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Phototherapy of Tumors

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Lasers provide a means of delivering high intensity light to small well-defined areas under precise control. The biological response depends on the light wavelength and intensity and the absorption characteristics of the target organ. The most important effects are thermal and include tissue vaporization, necrosis with later sloughing, and necrosis stimulating an inflammatory response which may lead to local fibrosis. The Carbon Dioxide Laser can cut or vaporize neoplastic tissue in areas accessible to rigid endoscopy, but the more penetrating Nd YAG and Argon laser beams can be transmitted via flexible fibers and have greater potential for destroying larger tumors without unacceptable damage to surrounding areas. More selective tumor phototherapy is possible in some organs by sensitization with HpD (hematoporphyrin derivative) and subsequent treatment with a dye laser. This effect is non-thermal and depends on the production of singlet oxygen by activated HpD. The precision possible for local treatment of solid tumors with lasers is greater than for almost any other techniques, but careful quantitative studies are needed to establish the appropriate treatment parameters in any particular situation.

It was only 3 years after the first reported practical laser action in 1960 that publications began to appear on the use of lasers in tumor therapy. McGuff et al. [1] reported cures by use of a ruby laser of melanomas transplanted to the hamster cheek pouch. Minton et al. [2] reported the destruction of transplanted melanomas and sarcomas in mice with a neodymium laser and showed that tumor destruction was more effective when higher laser energies were used. Early clinical trials also seemed promising [3]. However, after the initial period of enthusiasm, the pace of development slowed. This was due in part to the technical difficulties of operating appropriate lasers and delivering the beam to the desired treatment areas in the body. More recently, the improved reliability and sophistication of lasers, and particularly, the introduction of more flexible delivery systems which can transmit a narrow, intense laser beam to the target area (either via fully flexible glass or quartz fibers, or articulated arrangements of rigid light guides) have opened up many more therapeutic possibilities. This review will outline some of the ways in which laser light can interact with biological systems as well as discuss the relevance of laser applications to tumor therapy in relation to other possible therapeutic modalities.

Interaction of Laser Light with Living Tissue

The biological effects of laser light on living tissue depend on many factors. The effects at each individual point depend on the intensity of the light, the absorption characteristics of the tissue at the wavelength used, and the biological response to the energy absorbed. However, it is not possible to keep the intensity of light constant throughout a finite volume of tissue; the absorption of energy in the superficial levels causes the intensity to fall as the light penetrates deeper, and it is often difficult even to maintain a constant intensity of light across the surface of an organ being treated. Thus, consideration of the effects of laser light must be divided into 2 stages—the reaction in small areas immediately under the beam where the intensity of the light is precisely known, and studies over larger volumes, which will cover a range of changes from the most severe in the center to no biological change in regions further from the beam where the light intensity is too low.

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Table 1. Interaction of laser light with living tissue.

Energy density (J/cm^2)	Biological effect
<4	Biostimulation
>4	Biosuppression
40	Nonthermal cytotoxic phototherapy with sensitizing agents
400	Photocoagulation } Thermal effects
4,000	Vaporization } Thermal effects

The effect of light of a particular intensity depends on the wavelength used. Table 1 gives an approximate guide to the range seen. In the late 1960's, Mester et al. noted that repeated pulses of low energy density (1 J/cm^2) ruby laser radiation stimulated hair growth in depilated mice, although above a certain intensity the effect became inhibitory. They carried out more detailed studies on wound healing in rats using low-power Argon and helium-neon lasers, which suggested that the laser stimulated collagen synthesis and capillary growth in regenerating areas. The studies also showed a significant increase in the tensile strength of healing skin wounds at 8 days [4–6]. Laser light at very low intensity is unlikely to be of direct value in tumor therapy. However, if a large tumor mass is being treated, the intensity may drop to give absorbed energies of this level at some distance from the main beam which could stimulate rather than repress tumor growth. There is some evidence that this might happen in practice. Gardner et al. [7] showed that solid mouse tumors, treated with a sublethal dose of light from a Nd YAG laser, regrew from the edges at a slightly faster rate than controls.

The next band of values for energy density have enormous potential for tumor therapy; these will be discussed below in the description of therapy with photosensitizing agents. At the top end of the scale, i.e., at the highest energy levels, all the biological effects produced arise from local absorption of the laser light as heat. Within this band, the changes seen vary from slow heating of extended volumes to vaporization of the exposed surface of various organs. Currently, thermal effects of lasers are the most widely used in tumor therapy.

