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Laser damage criteria have traditionally relied on fundoscopic and/or histological evidence. These methodologies have provided limited information regarding the functional impact of observed damage and more importantly, cannot assess the transition zone between temporary and permanent visual loss. Previously we have shown that transient and permanent visual deficits can be produced by long (msec) duration laser pulses at or slightly below traditional threshold levels for retinal injury. The present investigation extended these exposures to include Q-switched, 532 nm Nd/YAG pulses presented to awake, task-oriented nonhuman primates. At and above the ED_{50}, single pulses of minimal spot diameter (50 μ) produced only minor, transient shifts in acuity although repeated exposures lead to permanent deficits over time. At lower energies (10X below ED_{50}), minimal spot, single-pulsed exposures produced little observable consequence until either retinal spot sizes or the number of pulses were increased. At these lower energy levels, however, no permanent function loss was observed. Hence, the functional impact of single nsec pulses was more difficult to assess than longer msec exposures. Multiple nsec pulses and/or larger spot sizes produced visual deficits similar to those observed for msec exposures, suggesting both temporal and spatial summation at energy levels where no permanent effects have been noted.

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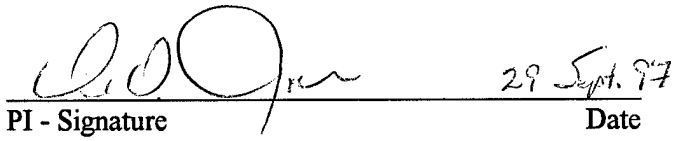

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Statement of Military Significance

The ability of the eye to efficiently capture and concentrate light energy onto the delicate neural tissue of the retina makes the eye one of the body's most vulnerable organs to accidental or intentional laser exposure. Establishment of reliable eye damage criteria and an adequate morphological database for various types of laser wavelengths and delivery systems has been an important mission for biomedical researchers and strategic planners since the original conception and use of lasers in a military setting. Equally important from a strategic military point of view, however, is the impact that any retinal alteration, whether temporary or permanent, has on the ability of a soldier to complete an ongoing visually guided mission. While permanent visual loss associated with distinct morphological damage is of course a serious concern it must also be recognized that even temporary shifts in visual acuity can occur at energy densities well below those associated with distinct tissue damage. These low level exposures which initially produce only transient acuity shifts can ultimately lead to subtle molecule changes within the tissue that might also permanently impact visual acuity. These less remarkable alterations can be easily overlooked during routine physical exams of the retina even though they can impact postexposure acuity on either a temporary or permanent basis. Our result suggests that significant shifts in postexposure visual sensitivity can occur at or below the ED_{50} level and that these shifts can be long lasting. Furthermore, we have shown that small punctate lesions from repetitive exposures to high energy but minimal spot laser sources can amass an acuity deficit similar to that seen with larger diameter exposures. Using a behavioral technique to measure on-going visual acuity, we have exposed awake, task-oriented rhesus monkeys to a variety of different laser systems which varied in output wavelength, energy density and temporal and spatial distribution on the retina. The results of this project are consistent with the results of our previous studies and have extended our performance criteria to include brief Q-switched pulses which irradiate only limited areas of the retina. These results also provide important data regarding the immediate consequences that both high and low level laser irradiation have on the ability of an organism to maintain on-going visual discriminations.

BACKGROUND

Light induced retinal damage from incident or prolonged exposure to laser sources in the field and workplace has potentially serious military implications. Technological advances in the development and employment of laser guided weapons on the modern battlefield has enhanced the usefulness of lasers and increased the likelihood of human exposure. At the same time, lasers are becoming more powerful and difficult to avoid due to their brief exposure duration and variety of emitting wavelengths. Standard battlefield lasers are easily capable of producing serious ocular damage leading to disruption of normal vision without providing the soldier sufficient warning or necessary time for defensive action. While permanent and irreversible tissue damage is a serious medical issue, even a temporary visual impairment could jeopardize the individual's ability to complete a visual-motor response and thereby imperil the soldier, fellow soldiers, and overall mission. The establishment of safe operating guidelines for lasers and the development of protective devices in which laser exposures are unavoidable must remain a high priority of any laser safety program. Furthermore, these guidelines must include the impact that cumulative exposures may produce as well as the immediate and long term consequences of single or repetitive Q-switched pulse exposures.

