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ULTRAVIOLET LASERS

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Biologic Effects of Laser Radiation

ULTRAVIOLET LASERS

Samuel Fine, S.M., M.D. and Edmund Klein, M.D.

There are three types of lasers in current use in physical and biological research. These are:

1. The solid state or crystal lasers
2. The gas laser
3. The semiconductor laser

All three types of lasers have been operated in both the continuous and pulsed mode. The highest peak power levels have been achieved with the solid state laser in the pulsed mode. These power levels have exceeded one gigawatt (10^9 watts) using a ruby crystal laser operating at 6943 Å, Q-switched. The highest continuous power levels, in excess of 500 watts, have been obtained with the CO_2 gas laser operating at 10 microns. Yttrium aluminum garnet (YALG) solid state units, operating at 1.06 microns (10,600 Å) have been reported to yield continuous power levels in excess of 175 watts. A fourth type of laser, the liquid laser, has been developed. However, significant power levels have not been achieved with this type of laser to date.

Since the output from these lasers is essentially parallel(the beam divergence is of the order of milliradians), the beam can be focused down to a small spot size. This results in a high power density at the irradiation site.

There are two ways in current use for producing relatively coherent ultraviolet radiation from lasers:

1. Frequency multiplication - especially but not exclusively with pulsed solid state lasers. Common examples of this are frequency doubling of ruby resulting in a wavelength of 3470 Å, and frequency quadrupling of neodymium resulting in 2650 Å from a base frequency of 10,600 Å.
2. Direct lasing action in the ultraviolet, especially with gaseous lasers.

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1. Frequency Multiplication

Excellent descriptions of the process are given by Franken (1), Giordemaine (2) and Terhune (3). Much of the description concerning frequency multiplication given below is taken from the article by Terhune (3).

When light intensity is low, the response of the irradiated system is linear and light is only attenuated and refracted. When the intensity is high, the response of the system is nonlinear, and harmonics of the fundamental frequency are generated in the system.

The mechanism for producing this effect is as follows: As electromagnetic energy passes through a material, the oscillating electric field of the light beam interacts with the electric charges of the atoms and molecules. The electron cloud about the nucleus is set into oscillation. The particles of the irradiated system can be considered as oscillating dipoles which, at low intensities of the incoming electric field (at low intensities of the incident radiation) radiate energy at the same frequency as the incoming wave. Since each dipole oscillates independently, the resultant radiation is scattered at the same wavelength as the incident radiation, but not all in the forward direction. This scattering process is called Rayleigh scattering.

For low light intensities, the magnitude of the induced oscillating dipole, P, is proportional to the magnitude of the incident electric field, E. That is:

$$P = X_1 E$$

Where X_1 is called the electric susceptibility of the medium. The electric susceptibility is related to the index of refraction of the medium by:

$$n = (1 + 4 \pi X_1)^{1/2}$$

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If the intensity of the radiation is high, the interaction with the atom or molecule is strong and the resultant displacement of the electron cloud is large. If the electrons can be considered as in a potential well, the excursion up the side of the well is large. The relationship between the electric field, E, and the induced dipole radiation, P, is no longer linear.

It can best be expressed by utilizing Maxwell's equations, from which a power series in E is obtained. This series is

$$P = X_1 E + X_2 E^2 + X_3 E^3 + X_4 \frac{\partial E}{\partial t} + X_5 BE^2 + \ldots\ldots$$

in which terms involving spatial derivatives have been omitted for simplicity.

All terms except the first are responsible for the non-linear effects. The incident radiation at the atom can be represented by a sine wave in the usual way, $E = A \sin wt$. The induced dipole radiation, P, is given by:

$$P = X_1 (A \sin wt) + X_2 (A \sin wt)^2 + X_3 (A \sin wt)^3 + X_4 Aw \cos wt + X_5 B(a \sin wt)^2$$

The second term can be written as:

$$X_2 (A \sin wt)^2 = \frac{X_2 A^2}{2} - \frac{X_2 A^2}{2} \cos 2 wt.$$

Consequently, the radiation from the dipole contains a component at twice the frequency of the incident radiation. The relative magnitude of the second harmonic will be dependent on the relative magnitude of X_2. In a similar manner, third harmonic generation is dependent on the E^3 term.