Thermal Effects

Three types of laser have suitable output beams: the carbon dioxide (CO_2) laser (wavelength 10,600 nm in the far infrared), the Nd YAG laser (wavelength 1,060 nm in the near infrared), and the Argon ion laser which has 2 main lines (at 488 and 514 nm) in the blue and green regions of the visible spectrum. The absorption characteristics of soft tissues vary

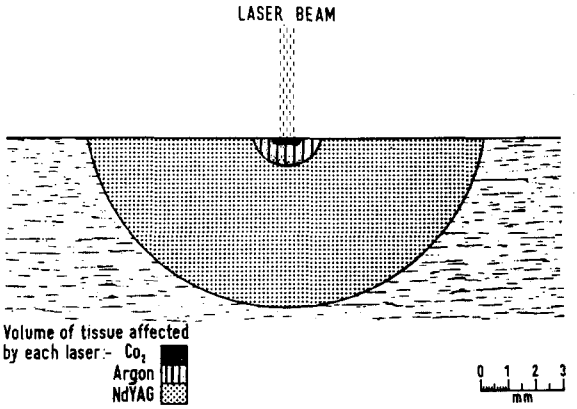


Fig. 1. Volume of tissue affected by different lasers.

enormously between these wavelengths, which give rise to quite different overall effects. The CO_2 laser beam is strongly absorbed in water, whereas the other two are absorbed more in pigmented cells. In each case, if sufficient energy is absorbed at the surface, the superficial cells will be destroyed and further application of the beam will bore a hole into the tissue. However, the differences arise in the extent of milder cell damage in surrounding areas. In richly vascularized tissue such as liver, the application of sufficient energy to vaporize just the surface cells only causes lesser damage to a depth of 0.1 mm with the CO_2 laser. When the same surface effect is produced with the Argon laser, milder damage extends for 1 mm and with the Nd YAG, it extends for 5 mm. These figures only apply for short laser exposure times (a few seconds). Slow heating of larger volumes occurs with lower powers and longer exposure times. Nevertheless, if lower energy levels are used, the extent of partial damage with the Argon and Nd YAG lasers is much less. Quantitative studies have shown that the extent of damage depends closely on the energy dissipated [8]. In addition to the effects directly below the exposed surface, light from these lasers is subject to scattering in all directions within the tissue, resulting in similar changes lateral to the area under the beam. The relative volumes affected are shown in Fig. 1.

When soft tissue absorbs a small amount of energy, it merely warms up. As the amount of energy increases, thermal contraction of the treated area occurs, most likely owing to the vaporization of water within the tissue without extensive cell necrosis. Still higher energies kill the cells in situ, and ultimately vaporize cellular material, leaving a crater. The essential difference between the 3 lasers is the volume of tissue that can be heated before vaporization of the superficial cells occurs, and this determines the suitable application for each laser. As the tissue shrinks, small vessels within the

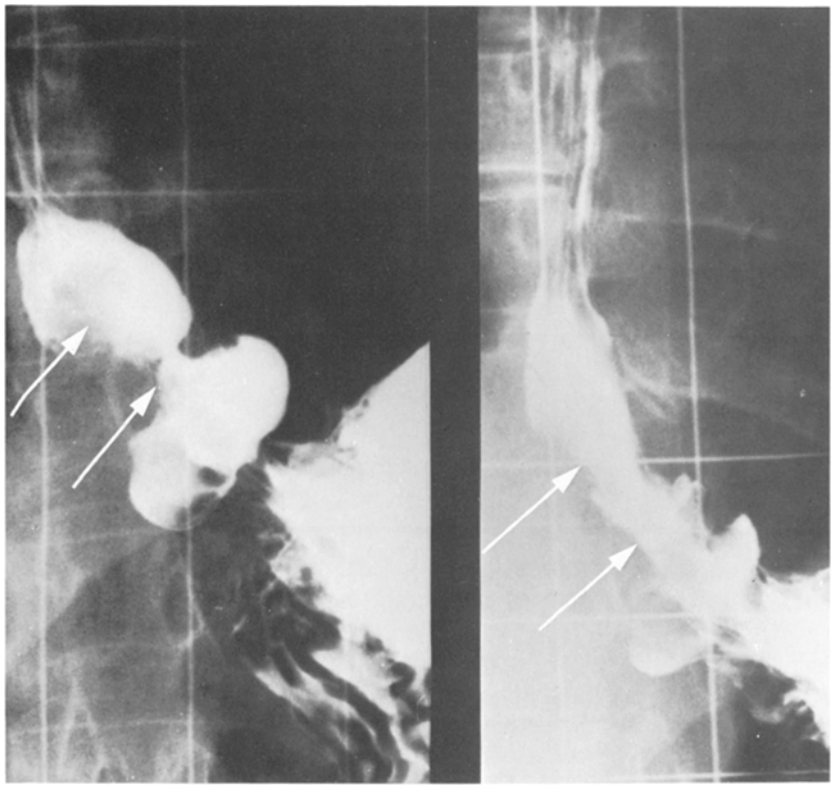


Fig. 2. Barium swallow before (*left*) and after (*right*) laser treatment in a patient with an adenocarcinoma at the gastroesophageal junction. The arrows indicate the extent of the tumor at the narrowest area.