Most laser wavelengths currently being employed are transmitted well by the ocular media of the eye. Together with the natural focusing capacity of the eye's optics, even brief exposures can lead to intense, and often damaging concentrations of light energy directed toward an extremely absorptive and highly susceptible retina. Given the optical nature of coherent light and the eye's natural focusing properties, a 10,000 fold increase in light energy can be expected during any laser irradiation. Additional concentrations of light energy, especially within a military setting, often occurs from the use of binoculars or other light enhancing devices. As a result, exposure to only a minimal amount of laser energy can result in significant damage to the eye. The location and magnitude of retinal damage produced depends upon the specific exposure parameters as well as the absorption characteristics of the tissue irradiated. The site of damage is also somewhat dependent upon the spectral and spatial characteristics of the exposure although for intense, prolonged exposures, damage at the optic nerve and receptor level is probable. As little as 5 μJ of 532 nm laser radiation can produce an ophthalmologically visible lesion while 150 μJ can lead to intraocular hemorrhage (1).

Historically, the original studies on the adverse effects of intense irradiation on vision dealt with solar retinitis (2). Since these original and more casual observations, more analytical investigations in the laboratory have focused on the mechanisms of light-induced damage as well as its deleterious impact on visual functioning. The goal of most studies has been to establish standards for safe viewing in situations

when a single, spatially discrete exposure is presented. The guidelines established have included recommendations for limiting the output power of lasers when the situation permits, and for issuing screening goggles for those required to work around potentially dangerous levels of light energy. While it is important that any standard established predicts the probability of damage in the single exposure condition, it is of equal concern in today's workplace to be able to predict the outcome of repeated, lower-level exposures over a prolonged period of time. Individual exposures either of low energy or involving a restricted retinal region may not initially produce any evident visual loss. Repeated exposures to the same region or surrounding areas may eventually accumulate and lead to irreversible morphological damage and significant permanent visual impairments. One of the primary objectives of the present study has been to quantify the cumulative nature of the damage mechanism as well as to elaborate the nature of the transient and permanent visual deficits that might result from a wide variety of exposure conditions simulating those found in the field.

For the single exposure condition, punctate lesions of the retina have been extensively investigated from a morphological standpoint for a variety of different laser delivery systems. Using suprathreshold dosage levels, gross pathological damage has been reported to occur in the cornea, pigment epithelium and in the outer segments of the photoreceptors (3-6). The total incident energy, wavelength and the duration of pulsed exposures largely determine the site and mechanism for the damage.

Different damage mechanisms have been proposed to explain the observed pathology. The two most cited mechanisms are the result of either thermal and mechanical (acoustic) insult. Generally, a thermal model has been attributed to those changes resulting from relatively long duration, low energy exposures to long wavelength coherent light. In this case, photochemical changes often within the outer segments of the photoreceptor produce toxic byproducts which ultimately disrupts or destroys normal cellular reactions. On the other hand, nanosecond pulses from Q-switched lasers normally produce photoacoustic explosions within the tissue which result in mechanical displacements of vital cellular activity quickly leading to the rupture of cellular membranes and tissue death. Pulses of sufficient power densities between 1 and 100 microseconds can produce a combination of mechanical and thermal damage.

Those energy levels associated with either type of damage mechanism are typically expressed in relation to their probability of creating visible lesions. Threshold, referred to as the ED_{50} level, is often defined as that energy condition in which damage is observed in at least 50% of the irradiated cases. While these types of exposures and damage mechanisms are readily apparent within a very brief period following exposure, more subtle and often delayed changes can be observed from either prolonged or repeated exposures at energy levels significantly below the ED_{50}. In these instances, actinic insult has been implicated as the mechanism that may produce permanent biochemical changes in the natural cyclic

mechanisms within the photoreceptor and which ultimately can affect the viability of the receptor cell itself (7, 8).

