Medical applications of the laser: A review of the state of the art

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The first major successful application within 4 years of the birth of laser (1960—T. Maiman) was in the field of medicine—eye treatment. Within the last few decades, two dozen books and a large number of major conference proceeding, elaborating many diverse applications of lasers in the biomedical field, have been published. There are at least 4 international journals covering various aspects of lasers in medicine. Although they are now widely used, particularly in surgery—as an effective and versatile scalpel—the mechanism of their interaction with tissue is not yet fully understood in many cases. While basic research on these aspects are ongoing in many laboratories all over the world, many successful clinical applications in gynaecology, gastroenterology, cancer treatment, cell necrosis (photodynamic therapy), ophthalmology, dermatology, dentistry etc. are in vogue. Laser coagulation seems to be the only effective treatment for diabetic retinopathy currently available in the market. Technology has progressed far ahead of science. The unique properties of the laser that make it the most effective and versatile scalpel for the most delicate surgery and also an effective tool in other applications, such as lithotripsy, keratoplasty etc. are presented in this review article. The mechanism of laser interaction with living tissue has also been reviewed to understand how lasers offer applications in so many diverse fields and have potential for even more esoteric future applications in both therapeutic and diagnostic applications. An overview of past (in the author's laboratory) and present basic research elsewhere in the fields of photodynamic therapy, laser lithotripsy and laser spectroscopy for early diagnosis of dysplasia is also given.

1. INTRODUCTION

When the laser was first demonstrated in the USA in 1960, it was hailed as "a tool looking for applications". Indeed applications it did turn out to have, and the speed and scope of such applications within a few decades have surpassed that of any other technological breakthroughs during that era. While the technology was still in its infancy, in 1965 the laser found effective medical application in eye treatment, in addition to many other diverse, fields. Within a decade lasers became standard tools for treatment of retinopathy and dermatological conditions. During the last two decades, the use of lasers has expanded to most fields of medicine and, in many cases, has revolutionized the way illnesses are treated and, in some cases, the way they are diagnosed. There are many medical specializations, for example gynaecology, gastroenterology, oncology, tissue necrosis, ophthalmology and dermatology, where lasers are now used routinely for treating patients.

Knowledge of the kinetics and dynamics of optical interactions with biological tissues are now almost within the grasp of practitioners, while basic and applied researches are still being actively pursued in laboratories all over the world to facilitate further technological developments for ever more effective clinical applications. Nevertheless, some slackening of the pace of increase in scope of such applications is discernible. This is due, primarily, to the slow growth of cohesion and lack of active collaboration between medical practitioners and laser scientists. As an exception to the general trend, however, being a big money spinner, the use of lasers in cosmetic surgery has advanced in leaps and bounds.

The applications of lasers in medicine can be categorized into two major disciplines: diagnostics and therapeutics. Almost all the applications mentioned above are in the therapeutic field, making use of the laser as an efficient and effective scalpel or a versatile healing stick. To appreciate how the laser has made such a great impact on medical applications, and for better utilization of this tool, it is necessary to understand the nature and unique properties of the laser as a light source and the mechanism by which it interacts with living tissues.

2. COMPARISON OF THERMAL AND LASER LIGHT SOURCES

Light sources may be characterized by five major parameters, defined as follows:

1. Line width: purity of colour (monochromacity) of the emitted radiation.

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2. Pulse width: temporal/spatial extent of the beam emanating from the source.

3. Pulse repetition rate: rate of emission of pulses of light from the source.

4. Beam divergence: extent of parallelism of the beam emanating from the source.

5. Spectral radiance: strength of the source per unit line width (i.e., power per unit area and per unit wavelength unit).

Typical values of these parameters are compared for laser and thermal sources in Table 1, from which it is clear that the laser provides a highly monochromatic and practically nondivergent source of light with a very high spectral radiance. Lasers operating at many discrete wavelengths within the UV–vis–IR bands are now commercially available (Fig. 1b). Because of its high degree of directionality, a laser beam of wavelength λ lends itself to be focused by lenses down to a diffraction-limited spot diameter a, given by eqn (1):

$$a = 1.22 \times \lambda \times f / D, \qquad (1)$$

where f is the focal length of the lens and D the diameter of the laser beam impinging on the lens. Thence, a 1 mm diameter He–Ne laser, operating at a wavelength of 633 nm and 1 mW output power (such specifications correspond to those of a common laboratory tool used for alignment purposes) will have a beam diameter of ~ 8 μm at the focal point of a 50 mm focal length lens, giving a power density of ~ 2×10^7 W m^{-2} (i.e., 2 kW cm^{-2}). In essence it can be concluded that, although a coherent and directional light beam can be produced from a thermal source using many spectral filters and collimating lenses, the intensity available from even a small laser (such as a pointer) would be many orders of magnitude higher than that from a thus "monochromated" and collimated conventional light source.