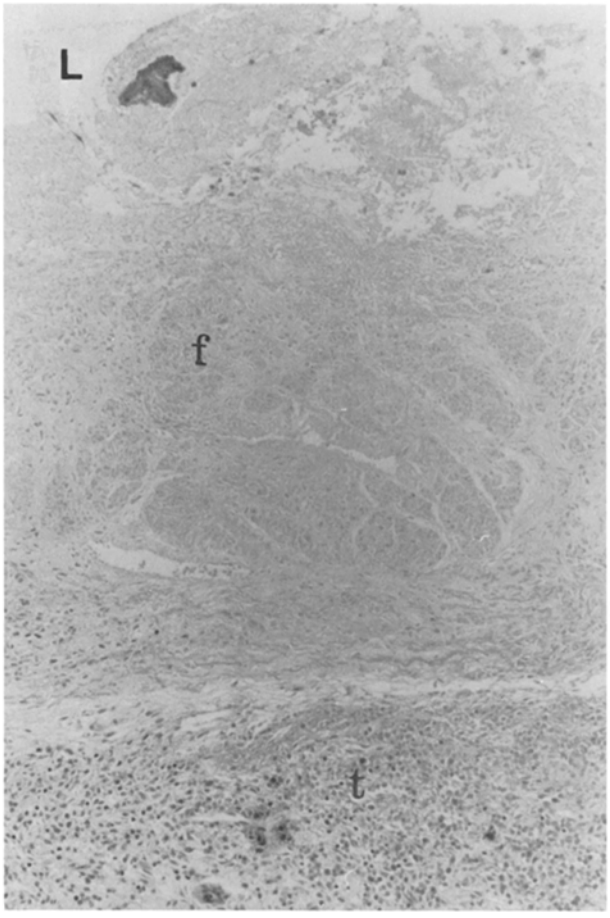
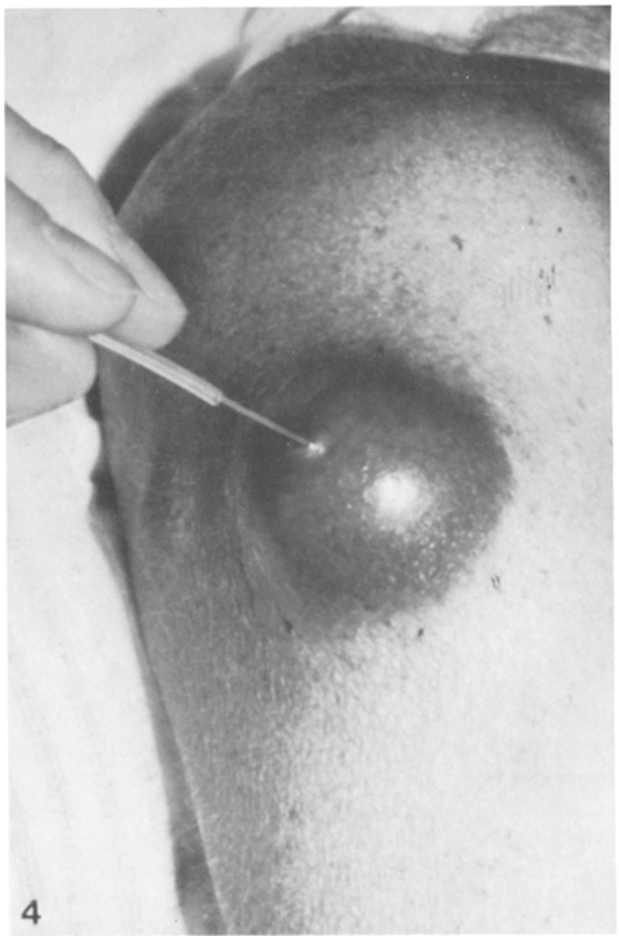


Fig. 3. Post mortem section of a squamous carcinoma of the esophagus treated with Nd YAG laser 15 weeks previously. L = esophageal lumen; f = fibrosis in areas of laser-induced tumor necrosis; t = viable tumor (Hematoxylin and Eosin). The presence of true fibrosis was confirmed using the elastic Van Gieson stain.

treated area may be sealed, and by this mechanism hemorrhage can be arrested. Thrombosis in occluded vessels only occurs as a secondary effect [9]. This works best when the volume heated is large as with the Nd YAG and to a lesser extent with the Argon laser. The Nd YAG can seal vessels up to about 1 mm in diameter in suitable supporting tissue. This is of value in the endoscopic treatment of hemorrhage from peptic ulcers when arteries can be identified in the ulcer crater. It is less useful in the treatment of hemorrhage from tumors, as the bleeding more often comes from diffuse areas and thermal treatment of areas that are already necrotic may make the bleeding worse rather than better. The value of the Nd YAG laser in tumor therapy is in thermal necrosis of neoplastic areas as described below.