The oscillations of the electron in the potential well can perhaps be understood, in some respects, in a very simplified model, as analogous to the oscillations of a pendulum. For small displacements, the pendulum can be considered as a linear system. However, as the magnitude of oscillation is increased, this approximation becomes invalid and harmonics are required to

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describe the oscillations of the pendulum correctly. Ultimately, of course, as more energy is transfered to the system(as the power is increased) increasing displacement of the pendulum is produced and the pendulum eventually swings through 360°, just as the electron escapes from the potential well and ionization is produced.

However, there is another problem associated with the production of harmonics. The velocity of light (electromagnetic radiation) within a material is dependent on wavelength. This can be observed by the production of a spectrum when a prism is irradiated with white light. Although the incident coherent laser radiation travels at a specific velocity through the crystal, resulting in phase coherent excitation of the dipoles, the harmonics generated by the dipole radiators will not be in phase since the distance from one oscillator to the next in the crystal is:

$$d = K_1 \frac{V_{\lambda\ \text{incident}}}{f_{\lambda\ \text{incident}}} \neq nK \frac{V_{\lambda\ \text{harmonic}}}{f_{\lambda\ \text{harmonic}}}$$

where V_λ is the velocity in the crystal.

In this case, therefore, destructive interference would occur between the harmonic radiation from the dipoles and very little, if any, resultant coherent harmonic radiation would be produced.

It is, however, possible to make:

$$\frac{V_{\lambda\ \text{incident}}}{f_{\lambda\ \text{incident}}} = n \frac{V_{\lambda\ \text{harmonic}}}{f_{\lambda\ \text{harmonic}}}$$

by using a double refracting material in which the velocities of propogation along different optical axes differ, depending on the polarization of the beam. By suitably rotating the crystal, it is possible to match the velocity of the harmonic with that of the incident fundamental and thus obtain constructive superposition of the harmonic radiation from the multiple oscillating dipoles.

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With these techniques, using ammonium dihydrogen phosphate (ADP) crystals, over 20% conversion efficiency to 3470 Å has been obtained from high peak power incident 6943 Å ruby irradiation. Similarly, using symmetric crystals, such as calcite and NaCl, third harmonic generation at 2313 Å has been obtained on ruby laser irradiation. It should be noted that although the peak power levels achieved are high - in the kilowatt or megawatt range, the total energy per pulse at higher(harmonic) frequencies is low, since the pulse duration is short, and energy = power x time.

Quadruple frequency multiplication of a 1.06 micron neodymium pulsed laser has been reported by Johnson (4). Power levels of 2.4 kw were obtained at 2650 A, using successive frequency doubling through two potassium dihydrogen phosphate (KDP) crystals. Proper care had to be taken to insure proper polarization of the beam, and correct orientation of the crystals.

2. Direct Ultraviolet Lasing

a. Gas Lasers

A second area in which coherent ultraviolet radiation has been produced is with gas lasers. Lasing from 3000 Å to 4000 Å with the strongest line at 3371 Å, from a pulsed nitrogen laser was reported by Heard (5). The power output was of the order of 10w summed over many lines. The pulse duration was as short as 20 n sec (20×10^{-9} sec). The output radiation was believed to be produced as a result of inversion in the triplet state of nitrogen. Recent outputs of 300 kilowatts have been reported by Avco-Everett Research Laboratory. Their 50kw unit has a pulse duration of 10-20 n sec. The energy output per pulse for the 300kw unit is consequently only about 3 millijoules (25). Similar peak power levels have been achieved by Heard. As is evident, although the peak power levels are high, the total energy per pulse is low with these devices. However, if the beam is focused to a 100 micron diameter spot, power densities of the order of

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3 gigawatts/cm^2 and energy densities of the order of 30 joules/cm^2 can be achieved.

Studies on the rotational structure associated with the pulsed nitrogen laser spectrum at 3371 Å and 3577 Å have been reported by Kaslin, et.al.(6). They found a super-radiance effect, which consists of the observation of a directed radiation beam similar to that of a laser in the absence of a resonator, i.e., without mirrors or with only one mirror. A standard spectrograph was employed. To facilitate interpretation, they photographed the spectrum of spontaneous emission. Results were compared against iron and titanium lines.

In September,1964 Heard reported pulsed laser emission at 3545 Å in a mercury discharge, doped with argon (7). In May, 1965 Bridges and Chester reported pulsed ultraviolet laser emission in ionized gas lasers (8). Dielectric coated quartz mirrors were used to produce the transitions at the shorter wavelengths.