Table 1. Comparison of a typical laser source with a "monochromated" conventional light source.

Feature	Attributes	Thermal source	Laser source
Line width & coherence	Width of an emission line in wavelength domain	~ 0.01 nm (e.g. sodium discharge lamp, coherence length ~ 0.05 m)	< 0.0001 nm (e.g. He–Ne laser, coherence length ~ 50 m)
Pulse width (duration)	Extent of the pulse in time and space domains	10^{-6} s (e.g. electromechanical switch) → 300 m spatial extent	$<10^{-8}$ s → 3 m spatial extent (~ 10^{-12} s → 3 mm for mode-locked lasers)
Beam divergence (unidirectionality)	Angle over which light beam diverges from its source	10^{-2} radians (e.g. searchlight)	~10^{-9} radians (specially collimated beam)
Pulse repetition rate	The rate at which pulses are radiated from the source	~ 10^3 Hz, limited either by the speed of a mechanical chopper or the electrical properties of lamp circuitry	~ 10^5 Hz using an electroöptical modulator
Radiance	Source strength	~2×10^7 W m^{-2} sr^{-1} (the sun radiating over 10^{15} Hz bandwidth)	3×10^7 W m^{-2} sr^{-1} (e.g. 1 mW common He–Ne laser radiating over 10^6 Hz)
Spectral radiance	Per wavelength unit	2×10^{-8} W m^{-2} sr^{-1} Hz^{-1} (the sun's radiation received at Earth's surface)	3×10^1 W m^{-2} sr^{-1} Hz^{-1} (e.g. a small He–Ne laser radiating per wavenumber unit

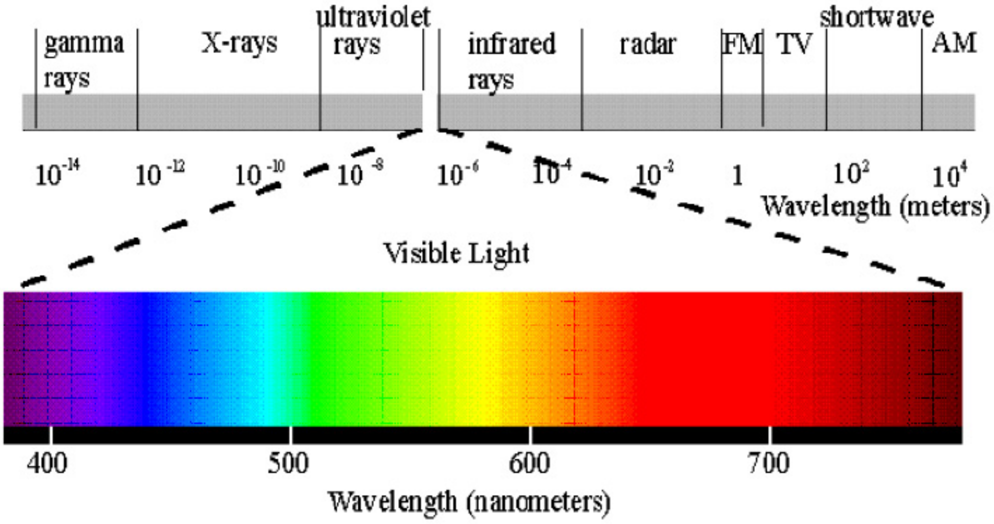

Figure 1a. Electromagnetic spectrum and the range of visible wavelengths.