As morphological techniques for detecting minimal retinal alterations have been refined, the threshold energy densities leading to retinal damage have decreased. With lower exposure energies there has been a shift in the site of primary anatomical alteration from the pigment epithelial layer to the outer segments of the photoreceptors themselves (9, 10). Because this site is the location where the initial transduction of light energy to electrochemical energy occurs, it is important to also consider the functional consequences of the induced changes. Since, the density and type of photoreceptors within the retina are not uniform, different functional consequences may be expected. In primates, a well established foveal region exists where the density of photoreceptors is the highest and where cone type receptors predominate. Outside the fovea, rod type photoreceptors increase in numbers but remain considerably less densely packed than cones. Differences in the type of receptor cell, position on the retina, and neural interactions with second order neurons all contribute to the unique functional roles for rods and cones. Cones are typically associated with color vision and with the resolution of fine spatial detail while rods appear achromatic in nature and serve primarily as brightness and movement detectors and not spatial analyzers. Therefore, the most obvious visual acuity deficits should be produced by foveal or macular irradiation, which largely disrupt cone vision. Similar exposures in more peripheral portions of the retina would be expected to destroy fewer photoreceptors and produce more subtle losses in movement detection and night vision, largely sparing color vision and the ability to see detail (visual acuity).

The development of functional criteria to assess laser irradiation may be an even more sensitive measure of subtle changes in retinal morphology and photochemistry. This criterion also enables one to predict changes in task-related, visual performance that accompany accidental exposures. Of course, permanent changes in the ability of observers to perform visually following exposure is an important legal issue in cases in which medical liability and work disability are pending. However, even transient changes in visual functioning could be of utmost concern to mission planners in situations where the successful completion of a mission is dependent upon continued high resolution visual guided. It is reasonable to assume that minute enzyme changes within photoreceptors may be produced by single pulse exposures at energy levels just below the established ED_{50} or with repetitive low energy exposures and that these subtle changes may not be immediately revealed by more conventional morphological techniques. These rather subtle changes, however, may seriously alter the overall functioning and transmission properties of photoreceptors, and hence disrupt normal visual sensitivity independent of any obvious structural alterations. The majority of functional studies to date have employed relatively large diameter and intense power densities which produce not only permanent changes in visual performance, but also severe, irre-

versible morphological disruptions as well (6, 11, 12, 13). The power levels employed in these studies produced changes in visual acuity ranging from 40 to 80%, the exact amount of the deficit reported being directly linked to the amount of foveal-macular tissue exposed (14, 15, 16). Unfortunately, in virtually all previous functional studies dealing with punctate exposures, postexposure measurements of visual performance had to be delayed at least 24 hours because anesthesia was required to properly position the exposure on the fovea. The use of anesthesia eliminated the possibility of determining any dazzle or transient flash effects produced by exposures at power densities at or below the ED_{50} for permanent visual loss. Even for those energy densities significantly above the ED_{50}, it is reasonable to assume that much like morphological damage, the magnitude of the functional alteration may change over time as edema and structural changes occur. Transient changes in optical opacity as a result of hemorrhages, edema and changes in the fine ultrastructure of the retina can have drastic immediate consequences on both fine foveal and coarse peripheral vision. In some missions, the immediate change in one's ability to continue a visually-guided task may be as important a consideration for both the individual and the mission as would be the permanency of these changes. The inability of previous studies to measure these types of induced changes in visual performance has been a serious limitation of these studies in attempting to develop a functional approach to laser safety.

The development of a technique to expose and measure visual acuity in an awake, task-oriented animal was established in the early phases of this effort. This technique not only eliminated the need for anesthesia for placement of exposures on the fovea but also increased the speed of performance measurements without loss of resolution (24). Voluntary fixations on a known point within an animal's visual field allows for accurate placements of laser pulses on specified areas of the retinal mosaic.

Human experimentation in the area of suprathreshold retinal lesions is virtually impossible since intentional burns can only be performed on eyes that are slated for immediate enucleation. Enucleation is rarely performed on eyes which do not suffer from severe retinopathies in which a substantial loss of vision has already occurred. Furthermore, it is extremely difficult to complete functional follow-up on these subjects prior to enucleation (16-17). As an alternative, animal models have been developed using the rhesus as the human prototype. The selection of the rhesus stems from inherent morphological (18 - 21) and functional (20, 23-28) similarities between the two species. While the retinal physiology and presumed visual experiences of humans and monkeys may be quite similar, the cognitive decisions regarding target recognition may be quite different between the two species because of differences in reasoning abilities. A possible indication of such differences may come from an analysis of the manner in which each species adjusted to degraded images either through morphological changes within the retina resulting from laser irradiation or through artificial degradation of the target in intact organisms. As part

of this effort we have also explored how humans respond to briefly presented targets and what impact targets degradation have on their ability to maintain a consistent threshold acuity.