The CO_2 Laser

The volume heated by the CO_2 laser [10] is so small that it has little practical value for stopping major



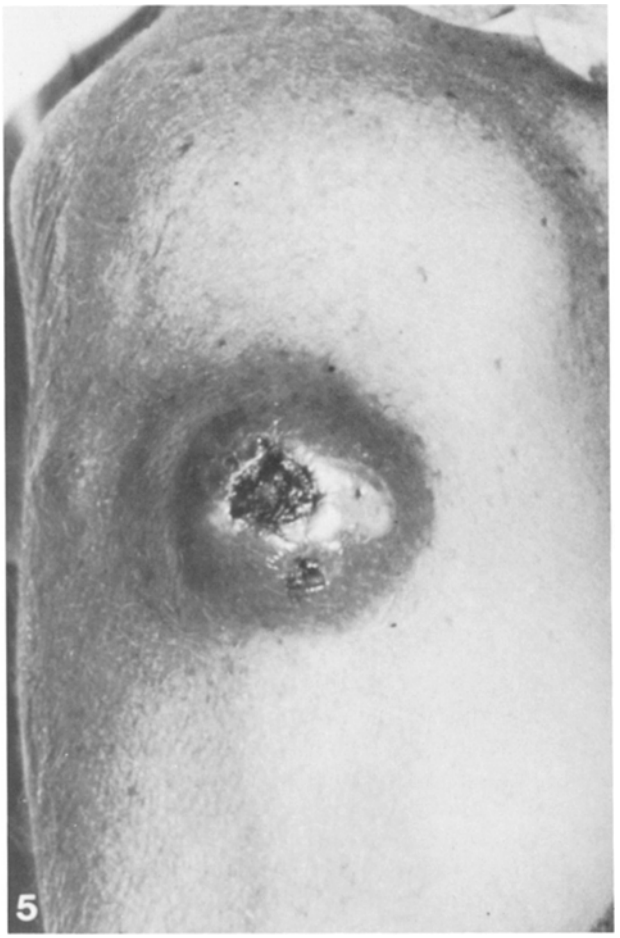


Fig. 4. A 400-μm glass fiber inserted into a cutaneous secondary deposit from a squamous carcinoma of the bronchus.

Fig. 5. Same lesion as Fig. 4, 2 days after interstitial treatment (Nd YAG laser 20 watts, 10 sec = 200 Joules).

hemorrhage although, if a large beam spot size is used, some superficial contraction can be produced to seal capillary oozing. In contrast, the highly localized effect of this laser makes it eminently suitable as a laser knife, the cells immediately under the beam being vaporized with minimal damage to adjacent areas. This beam can be used to cut through tissue or to scan across the surface of an organ to vaporize the superficial layers to any desired depth.

The CO_2 laser is a surgical instrument. To date, it has been used in a wider range of surgical applications for the treatment of benign and malignant disease than any of the other lasers. It can cut and vaporize diseased tissue in a precisely controlled manner. In gynecology, its precision makes it one of the best methods for treatment of early malignant disease of the vulva, vagina, and cervix. In laryngeal surgery, benign and early malignant tumors can be removed with less damage to the surrounding tissue than with any other modality. These applications are described in other papers in this symposium. However, its limitations must be remembered. Any bleeding more than oozing must be stopped by other means. As a knife, in areas accessible to a conventional scalpel, it has no major advantage except in those instances in which mechanical drag from a blade can be hazardous such as when cutting tough tissue as in surgery on the spinal cord. In addition, the only flexible fibers currently available to transmit the CO_2 beam are toxic, expensive, and relatively inefficient. This limits present endoscopic applications to rigid instruments.

Argon and Nd YAG Lasers

Although the Argon ion and Nd YAG lasers have not been as extensively studied as the CO_2 laser in tumor therapy, they do have 2 major advantages. First, the beam from each can be transmitted via fully flexible single fibers (200–600 μm in diameter),

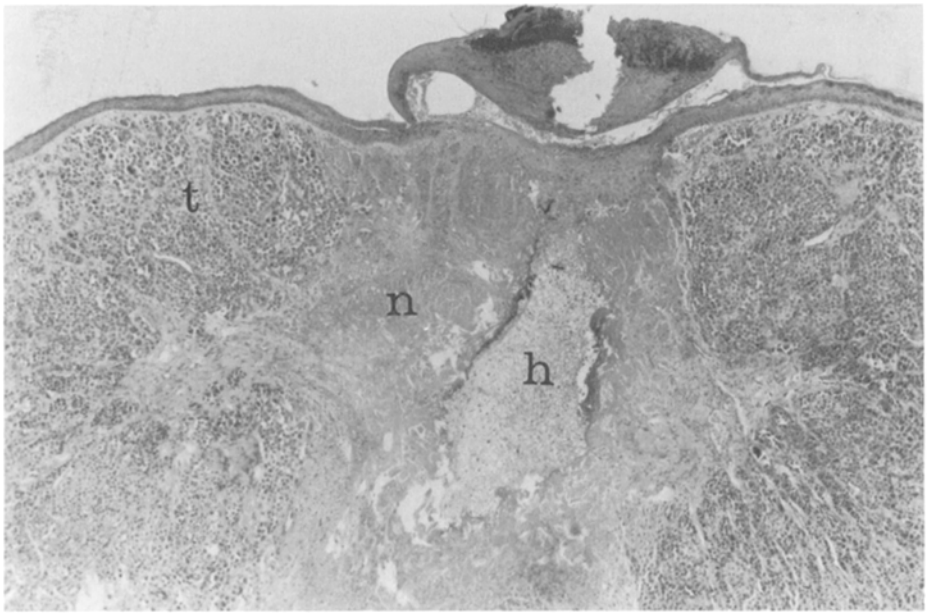


Fig. 6. Cutaneous secondary deposit from a malignant melanoma excised 5 days after treatment (Nd YAG laser, 5 watts, 15 sec = 75 Joules). h = hole where fiber was inserted; n = necrotic tumor; t = viable tumor (H&E).

so they can be used in conjunction with flexible fiberoptic endoscopes. Second, the lower absorption coefficients at these wavelengths make it possible to heat larger volumes of tissue.