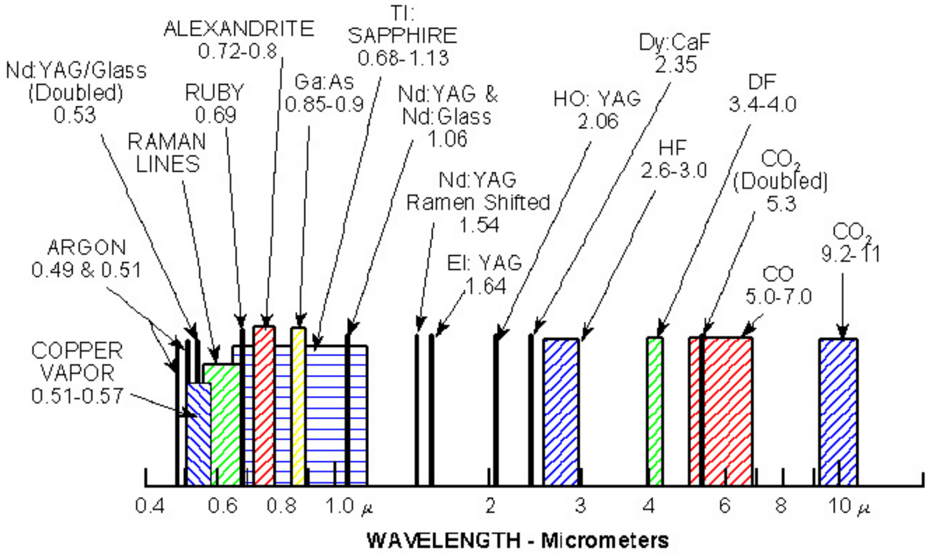

Figure 1b. Range of wavelengths for commercially available lasers.

3. INTERACTION OF LASER BEAMS WITH BIOLOGICAL TISSUE

Absorption

The interaction mechanism is governed by both the properties of the laser beam (Table 1) and the optical and thermal properties of the tissue. Absorption is a prerequisite for any effect on the tissue, which is always accompanied by scattering and reflexion as explained schematically in Fig. 2. Penetration diminishes following an exponential law relating the incident intensity I_i (e.g. W cm^{-2}) to the transmitted intensity I_t and the depth of penetration into the sample d (e.g. cm):

$$I_t = I_i \exp\,[-\alpha(\lambda)\, d_p] \qquad (2)$$

where $\alpha(\lambda)$ (e.g. in units of cm^{-1}) is the absorption coefficient.

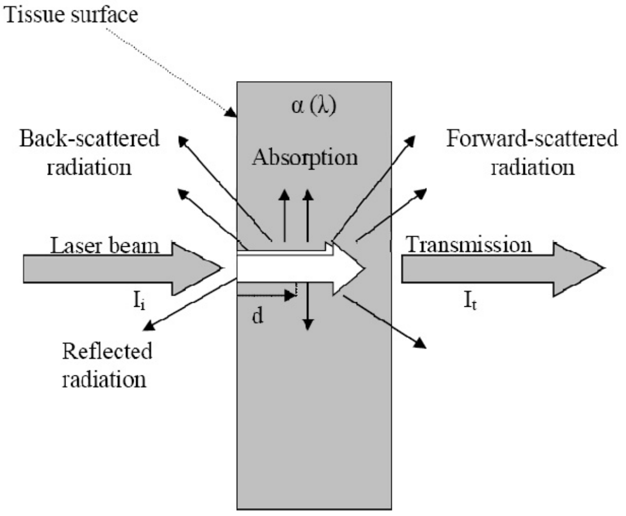

Figure 2. Laser interaction processes with mammalian tissue, schematically explained.

It is clear from eqn (2) that the fraction of light intensity absorbed,

$$I_a = 1 - I_t/I_i = \exp\,[-\,\alpha(\lambda)\, d]\,, \qquad (3)$$

is dependent on $\alpha(\lambda)$, the wavelength-dependent absorption coefficient of the tissue. The penetration depth d_p is defined as the depth at which the intensity incident on the surface (I_i) is reduced by a factor of (1/e) ~ 0.32, i.e.

$$d_p = 1/\alpha(\lambda). \qquad (4)$$

Although scattering losses can often be neglected, surface reflexion for some tissues, particularly in the visible wavelengths, can be quite high (30–50%) and needs to be considered when lasers are applied in various clinical procedures.