METHODS

The behavioral paradigm used for exposing awake, task-oriented animals has been the subject of numerous research papers (24 - 29). This method permits the accurate placement of single, spatially-isolated exposures onto the fovea in an awake, task-oriented animal by requiring the animal to maintain central fixation for prolonged periods of time. In order to simulate field conditions, all exposures were of brief nanosecond or millisecond duration (single or multiple Q-switched pulses). For these types of exposures, accurate positioning of the beam onto the fovea is critical for producing a visual acuity deficit. Exposures outside this region, unless extremely large in diameter, produce little or no acuity deficit since the animal can "look around" the exposure site(s) and use other, equally or more sensitive, retinal regions to make the required discrimination. Positioning the exposure onto the retina in the absence of anesthesia was the first step necessary to measure the immediate behavioral consequences of near threshold exposures and to follow any initial changes in the deficit during the recovery process. Every attempt was made to make the exposure and assessment paradigms as similar as possible to those conditions under which soldiers might be exposed. In addition, the paradigm was structured to accommodate the morphological parameters used by others so our data could become part of a larger data base for the establishment of a multi-faceted safety criteria.

Subjects. A colony of six rhesus monkeys between the ages of 1 and 14 years was established. All animals were males and had normal vision. These animals were individually housed in standard primate cages in a climate-controlled room in accordance with USDA standards. In addition, these animals were maintained in accordance with the procedures outlined for nonhuman primates in the "Guide and Use of Laboratory Animals" prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources. The protocol for this project was approved by the institution's IACUC and was inspected regularly by the USDA. Consistent with current USDA regulations (Authority: 7 U.S.C. 2131-2157; 7 CFR 2.17, 2.51, and 371.2g) and federal and local IACUC specifications on primate enrichment, our animals were assessed on a daily basis as to their psychological well being and every attempt was made to provide these animals with enriching experiences while housed in our laboratory (see Appendix C).

Apparatus. Animals were tested in a portable restraint device which was sparingly used outside the actual test session. At all other times the animals were housed in large primate cages within a primate

housing facility. A plexiglas restraint device was used to transport animals to and from the housing colony and to immobilize animals during testing. This box was mounted on a mobile hydraulic lift platform and could be positioned in front of the exit door of an animal's home cage. After securely attaching the box to an animal's cage, the cage door was opened and the animal encouraged to enter the portable device. Animals were trained using positive reinforcement, liquid Tang and fruit, to voluntarily enter the plexiglas box thereby eliminating the need for drugs, unnecessary force, or chronic restraint (29) to immobilize them. Verbal, facial, and tactile feedback from the animal handler were also important reinforcing signals. Once inside the restraint device the animal was then trained to place his head through an opening in the box just large enough to accommodate this portion of his body. Animals had already been chronically fitted with a custom neck collar containing metal loops which were used to attach the collar to the top of box to hold the animal's head outside the box. This apparatus was essential for transporting the animals to and from the laboratory and for aligning the animal's line of fixation and distance from the viewing screen within the testing apparatus.

A customized "hat" was manufactured for each animal and fixed to the top of the restraint device once the animal's collar was firmly attached to the box. This molded plastic "hat" had an inner, high density foam liner with an inflatable air bladder to allow for superior stability of the head without undue force or discomfort. The customized head restraint had openings for the animal's pinnae and a chin strap for reducing vertical head movements. This "hat" prevented the animal from moving his head in any direction and while restrictive, appeared not discomforting. Maintaining the animal's position and line of sight within the test apparatus was critical for both accurate visual acuity measurements and for increasing the probability that laser exposures irradiated the fovea.