The lines observed in the ionized gas lasers by Bridges and Chester were between the following ranges:

Ne	2678 Å - 3392 Å
Ar	2753 Å - 5502 Å
Kr	3239 Å - 8000 Å
Xe	2983 Å - 6270 Å
O	2984 Å - 5592 Å

The criteria used to determine whether a line lased included good collimation of the beam (small divergence) and the mode structure present as indicated by vacuum grease on white paper, or if the beam could be observed on a spectrographic plate at a distance of 60 m., with no interposed collimating optics.

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A theory on which lasing action occurs in the ionized laser is that of E.I.Gordon as reported in the paper by Bridges and Chester (8), and is as follows:

The upper laser level is populated by two successive electron collisions.

1. The ground state(unexcited)ion is produced by a single electron collision.
2. The excited ion is produced by a second electron collision. This excites the ion to the upper laser level.
3. The excited ion drops to the lower laser level, with coincident emission of an ultraviolet photon.
4. Depopulation of the lower laser level to the ion ground state occurs by vacuum ultraviolet radiation.
5. This ultraviolet radiation can, however, be increasingly trapped as the ion density builds up, limiting the operation of the laser.

Fifty-five pulsed ultraviolet laser transitions were reported by Cheo and Cooper in ionized N, O, Ne, Ar, Kr, and Xe in the 2300 Å - 4000 Å spectral line region using pulsed excitation in June, 1965 (9). Two-thirds of these lines were identified, nearly all assigned to doubly or triply ionized species. The tube was 4 mm x 1 meter; the resonant cavity was nearly confocal in configuration; the optimum gas pressure range was 1 to 100 microns depending on the type of gas and the wavelength. Wavelengths were determined spectrographically with a 1 1/2 meter Bausch and Lomb instrument.

To ascertain stimulated rather than spontaneous emission, two measurements were made, one with a high Q cavity and the second with the Q decreased by tilting the mirror nearest the spectrograph. A second check was made with a monochromater--photomultiplier--oscilloscope system by tilting the mirror. The

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current dependence of laser output power was made for a number of lines. The lasing pulse duration was ~0.1 to 1 microsecond for all doubly and triply ionized lines. No power values were given. The shortest wavelength observed was the 2358 Å Ne II line.

Thirty laser oscillations in the wavelength range 2600 - 6700 Å were reported by Cheo and Cooper from singly and multiply ionized chlorine, phosophorus and fluorine atoms in pulsed Cl_2, PF_5 and SF_6 gas discharges (10). Pulse widths of the order of microseconds were obtained.

Dana, et. al., reported 29 lines, pulsed from 2800 Å to 4000 Å in ionized neon, argon and xenon (11). No power values were given, however.

Continuously operating (CW) rather than pulsed ultraviolet ionized gas lasing has been reported by R. Paananen (12). Singly ionized neon has been lased at 30 milliwatts at 3324 Å. Doubly ionized krypton power at 3507 Å was about 13 milliwatts. It is expected that early attainment of one watt or more CW in the ultraviolet will be achieved in the near future following solution of the serious overheating and outgassing problems within the laser cavity.

b. Solid State or Crystal Lasers

Single crystal KBr rods from Harshaw Chemicals, 1/2 in. diameter and 2 in. long were fabricated in the form of Fabry-Perot resonators by Fink (13). The rod ends were optically polished and aluminum reflecting coatings were deposited. Metallic coatings were used, since it is difficult to design multilayer dielectric coatings with high reflectance and low absorption in the ultraviolet. The pumping lamp was a low pressure, spiral, 30 watt mercury arc lamp designed to give about 2 watts CW of pumping radiation at 1849 Å. A liquid nitrogen cryostat of suprasil quartz was employed to enhance optical transmission in the ultraviolet.

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Stimulated emission was produced at 3150 Å. The criteria for stimulated emission were:

a. The line narrowed from 56 Å to 27 Å as the power input was increased to 30 watts. This represented a substantial narrowing of line width from spontaneous line width (300 Å in KBr).

b. The far field pattern was considered to sharpen as the mercury arc pump power was increased, indicating that the beam was highly collimated.

The laser transition process was considered as possibly due to radiative recombination of a localized, intrinsic, or defect exciton. No information was given as to power output.

c. Semiconductor Lasers

Although a sharp line has been reported in the electroluminescence of SiC p-n junctions at 4560 Å, the evidence for laser action is inconclusive (14). Second harmonic radiation at 4200 Å has been observed to accompany the fundamental 8400 Å radiation of GaAs, but the power ratio is 10^{-10} (14). This may also occur with semiconductor alloys which operate in the visible. However, the efficiency is low.