4. EFFECTS OF ABSORBED LASER RADIATION ON TISSUE

The effects of a laser beam on tissue depend upon the mechanism by which the absorbed optical energy is dissipated in the sample. It is to be noted that light, as a small portion within the vast electromagnetic spectrum (Fig. 1a), is a wave in its motion and a stream of particles (photons) in its interaction with matter (e.g., biological tissue) [1]. Thus each photon (quantum) has a specific quantity of energy, E_p and also, at the same time, as an electromagnetic wave, it has an associated wavelength λ. These two quantities are related as $E_p = h/\lambda$, where h is known as Planck's constant. This indicates that shorter wavelengths correspond to higher photon energies. Absorption of light having low photon energies, such as those within the IR band, gives rise to thermal effects whereas absorption of light having high photon energies, such as those within the UV–visible band, generally gives rise to photoelectric effects.

4.1 Thermal effects

These are dynamic processes where the energy carried by the long-wavelength light (red–IR) is converted into heat [2,3], which is then transferred to surrounding tissues (increasing the heated volume), eventually causing denaturation (modification) or destruction of the molecular structures constituting the tissues (mainly, of course, proteins), with the actual course of events depending upon the laser parameters and the photothermal properties of the tissue. For example, at temperatures above 50 °C irreversible cell necrosis may occur followed by desiccation, blanching and shrinking of tissues through denaturation of collagen and other proteins within a time span of a second or so. At temperatures above 100 °C volatilization (burning of the tissue) occurs within a fraction of a second. In the zone between the volatilization region and the region of unaffected tissue lies the lower-temperature zone affected by coagulation necrosis. This seals the blood vessels, thus causing no bleeding during laser surgery. Laser beam delivery is conducted by a hand piece for general surgery and dermatological conditions, through a microscope in the treatment of otorhinolaryngological (ENT) and ophthalmological conditions, or through fibre optics (an endoscope) for treatment of gastroenterological, respiratory, urological etc. complaints, and also in angioplasty under radiological guidance.

Here are some major applications of lasers in both therapeutic and diagnostic fields.

Laser coagulation in retinopathy. Sealing of undesirable blood vessels and attaching detached retinal spots by a laser beam are the two most effective and perhaps the only reliable treatments available for retinopathy, based on photocoagulation [4], which involves focusing a suitable laser beam through a special lens to extremely small spots onto selected points of the retina. There are two types of treatment depending upon the type of retinopathy:

(a) Diabetic maculopathy: This is a condition of leaking blood vessels on the retina as a result of prolonged diabetes. It is treated by applying a focused laser beam in the region of the macula to seal the leaking vessels [5].

(b) Proliferative diabetic retinopathy: This is a condition of undesirable proliferation of minute blood vessels causing more extensive leakage and obscuring of vision. The treatment requires more extensive application of the laser over a wider area of the retina. It helps the abnormal new vessels to shrink and disappear. More than one sitting may be required to complete the treatment.

Lasers used for treatments need to operate in the near-UV or visible wavelengths for good transmission through the cornea and vitreous parts of the eye to reach the retina without affecting the surroundings. The level of power to be used for these treatments needs to be decided by judiciously considering the length of laser pulse (or the duration of the laser irradiation in the case of a continuous beam), the condition of the retina, and the stage of developent of the retinopathy. In general, the power required is at the level of a few to a few hundred milliwatts. For proliferative retinopathy, 3–4 thousand burns (welding spots) are usually needed with a pulsed laser and the most widely used type is the green (490 nm) Ar-ion laser.

The laser treatment may have a few side effects, such as a decrease in the peripheral field of vision, decrease in colour vision and difficulty in seeing at night. Sometimes it may also reduce the central vision. This is usually temporary, but sometimes may not improve. It is worth keeping in mind, however, that in general hardly any medical treatment can take place without any side effects; the risk associated with the laser treatment is far less than the risk of not having the treatment in most cases.

4.2 Optomechanical effects

Although mechanical in character the effect is essentially preceded by a prompt thermal response. Laser beams having high radiance ($>10^{10}$ W cm^{-2}) and short pulse length ($\leq 10^{-9}$ s) can produce a shock wave in a condensed (solid or liquid) medium. The shock wave is produced due to either explosive vaporization or ejection of material from the surface of the target (recoil effect), or due to the collapse of laser-produced bubbles in liquids (cavitation). The propagation of such waves in solid media causes localized and selective destruction of tissues.[1] This phenomenon is utilized in breaking and removing the membranes that often develop after the incorporation of an artificial lens, causing obscuration of vision. the mechanism of laser lithotripsy [6] of urinary calculi (*vide infra*) is considered to be cavitation.