Current clinical use of these lasers for tumor therapy is relatively crude. They are being used with flexible endoscopes in cases unsuitable for surgery or radiotherapy for the palliative recanalization of advanced malignant neoplasms that are obstructing the main airways or the upper gastrointestinal tract. Treatment of bronchial neoplasms is described elsewhere in this symposium. We have treated 5 patients with advanced inoperable malignancy of the esophagus or stomach, and have succeeded in providing good symptomatic relief of dysphagia in all (4 with the Nd YAG and 1 with the Argon laser [11]). There were no major complications. Treatment was carried out using standard endoscopes, the only modification required being a filter in the eyepiece of the instrument protecting the endoscopist's eye from back-scattered laser radiation. The laser fiber was passed through the biopsy channel and its tip held 5–10 mm above the target area. The instrument was fired at nodules of tumor protruding into the lumen in the narrowest areas. Care was taken to avoid firing at the gut wall to minimize the risk of perforation. During treatment, the target area initially whitened, probably because of protein denaturation; this was followed by charring and vaporization. Charred and denatured tumor sloughed over 2–3 days or could have been removed by endoscopic brushing, thereby exposing deeper areas for further treatment. Up to 6 treatments were needed on each patient. Barium studies before and after treatment of an adenocarcinoma of the gastric fundus are shown in Fig. 2. The slight bleeding occasionally seen could be stopped by further laser shots directed at the bleeding point. Two patients had recurrent dysphagia after 3 months. The others, up to the time of their deaths from disseminated malignancy, were able to swallow. The main alternative endoscopic treatment for these patients is the insertion of a Celestin tube. This can be done in one session, whereas laser therapy takes several. However, laser therapy can be applied in areas where prosthetic tubes cannot be readily inserted (e.g., the gastric outflow tract or the upper third of the esophagus) and this option does not require a foreign body to be left in situ. Larger trials are required to assess the relative merits of the 2 approaches [12].

Laser treatment of these advanced tumors in both the gastrointestinal tract and the airways is designed to de-bulk the tumor mass and slow the rate of regrowth in the area of most severe obstruction by causing necrosis and fibrosis of the tumor surface. No attempt is made to control the precise extent of necrosis, apart from ensuring that the risk of perforation is minimized. Figure 3 shows a section taken at post mortem from a patient who had had successful laser palliation of dysphagia from esophageal carcinoma 15 weeks earlier. Close to the esophageal lumen, some fibrosis can be seen in areas of laser-indu tumor necrosis. Fibrosis of this nature would nc ormally be expected in a squamous carcinoma his site. Deeper layers of tumor appear viable.

Small benign polyps of the colon have been treated in a more controlled fashion using both the Argon [13] and Nd YAG [14] lasers. In these cases,

the laser beam was applied until the polyp blanched, but no attempt was made to vaporize cells. This limited the depth of damage, making the risk of perforation extremely low. The tissue necrosed by therapy sloughed over a few days and any residual polyp could be treated again. This approach is useful when there are large numbers of small sessile lesions as in familial polyposis coli if the rectum has been preserved after colectomy, and is probably faster and easier than alternative diathermy techniques.

There have been recent reports from Japan of the endoscopic treatment of early gastric cancer with the Nd YAG laser in patients considered unsuitable for surgery [15, 16]. The amount of energy that the stomach can absorb without risk of perforation is well known [8], and malignant areas can certainly be destroyed by laser irradiation. The major problem is to determine the extent of disease in width and depth. Until this can be done reliably without surgery, any treatment other than resection would appear unethical—except in exceptional circumstances when surgery is not possible.

Interstitial Therapy

In reports of the use of Argon and Nd YAG laser beams transmitted via flexible fibers, the tip of the fiber is held above the surface of the target area (external therapy) and great care is taken to keep the fiber tip clean. If the laser is fired when there is a small amount of cellular debris on the fiber tip, the energy will be absorbed in the debris thereby heating the tip to a temperature that may be high enough to destroy it. However, if the tip is inserted *into* the tissue, it is in direct thermal contact with a much larger volume (interstitial therapy). Consequently, a larger quantity of energy is required to heat the tip sufficiently to damage it, as the heat is conducted away through the organ. If the energy dissipated is kept below this level, the tip will not be damaged. In practice this means that tissue adjacent to the fiber tip can be heated to any temperature up to about 100°C and maintained as long as desired. The laser power input through the fiber is balanced by thermal conduction of energy away from the vicinity of the fiber tip. Within the tissue, the fiber tip acts as a point source of energy, and the distribution of effects around it is roughly spherical. The extent of irreversible and reversible tissue damage will depend on both the laser power and the exposure time under given conditions for any particular target organ. All energy transmitted down the fiber is absorbed in the tissue (apart from the very small amount reflected back up the fiber); in contrast, when the fiber is held above the target (external therapy), the precise amount absorbed depends on the nature of the surface under the beam. A considerable percentage may be lost by reflection. Figure 4 shows a single 400-μm glass fiber inserted 3 mm into a cutaneous secondary deposit from a squamous carcinoma of the bronchus. Under local anesthesia, a large-gauge needle was inserted into the tumor and the fiber inserted through the needle. Following this, the needle was withdrawn over the fiber, leaving the bare tip embedded in the tumor. [An alternative method for insertion is to hold the tip against the tumor surface and fire the laser for a very short period (i.e., 0.1 sec). This can be enough to break the surface sufficiently to insert the fiber, and in soft tumors, the fiber has enough mechanical strength to be advanced deeper on its own]. The proximal end was attached to an Nd YAG laser (Fiberlase 100, Barr and Stroud Limited, Glasgow, Scotland) and a power of 20 watts was applied for 10 sec (200 J). Following this, the fiber was removed and showed no signs of damage. The patient had no discomfort during or after the procedure, and 2 days later the appearance was as shown in Fig. 5, with local necrosis around the treated spot.