BIOLOGICAL STUDIES AND APPLICATIONS

The possibility of frequency doubling in various components of the skin similar to that observed in crystals, was considered by Fine (15) at the First Annual Conference on Biological Effects of Laser Radiation in 1964. This might result in cells deep in the skin being exposed to a higher intensity of ultraviolet radiation than occurs under normal conditions.

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Zaret considered the possibility of harmonic generation being produced at the pigment granules within the retinal pigment epithelial cells on ruby laser radiation. This site is not normally exposed to ultraviolet radiation at this wavelength (16).

Crystals of 3, 4 benzpyrene and 1,2, benzanthracene, irradiated with a pulsed ruby laser at 6940 Å emitted narrow line radiation at 3470 Å (17). This observation is of interest since these crystals are essentially opaque to incident radiation at 3470 Å. The efficiency of second harmonic generation was about 5×10^{-6}. Optical second harmonic generation was also considered by Rieckhoff and Peticolas (18) to be produced in 24 crystalline amino acids on Q-switched 10 Mw ruby irradiation. Efficiencies of the same order of magnitude as obtained from potassium dihydrogen phosphate (KH_2PO_4) cyrstals were observed. Each sample was in the form of a powdered layer. Second harmonic generation radiation was determined spectrographically for L-Tryptophan. Optically active sugars showed a second harmonic generation efficiency one order of magnitude less than that obtained from KH_2PO_4.

Preliminary studies on the interaction of ultraviolet radiation on biological systems have been initiated by Klein and Fine (19). These were carried out with the pulsed nitrogen laser in collaboration with H.G.Heard of Energy Systems and with radiation at 2650 Å quadrupled from neodymium at 10,600 Å in collaboration with W.Haynie of Eastman Kodak Company. In both cases the energy and energy density achieved per pulse was very low; consequently, there were no major changes observed. With current equipment, it is possible that studies yielding positive results can be obtained.

Another area of interest insofar as ultraviolet radiation is concerned is two-photon processes - another non-linear phenomenon. This process involves the simultaneous absorption of two laser photons, each for example at 6943 Å,

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thereby exciting a resonance in the ultraviolet at twice the frequency. This phenomenon differs from frequency doubling. In the two photon processes, a material which is essentially transparent for a single photon would absorb two photons simultaneously. Spectroscopically the ultraviolet resonances excited by the two-photon processes differ from those produced by irradiation at twice the fundamental frequency. For example, the transitions may differ in the two cases. Two-photon effects at ultraviolet wavelengths have been observed by Kaiser and Garrett (20); in crystalline KI by Hopfield, et.al.,(21); in anthracene single crystals by Hasegawa (22); and in I^- and C_s by Hall (23) using the second harmonic of ruby and the second harmonic of neodymium. Rounds, et.al., (24) have reported two-photon absorption in reduced nicotinamide-adenine-dinucleotide (NADH), in solution, on ruby laser irradiation.

The high power densities and relative monochromaticity achievable with ultraviolet lasers should permit optimum disinfection and sterilization under usual conditions; the minimal beam divergence should permit disinfection and sterilization at a distance for special purposes as for the space program(26).

Microscopy holography and microbeams are areas in which ultraviolet lasers will be applied. Wavefront reconstruction, or holography, has been an area of vigorous research following the advent of lasers. Results of this research are already being considered for application in engineering, optical design, microscopy, materials testing, interferometry, meteorological surveillance, and in communications.

The original impetus for current research in holography was established to improve resolution in electron microscopy (27). The strict coherence and stability requirements of holography have not as yet been satisfied for wavefront reconstruction in electron and X-ray microscopy (28). However, current investigations for holographic microscopy using visible laser illumination have yielded high quality imagining systems with resolution approaching that of

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conventional nonholographic microscopes (29). Since magnification of a reconstructed image can be achieved without lenses, the resolution of this image is not limited by the numerical aperture of microscope optics as is the case in conventional microscopy. The resolution attainable in holographic microscopy should be limited only by the resolving power of the photographic emulsion and consequently should exceed that attainable with conventional microscopes. Resolution can also be improved using holography at ultraviolet laser wavelengths, and should provide significant information regarding biological systems.

In the area of optical design, holograms constructed using abberated optical systems have been used as corrector plates with the same optical system to cancel the original abberations(30). These techniques can be applied to ultraviolet microscopy.