In laser lithotripsy a cystoscope or ureteroscope (specialized kinds of endoscopes) is introduced into the patient's urethra, either directly or over a guide wire along the urinary tract, to come close to the kidney or bladder stone to be removed. A thin optical fibre is then inserted through the working channel of the endoscope to come in contact with the stone. Light from a high-power pulsed laser, normally a holmium-YAG laser operating at 2097 nm (in the infrared), is directed through the optical

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[1] Living tissue is of course a very complex, highly structured medium encompassing attributes of both liquids and solids, and sometimes described as "soft matter".

fibre. The laser beam acts like a hammer, eventually shattering the stone into small fragments which are removed through normal urinary functions or manually. The choice of this wavelength is based on the fact that it is strongly absorbed in water and a suitable laser is commercially available. However, such lasers as are presently used are bulky and expensive. Research, initiated as early as in 2009 in the author's laboratory [7] is now being conducted in several more laboratories to fully understand the mechanism of shockwave formation and the dynamics of stone fragmentation through a cavitation process. It is hoped that by a proper understanding of the mechanism, the procedure could be made more efficient and cost-effective; future laser lithotripters based on high-power diode lasers may be more portable and inexpensive than a holmium-YAG.

Urinary stones are crystals or agglomerates, composed mainly of oxalate, phosphate or urate, formed in the gall bladder or kidney. Most stones occur due to dietary factors or metabolic disorders, where abnormally high levels of certain elements, e.g. calcium, lead etc.,[2] or organic anions forming sparingly soluble compounds with common metabolic cations,[3] are present in the body. It is possible that the chemical compositions of the stones are influenced by the elements as active catalysts or chelating agents. Research in the author's laboratory addressed this issue by monitoring elemental constituents in uroliths by laser-induced plasma spectroscopy (LIPS) [8]. It is hoped that in the near future the technique could be used for *in vivo* analysis of stone compositions to facilitate follow-up laser lithotripsy. The advantages of the LIPS technique are that it does not require any special sample preparation and presentation effort, is minimally invasive and traumatic, and minimizes collateral damage to other tissues.

4.3 Photoablative effects

Photoablation is a photoelectric effect initiated by high-energy (short-wavelength) laser beams, operating in the UV wavelength band. Energy is directly delivered to the electronic structures of the molecules of the tissue, avoiding the relatively slower photothermal processes pathway (§4). The interaction causes breakage of molecular bonds and subsequent vaporization. High absorption of laser beams in the UV limits tissue incision depths to a few hundred micrometres (μm). Unlike with thermal effects, this does not produce coagulation at the edge of incision to stop bleeding. For photorefractive keratoplasty [9] (e.g. corneal transplants), UV lasers (e.g. ArF at 193 nm) has the advantage over a scalpel in that, lasers, unlike a scalpel, can be used with computer-aided devices to perform precision surgery on delicate tissues without applying any pressure.[4]

4.4 Photochemical effects

These are also photoelectric effects, where the laser is used to selectively excite molecules of a drug called a photosensitizer administered to the host. The excited molecules react with ambient oxygen to convert them into singlet oxygen, or with water molecules to produce hydroxyl radicals. Both of these are cytotoxic and cause necrosis (killing) of tissue cells. The advantage of this process is that the sensitizer[5] can safely be administered by intravenous injection. The drug is preferentially (temporarily) accumulated in cells having unusual metabolic activities due to cancer, or a precancerous state of the tissue or cell (dysplasia). The most important criteria for the successful application of this *photodynamic therapy* (PDT) [10,11] are to find a sensitizer that does not have any adverse side effects on health and which has a strong, isolated and narrow absorption line in the visible band matching the emission line of a suitable commercial laser (preferably a small, low-cost diode laser) operating in the blue-green region. The potential of PDT for the treatment of dysplasia of the lower oesophagus (Barrett's oesophagus) [12], multifocal bladder cancers, dermatological conditions etc. has been demonstrated in laboratory experiments. Although the technique is finding increasing clinical applications there are many problems and issues that need to be solved before it can find much wider and more effective clinical applications. Because of the evidently great potential of the technique, research into various aspects of PDT is being pursued with vigour in many laboratories (including early work in the author's laboratory) and is further reviewed in §5.

