a light source. These wavelengths are near the isosbestic wavelength of oxy and deoxyhemoglobin (i.e., 810 nm) so that changes in blood oxygenation have no effect on the measurement. Some LDV systems are equipped with different light sources (e.g., green, red, or near-infrared), which allow measurement from different tissue layer depths because light penetration depth is wavelength-dependent. Typical output powers used in LDV range from 1 to 15 mW.

In most LDV systems, the laser output is coupled through a small focusing lens into the polished end of a flexible plastic or silica optical fiber (25 to 1000 μm core diameter), which illuminates the blood directly in invasive measurements or the surface of the skin in noninvasive applications. Light backscattered from the biological media is collected either by the same optical fiber used for illumination or by a separate receiving fiber mounted in close proximity to the illuminating fiber tip. A rigid probe helps to maintain the two optical fiber tips parallel to each other and also perpendicular to the surface of the illuminated sample. Depending on the application, a wide selection of probe geometries and sizes are available commercially. In invasive applications, the optical fibers can also be inserted through a catheter for measurement of flow inside a blood vessel. In most noninvasive applications, the flow probes are attached to the surface of the skin by a double-sided adhesive ring. Because blood perfusion is strongly dependent on skin temperature, some LDV systems also have probes with built-in heaters to control and monitor skin temperature.

Absolute calibration of an LDV instrument is inherently difficult to obtain because blood flow in the skin is highly complex and variable. Because accurate calibration standards or suitable physical models of blood flow through the skin do not exist, instrument calibration is usually accomplished empirically either from an artificial tissue phantom, which is often made out of a colloidal suspension of latex particles, or by comparing the relative output from the laser Doppler instrument with other independent methods for measuring blood flow.

In practice, most commercial systems express and display the Doppler-shifted quantity measured by the instrument either in terms of blood flow (in units of milliliters per minute per 100 g of tissue), blood volume (in milliliters of blood per 100 g of tissue), or blood velocity (in centimeters per second).

The clinical and medical research applications of LDV range from cutaneous studies of ischemia in the legs (27) to general subcutaneous physiological investigations related to the response of various organs to physical (temperature, pressure) and chemical (pharmacological agents) perturbations that can alter local blood perfusion. LDV has been used extensively in dermatology to assess cutaneous microvascular disease (28,29), arteriosclerosis, or diabetic microangiopathy; in plastic surgery to determine the postoperative survival of skin grafts; in ophthalmology to evaluate retinal blood flow (30,31); and in evaluating skeletal muscles (32). To date, LDV remains mainly an experimental method. Although it has been widely used as a research and clinical tool since the mid 1970s, LDV has not reached the stage of routine clinical application.

Fluorescence Spectroscopy

Many dyes that absorb energy can reemit some of this energy as fluorescence. Laser-induced fluorescence emission is currently being investigated for the early detection, localization, and imaging of normal and abnormal tissues, determining whether a tumor is malignant or benign and identifying excessive areas of atherosclerotic plaque. One of the future goals is to incorporate this technique into special fiber optic based guidance systems used during ablation or laser angioplasty particularly inside the coronary arteries.

Diffuse Reflectance and Transillumination Spectroscopy

Several methods are being developed to measure the absorption spectra of tissues illuminated by laser light. In a relatively new technique known as photon time-of-flight spectroscopy, researchers are trying to measure the temporal spreading of very short pulses of laser light as photons undergo multiple scattering in the tissue. By measuring the time it takes the light to travel through the tissue it is possible to estimate how much light scattering and absorption occurs. Some of these time-resolved or "photon migration" methods are being evaluated clinically as a potential alternative to ionizing radiation used in X-ray mammography for early noninvasive diagnosis of breast cancer.

LASER SAFETY

It is essential that all medical personnel using lasers have a thorough knowledge of the potential hazards involved and become familiar with proper methods to minimize the chances of accidental injuries.