Pulsed laser holography has been used to stop high speed motion where the velocities involved are similar to those resolved by conventional high speed photography (31). Wavefront reconstruction at a later time, using a pulsed laser microhologram, allows the observer to focus to any depth of the image and examine time varying details of the original object that are lost in ordinary, two dimensional, photomicrographs. The holographic microscope has also been used successfully in applications where conventional polarizing microscopes have proven useful (32).

Laser illumination has also been considered for non-holographic microscopy. Applications in these areas include interference and phase contrast microscopy and may be pertinent at ultraviolet wavelengths.

Optical spatial filtering techniques using coherent laser illumination have been successfully employed in character recognition (33). These techniques in conjunction with the use of ultraviolet lasers may allow information to be obtained concerning cells and cellular processes. Techniques of pattern recognition can be applied to the investigation and characterization

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of micro-organisms, such as bacteria or other types of cells. It may permit serious consideration to be given to the differential diagnosis of various unicellular or more highly organized species. The use of more than one wavelength, either concurrently or sequentially, may enhance the recognition of specific organisms or isolated cells, thus providing a signature for the biological system.

The use of non-laser microbeam techniques by Zirkle, Bloom, Uretz and others, is discussed by Curtis (34). Visible wavelength laser microbeam techniques have been used by Bessis (35,36), and others and have been reviewed by Fine and Klein (37). With the advent of ultraviolet lasers, ultraviolet microbeams of high intensity and of a spot size less than 0.5 microns in diameter will become available, which may lead to the ultraviolet laser microbeam irradiation of individual cells and parts of cells as a tool in radiobiology.

The application of the laser to Raman spectroscopy has been discussed by many authors including Garmire, Pandarese, and Townes (38), Porto (39), Weber(40) and Jones and Jones (41). In general, helium-neon lasers at 6328 Å and pulsed ruby lasers at 6943 Å have been used. Ionized argon lasers for Raman spectroscopy have also been used (42,43). The high intensity obtainable with lasers will permit Stokes and anti-Stokes lines of many orders to be obtained (38). The narrow band width of this focusable radiation simplifies the design of miniaturized cells, and permits the measurement of Raman spectra in small samples and concentrations (41). Although the ultraviolet lasers will probably replace the ultraviolet sources such as the mercury lamp presently used for Raman spectroscopy at ultraviolet wavelengths, the fluorescence and decomposition of materials on ultraviolet irradiation may result in problems similar to those encountered using standard sources. The short and controllable pulse duration at high intensities and at narrow bandwidth, available with ultraviolet lasers, may prove of significance in this area of research. Modulation techniques in conjunction with laser

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radiation may allow improvement of the signal to noise ratio.

In addition to the specific areas to which reference has been made above, the potential hazards of ultraviolet radiation at high intensities as available from lasers require attention. These hazards include those of standard low intensity ultraviolet sources in addition to other injurious changes which may be induced as the intensity is increased. The injurious effects may thus exceed in rate of onset, and complexity, the acute burns and the delayed reactions, such as mutagenesis or carcinogenesis and photosensitization encountered with standard ultraviolet sources. Hazards of ultraviolet laser radiation are, therefore, of particular significance in regard to the eyes and the mucocutaneous tissues.

Applications of ultraviolet radiation to clinical medicine are beyond the scope of this discussion. Ultraviolet radiation as a therapeutic modality in Dermatology may be facilitated by laser devices. The high degree of monochromaticity of laser radiation may provide more adequate selection of desirable wavelength and consequent reduction of injurious components. The high intensity at which laser radiation is available, in conjunction with attainable small spot sizes and variable pulse duration, permits restriction of the extent of the irradiation to a specific site. Limitation to the area involved by the lesion may therefore be facilitated.

Ultraviolet laser radiation may be useful in diagnostic procedures, such as the detection of trichophyton infection and other in vivo or in vitro determinations involving fluorescence. The high intensity and narrow band width of laser radiation may increase the sensitivity of these procedures, thus permitting earlier detection and more adequate differentiation of clinically significant findings from nonspecific phenomena, than has been currently attained. Localization of specific (exogenous) agents as the result of pathological processes

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may be more effectively established by ultraviolet laser radiation used as a diagnostic tool than by previously available ultraviolet sources. Studies by Bardos, Fine, Ambrus, and Klein are underway to determine the effects of porphyrin derivatives which were synthesized with the dual objective to bind specific, biologically significant macromolecules, such as DNA, and to have absorption bands at the wavelengths of the available laser radiation.

The observations and consideration presented above suggest that laser radiation, particularly in the ultraviolet region of the spectrum, may have significant implications for biomedical research.

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