The nature and extent of damage in a lesion similar to this is illustrated in Fig. 6, which shows a section of a cutaneous secondary deposit from a malignant melanoma excised 5 days after treatment with the Nd YAG laser at 5 watts for 15 sec (75 J). The central hole is that made for insertion of the fiber. Immediately adjacent to this is a circular zone of necrotic tumor, which by 5 days has become clearly demarcated from viable tumor. Permission for these pilot studies on cutaneous deposits from different tumor types was given by the Ethical Committee of University College Hospital, London. However, more detailed studies must be done in an animal model. Quantitative studies in animal tumors are under way, but it is already known from external experiments (fiber held above the target) that the extent and severity of damage to normal tissue depends closely on the energy applied. The ultimate fate of treated areas varies from immediate vaporization or delayed sloughing, to replacement of previously functioning tissue by fibrous tissue without loss of mechanical integrity of the organ during the process. (Following Nd YAG laser treatment, it was possible to produce a full-thickness scar in the stomach wall of a dog without causing perforation [8]). These results may be summarized as follows:

1. Laser treatment may be centered on any spot accessible to a single fiber within or on the surface of an organ.

2. The extent and severity of laser damage depend on the energy dissipated and are reasonably predictable for each tissue.

3. Laser treatment may replace functioning tissue (normal or neoplastic) by regenerative fibrous tissue without breakdown of the mechanical integrity of the organ during healing.

The range of thermal effects seen after Nd YAG laser treatment may be summarized as follows: (a) tumor cell vaporization; (b) tumor cell death with delayed sloughing; (c) tumor cell death, but tissue repair with fibrosis; and (d) remaining viable tumor. In some cases, all effects may be seen in one tumor, varying with the distance from the laser fiber. However, if subsequent studies show that the extent of these effects is predictable, the Nd YAG laser could find a useful place in the local treatment of solid tumors.

Phototherapy with Selective Photosensitization

In the light intensity range just below that required to produce thermal effects in living tissue, illumination of most organs with light in the visible or infrared region of the spectrum has little effect. However, pretreatment of the target tissue with certain photosensitizing agents can enable light of this intensity to produce a severe cytotoxic effect. Some of these photosensitizing agents are retained selectively in malignant tissue, which gives this approach an enormous potential in tumor therapy.

It has been known for many years that neoplastic and traumatized tissues have an affinity for porphyrins, and that such areas can be detected by fluorescence of the porphyrins under ultraviolet light [17]. The selectivity for malignant tumors was improved using an acetic and sulfuric acid derivative of hematoporphyrin, known as hematoporphyrin derivative (HpD) [18]. Most work in recent years has concentrated on this substance as the best photosensitizing agent available. The active components have been isolated and synthesized [19]. The mechanism of the cytotoxic effect [20] occurs in the following manner: First, incident laser light activates HpD. The activated HpD then converts triplet O_2 to excited singlet O_2. Finally, singlet O_2 is cytotoxic to the cell membrane. The lifetime of singlet O_2 is too short for it to move more than a few cell diameters from the site of production and so the effect is localized to the areas of high HpD concentration. It appears to be a threshold reaction, so if the amount of singlet O_2 present is too low (as in areas of low HpD concentration or poor light penetration), cells survive [21]. This makes selective destruction of malignant tumors a real possibility in areas in which the surrounding normal tissue has a low affinity for HpD. This is the case with skin (although photosensitivity in the skin persists for several weeks after administration). Unfortunately, it is not usually so in internal organs such as the liver and kidneys [22], although with some specific tumors, high tumor/liver HpD concentration ratios can be obtained [23].

Experimental studies on single cell layers harvested from tumor-bearing mice pretreated with HpD have quantified the cytotoxic effects closely in relation to the HpD concentration in the cells and the light energy applied [21]. However, quantitative studies on the treatment of solid tumors in whole animals are much more difficult to carry out and few have been reported. Berenbaum et al. [19] used a very effective technique to assess the biological activity of the components of HpD in subcutaneous tumors in mice. The tumor, sensitized with the HpD component under study, was exposed to a predetermined amount of light chosen so that only part of the tumor would be damaged. The animal was sacrificed exactly 24 hours after treatment and the depth of necrosis within the tumor measured.