5. PHOTODYNAMIC THERAPY

Photosensitizing chemicals such as, protoporphyrin IX, Photofrin, haematoporphyrin derivative (HpD), bacteriochlorin, benzoporphyrin derivatives etc. are being investigated for use as sensitizers in PDT. The criteria for an ideal sensitizer are:

- A single compound
- High absorbance in an isolated and narrow wavelength band in the visible (preferably red) wavelength region

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[2] Magnesium is known to have a preventive action [7a].

[3] E.g. oxalate. Perhaps surprisingly, excessive vitamin C (ascorbic acid) may play a rôle in promoting kidney stones [7b].

[4] Here we do not exclude the possibility that, in the future, computer control may extend to microrobots able to manipulate scalpels.

[5] E.g., Photofrin (patented by QLT Inc., Canada).

- High quantum yield of triplet formation
- High efficiency for cytotoxic oxygen species generation
- Good selectivity for deposition only into malignant tissues
- No dark toxicity.

Amino levulinic acid (ALA)-mediated protoporphyrin IX (PpIX) (Fig. 3) has several advantages over other sensitizers. The drug (ALA) can be administered safely into the bloodstream through intravenous injection, or applied to the skin as a cream. The optimum therapeutic drug concentration is reached between 2 and 4 h following ALA administration and there is rapid systemic clearance of ALA-mediated PpIX within 24 h. This effectively excludes prolonged cutaneous photosensitivity, hence allows repeated treatment every 48 h without risk of damage to normal tissue. Additionally, the high fluorescence yield and wavelength selectivity of PpIX fluorescence allow *in situ* monitoring of its concentration before the commencement of laser beam delivery for treatment. Since the sensitizer stays for a (desirably) relatively short period and is subject to rapid removal by photobleaching, real-time monitoring is essential for effective PDT.

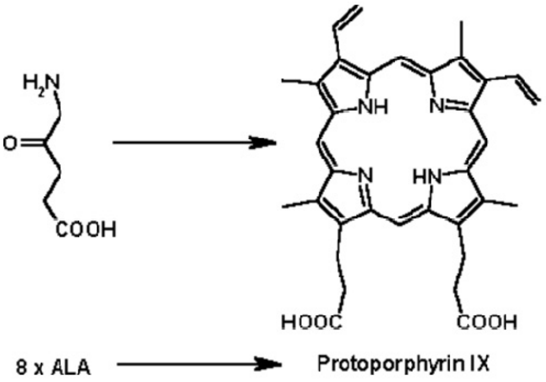

Figure 3. Chemical structure of ALA and PpIX.

Certain types of tumour tissue exhibit increased accumulation of ALA-induced PpIX. The activity of the enzyme ferrochelatase, which catalyses the insertion of Fe^{2+} into the porphyrin ring, is lower than normal in some tumours. Consequently the final conversion to haemoglobin is slower, which results in prolonged elevation of PpIX levels. Additionally, topically applied ALA cannot readily penetrate the keratinous layer of normal skin but can penetrate malignant lesions. This further enhances the tumour specificity whilst practically eliminating photosensitization of healthy skin.

Although ALA-meditated PpIX photosensitization offers some advantages over HpD and Photofrin, there are still drawbacks associated with the treatment. Because photosensitization is still porphyrin-mediated, excitation of PpIX also occurs at 630 nm, offering no advantage over HpD regarding the depth of tissue penetration. The hydrophilic nature of ALA restricts drug penetration through the keratinous tissues of normal skin. This problem may, however, be alleviated by the use of lipophilic ALA esters that can penetrate cells more easily. The application of PDT for both early *diagnosis* of carcinoma from detection of sensitizer-mediated and UV-laser-induced fluorescence and subsequent treatment using a specific laser wavelength has great potential for future medical procedures and is summarized in §6.

6. DIAGNOSTIC APPLICATIONS OF LASERS

The major and most promising application of lasers for medical diagnostics is in the early detection of carcinoma [13]. While 100% consensus is normally achieved for the diagnosis of fully developed carcinoma among histopathologists, the consensus has been found to be only 65% for the diagnosis of dysplasia. The prospect of using laser spectroscopy, in particular spectroscopy based on Raman scattering, has shown promise for the diagnosis of dysplasia with 95% specificity and the prospect of further improvement has been investigated in the author's laboratory a few decades ago [14]. In recent times the technique is being clinically used in some diagnostic centres and further R&D for greater improvement in specificity and cost-effectiveness is ongoing in many major laboratories throughout the world [15].