Once inside the light-tight, sound attenuated test chamber the mobile restraint device was anchored to the chamber and the animal's pupil aligned to a 5.0 mm diameter iris diaphragm attached to the test box. All visual acuity measurements were made under monocular conditions after the animal had dark adapted. Laser exposures were presented in a Maxwellian view through the diaphragm on the facemask. Visual targets were projected onto a rear-projection screen mounted on the far wall of the test chamber. The viewing screen subtended a 4^0 visual angle at a distance of 1 m from the subject's pupil. Two programmable carousel slide projectors with coded slide controls were mounted on the outside of the test chamber within a darken outer room. One of the projectors served as an image source while the second provided diffuse background luminance when contrast levels were varied. Luminances and wavelengths of the background were controlled by neutral density and interference filters placed in the optical pathway of each projector. Landolt ring targets of different ring diameters were photographically produced on high contrast film. Each slide consisted of a single, darkened ring centered on a light background that was

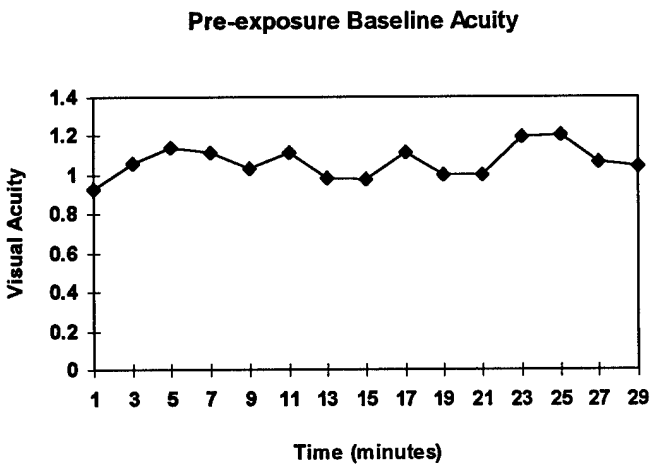

Figure 1. Pre-exposure baseline acuity. In this figure an animal's threshold acuity was tracked using maximum photopic viewing conditions. The animal's established acuity level of 1.1 (min of arc)$^{-1}$ or a Snellen acuity of 20/18 was typical for an animal under these viewing conditions. The animal's ongoing acuity was tracked for 30 minutes without a break and during this period his average threshold acuity for any running two minutes never dropped below 1.0 (min of arc)$^{-1}$ once his maximum threshold level was established. Similar to other animals this subject's false positive response rate was less than 10%. No negative reinforcement was applied during this test period. A criterion of two successive misses to threshold Landolt rings was typically used before shock was applied to the third consecutive miss. Normally a well trained animal avoided shock altogether once motivated to perform.

projected onto the viewing screen. The timing and order for the presentation of these targets was computer controlled by a Cyborg ISAAC A/D interface and IBM 286 microcomputer. A customized software package (Labsoft) which included Schmitt triggers allowed for rapid modifications of either the target being presented or the consequences to any elicited responses provided by the subject. Data analysis was on-line as well as electronically stored for later call-up and more elaborate analyses. Acuity data could be exported to Excel or Quattro Pro spreadsheets and analyzed by different biomedical statistical packages before being printed.

Discrimination Task. Animals were trained to press a lever when they detected the presence of a Landolt ring ("C") randomly positioned within a series of equal-sized completed rings ("0"). Failure to press the lever to the Landolt ring (miss) or pressing the lever during the presentation of gapless rings (false positive) resulted in the presentation of a discriminative tone and, on a variable reinforcement schedule, a brief, mild electrical shock which varied according to the type of error (miss versus false positive) made. The shock was mildly distressing but not painful. Subjects were initially trained to discriminate between Landolt rings and a white light background and gradually converted to detecting the presence of large Landolt rings from gapless rings. Due to the payoff matrix used, the number of false alarms was always extremely small (<10%) in trained subjects. Threshold acuity was derived by a modification of the von Bekesy tracking technique. In this technique, if the subject correctly detected a Landolt ring by pressing a lever, the next series of Landolt rings and gapless rings presented was 10% smaller while incorrect detection of a Landolt ring (miss) produced the presentation of rings 10% larger. The critical feature of the targets (gap in the Landolt "C") varied from 0.25' to 30' visual angle. The dark rings were presented against backgrounds of different wavelengths and luminances and, with a light from second diffusing projector, different contrasts. After an initial training session that lasted several months, stable baseline sensitivities were established for various viewing conditions including different background

luminances (scotopic and photopic acuity levels), contrast levels (20% to 90%) and wavelengths (420 to 680 nm). The stability of an animal's baseline acuity using the tracking technique is shown in Figure 1.