Clinical studies from several centers report encouraging results of phototherapy of malignant tumors including bronchial carcinomas [24, 25], breast carcinomas [26], malignant melanomas, and even gliomas [27]. However, the treatment regimens used have been empirical. There is no good evidence available to determine the optimum values for the dose of HpD, the time after administration before exposure to light, and the light intensity and exposure time, although rough guidelines can be found in the results of animal experiments. There is little available data (experimental or clinical) on the extent and severity of the necrosis produced around each treatment point under given conditions in normal or neoplastic tissue.

This has given rise to serious problems in the treatment of bronchial carcinomas with flexible bronchoscopes. Although tumors less than 3 cm in size have responded well, the only 2 tumors over 4 cm in size in one reported series of 10 patients bled massively 6 and 11 days after treatment. It was suspected that extensive tumor necrosis in an already necrotic carcinoma resulted in further hemorrhage and death [24]. Similar problems could be anticipated in the treatment of any internal tumors of moderate size, and further evaluation of the immediate and delayed response of all normal and neoplastic structures exposed to therapy is urgently needed in an animal model.

It has been suggested that long exposure times may deposit enough energy to produce some tissue heating, thereby producing biological effects of a thermal nature as well as those due to singlet O_2, but this has yet to be clarified [28]. Nevertheless, the relatively low energies involved mean that the light can be transmitted to the target organ by fibers using the external (no contact) or interstitial technique. The interstitial technique was first used in

this application by Dougherty et al. [26]. Most current phototherapy with HpD sensitization uses red light of a wavelength between 625 and 630 nm. This choice is a compromise. HpD has several absorption peaks from the ultraviolet region of the spectrum to the visible red, and the peak at 625 nm is the weakest and yet the longest wavelength at which a peak is seen. However, most animal tissues can absorb light heavily in the blue and green regions, which severely limits the penetrating power of light at these wavelengths. Absorption of red light in unsensitized tissues is less, which makes the peak at 625 nm the best choice. The most efficient source of light at this wavelength is a rhodamin B dye laser, as the laser source enables the light to be transmitted via a flexible fiber; non-laser sources (e.g., Xenon arc lamp or quartz halogen lamp with suitable filters) can be used if fiber transmission is not required, as with cutaneous lesions.

Phototherapy with HpD is extremely promising, but major problems remain to be overcome. Although its chemistry is reasonably well understood and the cytotoxic effects on cell cultures well documented, studies on whole animals and patients are largely empirical, and treatment of internal tumors may carry a high risk of serious complications. The selectivity of HpD for malignant tumors is only relative and does not apply in all organs, although more detailed pharmacodynamic studies may improve this if the mechanism of selective uptake and retention can be further elucidated. Nevertheless, the use of a laser and fiber transmission system does provide a separate degree of selectivity of defining the area to which the light is applied. HpD is the best photosensitizing agent currently available, but it is far from ideal as it only has a weak absorption peak in a suitable part of the spectrum. The search should continue for new agents with better characteristics.

Laser Therapy in Context

This review has looked at various ways in which lasers can be used in tumor therapy. This section will briefly review these applications in relation to alternative therapies.

The carbon dioxide laser is a surgical instrument. It can necrose and vaporize areas of tissue with much greater precision than diathermy or cryotherapy and can make exact incisions in any area accessible to rigid endoscopy, which is of particular value when these areas are not accessible to a conventional scalpel. However, it is of no special value for the in situ treatment of large tumors.

The thermal effects of lasers with greater tissue penetration (particularly the Nd YAG laser) and phototherapy with HpD sensitization must be seen in the context of the wide range of therapeutic possibilities open for the treatment of benign and malignant tumors considered unsuitable for surgical resection. Radiotherapy and chemotherapy have been in routine use for many years for suitable malignancies, although many tumors respond to neither. Local hyperthermia has been considered a possible useful modality for years. In the last decade interest has escalated and a recent supplement to the *British Journal of Cancer* was devoted to the topic [29]. In suitable cases it can be synergistic with chemotherapy or radiotherapy. The main heating techniques discussed were microwaves, radiofrequency induction heating, and ultrasound. Each has various advantages and disadvantages. The aim is always to maximize damage to tumor cells and minimize effects in normal areas. Reports that malignant cells are more heat sensitive than normal ones are probably incorrect and there is also no consistent difference between the heat response of hypoxic and oxic cells. However, there is now data to indicate that a low pH level, as might be expected inside tumors, may enhance thermal sensitivty [30]. Possible mechanisms for thermal cell death include direct damage to DNA, cell membrane damage, the heat-stimulated production of special proteins, and disruption of the microvasculature of the tumor. The implications for therapy are that the hyperthermia should be limited to the tumor area.