Raman scattering is the emission of light at a very specific wavelength, within an extremely narrow band, and is related to transitions within the vibrational modes of electronic levels of a molecular-specific site. The latter is known as the line position in the wavelength axis with respect to the wavelength of the exciting laser beam[6] in a graph of intensity versus wavelength (spectrum). Raman lines (spectra) constitute characteristic "fingerprints" of the molecules participating in the scattering process of the incident light. Any changes in this fingerprint can be related to a tell-tale "signature" of a possible disease (such as carcinoma), which lends itself to be used as a tool for noninvasive diagnosis. The only drawback is that Raman scattering is an extremely weak interaction process compared to Rayleigh scattering, reflexion, fluorescence etc., which usually grossly submerge

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[6] Although Raman himself was able to use the intense Indian sunlight to make his discovery, in most latitudes the weakness of Raman scattering makes the use of lasers practically mandatory (cf. eqn (1) and the immediately following text), and it is of course much more convenient.

Raman lines, hence innovative spectral and temporal filtering by sophisticated apparatus and processes are needed to retrieve Raman lines from optical and statistical noise levels that are typically many orders of magnitude higher than the intensity of the Raman lines [16]. Examples of the Raman spectra of tissue samples, histopathologically graded in terms of normal squamous, dysplastic and cancerous, are presented in Fig. 4. The differences are extremely small and cannot be discerned visually or even electronically. However, sophisticated statistical analysis of a large number of data points reveals differences in the fingerprints and allows conclusions to be drawn regarding the conditions of the tissues.

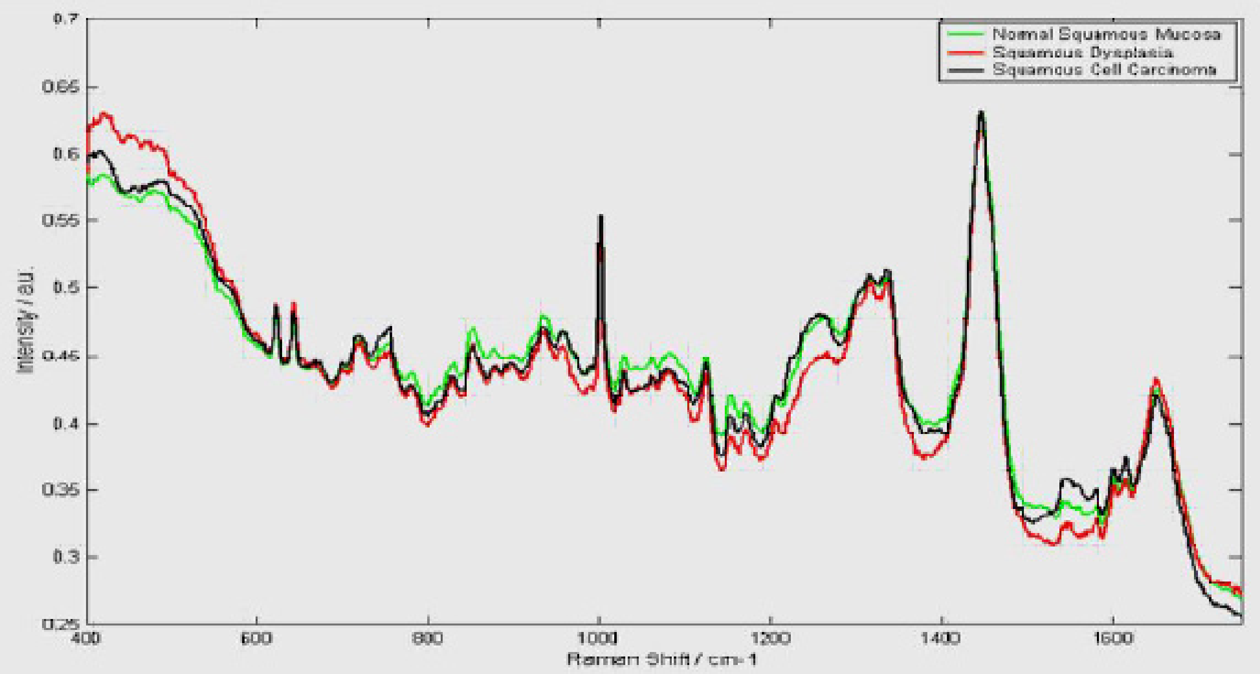

Figure 4. Raman spectra of squamous normal, dysplasia and carcinoma tissues (normalized with respect to the line at 1446 cm^{-1} of protein molecules).