Laser. Two different laser systems were used as exposure sources; a 4 W CW Argon laser (Spectra Physics Model 165/265) emitting 514.5 nm as the dominant wavelength and a pulsed, frequency doubled Nd/YAG laser (Molectron MY 32-20) with a 20 Hz pulse repetition frequency emitting 532 nm as the dominant wavelength. A third small HeNe laser was used primarily for aligning purposes. Each of the exposure lasers was mounted in parallel with the other laser on an optical bench outside the test chamber and testing room. The raw beam from either laser could be directed into the test chamber by rotating one of two mirrors within the optical pathway. The selected laser beam was first directed through several neutral density filters and a manual safety shutter before passing through a beam splitter. A portion of the attenuated beam from the beam splitter was incident upon a Scientech volume absorbing disc calorimeter (Model 362) and was used for monitoring output energy. The transmitted portion of the beam that passed through the beam splitter was controlled by an electronic shutter triggered by the animal's behavior. When this shutter was opened, the laser beam was diverted by a 4.5 cm diameter front surface mirror on the optical bench and directed through a small opening into the darkened, test chamber. The beam then passed through a focusing lens in front of the second 5 x 10 cm coated pellice beam splitter placed approximately 75 cm in front of an artificial pupil and at the intersection of the diverging laser beam and the beam from the image projector. Variations in the position and optical power of the focusing lens created at the pupil a minimal diameter beam which produced a focused beam diameter on the retina ranging from less than 50 μ to greater than 800 μ. The laser beam was positioned such that it was presented to the animal coaxial with a line between the artificial pupil and the gap in a specified, threshold Landolt ring. For determining the line of sight, a 1 mm aperture was placed at the plane of the cornea. A mirror, approximately 2 m behind the 1 mm aperture, was adjusted until it was normal to the line of sight.

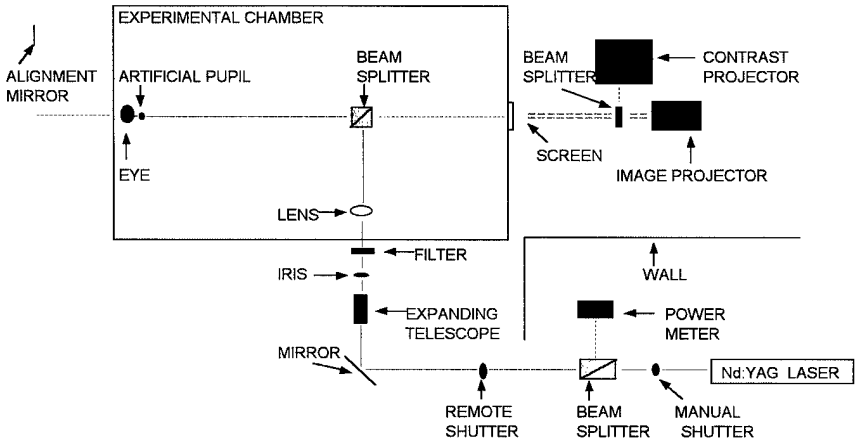

Figure 2. Diagram of the laser and image optical system. The laser beam from either a CW Argon or Q-switched Nd/YAG laser was presented using a Maxwellian view and coaxial to the gap in a threshold Landolt ring. The discriminanda was presented onto a rear projection screen as a darkened ring on a light background. Both the image and laser beam were made coaxial within the test chamber approximately one meter in front of a variable artificial pupil in front of the subject's eye. The animal was positioned such that only one eye was aligned to the beam and this beam entered through the center of the subject's pupil.

The beam splitter was then aligned with a coaxial beam from a HeNe laser such that the collimated HeNe beam, along with the Nd/YAG beam, passed through the 1 mm aperture and was reflected off the mirror back onto itself. Coaxial alignments with the line-of-sight were verified by noting that the reflected beam also passed through the 1 mm aperture and back onto the gap in a specified Landolt ring. Calibrations of the energy density at the cornea and laser head were made by our physicist prior to each exposure according to the method designed by our physicist in collaboration with personnel at Brooks AFB.