Superficial tumors are easy to heat by all techniques. Problems arise trying to achieve local heating in internal organs. For microwave and radiofrequency heating, both invasive and noninvasive techniques of applying heat energy have been tried [31]. At radio frequencies, the noninvasive applicators are either capacitative plates or inductive coils; for microwaves, radiative apertures are used. However, even using an array of applicators, it is extremely difficult to localize the effects adequately other than near the skin. The situation is better with invasive applicators that can be inserted into the tumor—the radiating monopole for microwaves and RF needle electrodes or implanted ferromagnetic seeds (selectively heated by external inductive coils) for radio frequencies. The penetration and severity of damage can be controlled by the frequency and total energy of the applied radiation. The volume of tumor that can be heated is comparable to that heated using a Nd YAG laser with the transmission fiber inserted into the tumor (radius of 1–2 cm from the treatment point). The radiating monopole is a miniature coaxial transmission line which can be made flexible and implanted surgically or inserted via body orifices.

The biological effect of ultrasound involves both heat and cavitation (a collection of phenomena

related to local mechanical stresses in the target organ [32]). Little work has yet been done on invasive, therapeutic probes, but ultrasound is a penetrating, directional, and even focusable radiation that may prove to have a useful role in cancer therapy, although a coupling medium is required to transmit the beam to tissue and penetration is severely restricted by gas or bone.

Until now, lasers have not been included in most discussions of hyperthermia techniques. However, the ability to deliver laser energy to the center of a tumor mass via a fiber (which can be passed through the biopsy channel of a standard flexible fiberoptic endoscope) means that the precision of local heating is at least as good as with any of the other techniques. It is also possible to use multiple fibers to obtain a more uniform light intensity through a larger volume of tissue. This is of added importance since tumor selectivity for all the purely thermal techniques only occurs if the pH level in the center of the tumor is lower than in surrounding normal tissue.

The situation is approaching when the precision possible for local hyperthermia treatment of a tumor mass by insertion of a fiber or microwave-radiating monopole exceeds the precision of localizing the extent of neoplastic tissue by current diagnostic techniques (conventional radiology, computerized axial tomography, ultrasound, endoscopy, etc.). The ideal solution is to develop a therapy that can kill cancer cells with greater selectivity so that treatment of normal areas does no harm. This does not exist. Radiotherapy is more toxic to some neoplastic cells than to normal ones. Although it can be precisely focused, cumulative toxicity to normal cells is still a major limiting factor. However, it is possible that the use of laser phototherapy, following selective sensitization with dyes like HpD, represents a step in the right direction.

Résumé

C'est seulement en 1960, 3 ans après la première publication concernant l'action du laser que les communications à propos de son emploi pour traiter les tumeurs apparurent. McGuff et ses collaborateurs rapportèrent d'abord la guérison par photothérapie (laser Rubis) de mélanomes transplantés sur la joue des hamsters. Minton et ses collaborateurs publièrent ensuite des cas de destruction de mélanomes et de sarcomes transplantés chez la souris par le laser Néodymium et démontrèrent que la destruction du processus tumoral était plus complète quand les lasers à hautes énergies étaient employés. Les premiers essais cliniques parurent prometteurs, puis après une période d'enthousiasme un certain scepticisme se fit jour. Ce phénomène était dû d'une part à la difficulté d'employer des lasers adequats, d'autre part à la difficulté d'atteindre par le rayonnement les parties du corps à traiter. L'amélioration ultérieure de l'appareillage devait entraîner le développement de la photothérapie tumorale. Les nouveaux lasers en effet grâce à leur souplesse permettent de transmettre un rayonnement intense et étroit à la zone à atteindre (grâce aux fibres en quartz, aux fibres en verre flexible) ou aux appareils articulés qui s'opposent aux appareils anciens rigides.

Cet article a pour but de définir les interactions entre le rayonnement des lasers et les différents systèmes biologiques ainsi que de discuter les indications de la photothérapie tumorale par rapport aux autres méthodes de traitement des tumeurs.

Resumen

El efecto biológico de la energía del laser depende de la intensidad de la luz, de las características de absorción de los tejidos, de la longitud de la onda y de la respuesta biológica a la energía absorbida. Los tejidos neoplásicos y los traumatizados poseen afinidad por las porfirinas. La captación selectiva por parte de los tejidos malignos puede ser incrementada mediante la utilización de un derivado de la hematoporfirina conocido como el derivado hematoporfirínico (HpD). El mecanismo del efecto citotóxico se basa en la activación del HpD por el haz de laser; el HpD activado convierte el oxígeno, cuyos electrones en su último orbital se encuentran en forma de tripleta, para convertirlos en oxígeno en donde, en sus últimos orbitales se encuentran sueltos o en forma de singleta. El oxigeno en forma de singleta es citotóxico para la membrana celular. El efecto es de tipo local, porque el oxígeno en forma de singleta posee una vida media corta y no puede moverse por más de una distancia correspondiente a unos pocos diámetros celulares a partir del lugar de su producción. El potencial de destrucción es máximo en los neoplasmas que tienen elevada afinidad por el HpD, en contraste con los tejidos normales de alrededor. Los estudios experimentales utilizando esta tecnología han demostrado un futuro promisorio, y esta modalidad terapéutica está siendo evaluada clínicamente.

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