To ensure safety and protect the personnel in the operating room, everyone must wear protective goggles and clothing to protect the eyes or skin from dangerous exposure to laser radiation. The eyes are especially vulnerable because the collimated laser beam incident on the cornea will be focused to a small and highly intense spot on the retina (33). For example, a visible, 10 mW/cm^2 laser beam could result in a 1000 W/cm^2 radiant exposure to the retina. This power density is more than enough to cause permanent damage to the retina. Laser emission in the UV and IR spectral regions produce ocular effects mainly at the cornea. Laser eye protection goggles must be matched with the type of laser being used because the protective properties of different goggle materials depend on wavelength and laser output intensity. To keep stray laser radiation at a minimum and to protect the surgical staff from potential exposure to misdirected laser beams or stray laser light, special nonreflecting matte surfaces should be used. CO_2 wavelengths can be attenuated considerably by ordinary clear glass or plastic goggles. For other types of lasers, such as argon or YAG, a colored blocking material must be used to protect the eyes. This could also become a limitation to the surgeon because the operating site must be viewed through the same color-tinted goggles that are used to protect the eyes.

In addition to optical safety, using high-energy lasers near combustible materials or flammable anesthetic gases may cause ignition and potential explosions. Several incidences have been reported where lasers have caused inadvertent explosions inside endotracheal tubes by igniting the inspired oxygen gas used during anesthesia.

Laser safety standards for health care facilities are available from the American National Standards Institute (ANSI) (34). The hazard standards published in 1993 by ANSI (e.g., series Z136.1 laser safety standards) list the maximum permissible exposure limits for different medical lasers and provide a detailed description of control measures to protect against potential hazards. These safety standards are also referenced by the Occupational Safety and Health Administration (OSHA) and other U.S. safety agencies as the basis of evaluating occupational safety hazards from the use of medical lasers. In addition, medical lasers are also grouped and classified according to four major hazard categories. In the United States, manufacturers must certify that all medical lasers meet the regulatory standards issued by the Food and Drug Administration (FDA). Each laser must bear a clearly marked label indicating compliance with the appropriate standard and denoting the laser hazard according to one of four general classifications. The higher the classification number, the greater the potential hazard.

Besides the risks associated with the exposure to harmful laser light, it is important to recognize also that many surgical lasers are equipped with a localized exhaust ventilation system to remove potentially hazardous airborne contaminants and effluent fumes generated during surgery. This risk can result for example from CO_2 lasers used for incision, ablation, and vaporization of tissues.

Additional hazards with some medical lasers are related to the use of toxic gases and dyes. For example, excimer lasers employ a toxic halogen gas, which must be kept in well-ventilated cabinets.

Most laser systems are equipped with a standby mode that prevents the beam from being emitted accidentally. A master key is often used to lock the control panel of most laser systems for added safety. Foot pedals are widely used to activate the laser delivery system. In most systems, a shutter mechanism is used to control the laser energy output that is delivered to the final destination.

LASER CLASSIFICATIONS

Lasers are classified according to their hazard potential, which depends on their optical wavelength and output power. A brief description of each classification follows.

Class 1 Lasers

Class 1 laser products produce very low power (e.g., semiconductor diode lasers used in video disc players); they pose no known hazard under normal operating conditions.

Class 2 Lasers

Class 2 laser products produce low-power visible light, normally used for brief periods during alignments (e.g., in radiology). These lasers are therefore considered safe for momentary viewing (0.25 s or less) unless an individual stares directly into the laser beam.

Class 3 Lasers

Class 3 laser products generally consist of medium-power lasers that pose potential hazards to a person during instantaneous exposure of the eyes. This classification is further subdivided into two subclassifications: Class 3A and Class 3B. Subclassification 3A lasers emit visible light with an average output power between 1 and 5 mW. Lasers that deliver visible light with an average output powers between 5 and 500 mW are subclassified in Class 3B.

Class 4 Lasers

Class 4 lasers include most surgical lasers that have an average output power in excess of 500 mW. Very stringent control measures are required for this class of lasers. These lasers produce a hazard not only from direct or specular reflection, but they may also be hazardous with diffuse reflection.

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