The assignments of the lines to specific molecular sites and vibrations have been carried out in our laboratories and elsewhere and are presented in Table 2 as an exemplar. The results of a statistical analysis of tissue biopsy samples are presented in Table 3.

Table 2. Assignment of major Raman lines (given in cm^{-1}) from biological tissues.

Line	**Assignment**	**Line**	**Assignment**
484	Glycogen	1082	Lipid/C–N stretch (in protein and DNA)
525	Disulphide		
643	Tyrosine	1124	?
719	Nucleotide peak	1172	Tyrosine
759	Tryptophan	1208	Thiamine
832–833	Tyrosine	1261	Lipid
853	Tyrosine	1306	Lipid
880	Tryptophan	1333	Guanine
936	Hydroxyproline (C–C protein backbone)	1446	Protein
		1547	Tryptophan
1003	Urea	1658	Amide I (C=O)
1004	Phenyl ring breathing mode		
1035	C–H bending of phenylalanine		

Table 3. Statistical analysis (see ref. 14) of Raman data from tissue biopsy samples.

	Predicted identification[7]			
Classification	Normal	Dysplasia	Carcinoma	Total
Normal	100	5	7	112
Dysplasia	4	34	0	38
Carcinoma	7	0	42	49
Sensitivity*	89%	90%	86%	
Specificity**	87%	93%	95%	

* Sensitivity of a test is the percentage of individuals with the disease who are classified as having the disease.
** Specificity of a test is the percentage of individuals without the disease who are classified as not having the disease.

For the Raman scattering procedure to be universally acceptable for clinical applications, further research is needed in the following areas:

- Evaluation of the chemical changes of cell constituents during dysplastic progression
- Correlation of Raman intensities/wavelength shifts of selected modes with such changes using a large number of samples and under myriads of different conditions
- Optimization of experimental parameters for signal:noise ratio improvements
- Evaluation of resonance excitation for Raman intensity enhancement [17] and evaluation of surface-enhanced Raman spectroscopy (SERS) for tissue samples
- Application of simpler statistical analysis protocols for accurate diagnoses.

7. CONCLUSIONS

Within the last few decades at least two dozen books and perhaps an equal number of specialized conference proceedings on many diverse aspects of laser applications in medicine have been published. Several international journals have produced special issues for articles on laser applications in medicine. Its clinical application in the treatment of retinopathy and other aspects of vision problems is invaluable and in some cases irreplaceable. Although lasers and laser spectroscopy are being used for other therapeutic and some diagnostic purposes, the comparative effectiveness of such procedures is often in question. This is primarily because the proliferation of laser clinical applications is not adequately underpinned by basic research on the relevant fundamental aspects of laser interaction with tissues. Since research in this field is still primarily driven by private enterprises as part of business propositions, the most effective and widespread application of lasers to biological tissues at present is in the field of cosmetic surgery [18], such as for the removal of tattoos, unwanted body hair or marks, etc. For much more effective use of lasers and laser spectroscopy—such as *in situ* identification of cancerous tissue to guide the surgeon while operating in excising what is necessary [13,19]—further focused research is needed to optimize laser parameters so that, for example, small and inexpensive lasers such as diode lasers could be used. Research is also needed for the optimization of beam delivery systems, searching for more cost-effective sensitizers for photodynamic therapy, and also better measurement and control of laser power as lasers could be a hazardous tool in the hand of an inexperienced surgeon, or where there is inadequate information on safety protocols, or about implementation procedures. It should also be mentioned that advanced metrology tools applicable to medicine often require light with the attributes of laser radiation (Table 1) [20].[8]

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[7] Predictions based on the analysis of Raman spectral data were carried out using a statistical procedure called "Principal Component Analysis". The results are compared with those from histopathology. For example, out of 49 samples with carcinoma, 42 were predicted by Raman spectral analysis and 7 as normal (false).

[8] These may start with quite fundamental research questions (e.g. [21]), but the answers are crucial for the effective development of biomedical surfaces, such as those of stents and a host of other artificial implants [22,23].

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