Laser Exposure. All exposures were presented to awake, task-oriented animals. Only one laser exposure was presented per day although in some cases the exposure consisted of repeated or delayed laser pulses within a relatively brief time period. Especially for exposures below the ED_{50}, a number of different viewing conditions (contrast levels and chromatic backgrounds) were used to assess visual performance prior to and immediately following exposure. All laser exposures were triggered by the animal's correct detection of a pre-determined threshold ring after a stable baseline acuity had been obtained. Observations of animals working under these conditions have shown that especially for threshold targets these animals normally maintain central fixation on the critical feature of the stimulus (gap) for several seconds following lever pressing, perhaps awaiting the consequence of their response. With large diameter exposures, this procedure has elicited reliable, immediate shifts in baseline visual acuity over 90% of the time. These shifts in postexposure acuity normally lasted anywhere from several minutes to months and presumably reflected shifts in the sensitivity of foveal receptors. A typical example of the impact that a brief and spatially isolated laser exposure had on ongoing visual acuity is shown in Figure 3. Prior to exposure this animal's baseline acuity under this specific viewing condition was 1.4 (min of arc)$^{-1}$ which corresponded to a Snellen acuity of 20/14. Immediately after a brief exposure to two successive Q-

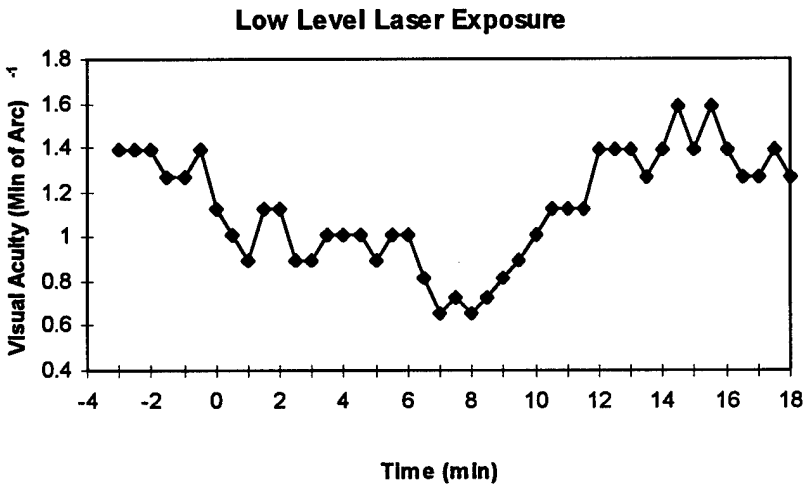

Figure 3. Sample raw data demonstrating the immediate drop in visual acuity following laser exposure. The ordinate indicates the various sizes of the gaps in presented Landolt rings. The scale is measured in discrete steps. The abscissa represents the presentation of the Landolt rings; corresponding times (in minutes) for representative trials are indicated relative to exposure. Two, 0.1 μJ Q-switched pulses presented within a 100 msec window of each other and irradiating a 300 μ diameter area of the central fovea were presented. This power density was significantly below the ED_{50} for this exposure condition. Stable pre- and postexposure acuity of 1.4 (min of arc)$^{-1}$ was established for this subject for this achromatic photopic viewing condition.

switched pulses with energy densities below ED_{50}, the animal's baseline acuity dropped abruptly to approximately 50% of its pre-exposure level (Snellen acuity of 20/29 or a visual acuity of 0.68 (min of arc)$^{-1}$). Acuity remained depressed for nearly eight minutes before gradually returning to its pre-exposure level. No long term acuity deficits were noted for this exposure condition and within 30 minutes of exposure the animal's baseline acuity and variability were within a normal operating range for this animal and viewing condition.

Using similar exposure conditions, immediate and significant shifts in visual acuity were not always apparent after laser irradiation. In these cases, it was presumed that eye movement just prior to exposure resulted in positioning the beam off-axis and onto the peripheral retina where no acuity deficit would have been noted due to the nature of the required visual task. The frequency of these exposures where no significant acuity shifts were apparent was quite low when either CW or multiple Q-switched exposures were made. Raising or lowering the exposure energy had little impact on the number of times exposures produced no apparent acuity shift. However, when very smaller diameter exposures (<50 μ) and/or single Q-switched pulses were used, the frequency of exposures producing no apparent acuity decrement increased significantly. It was presumed in these cases that the exposures did not involve large enough areas of the fovea to disrupt the necessary retinal functioning required for successful visual discriminations. Control sessions where no exposures were made, also produced no significant shifts in visual acuity and were randomly presented as a control.

Animals within this study were exposed to single and repetitive pulses at power levels both significantly above (10, 50 and 100 μJ) and below (0.01, 0.1, and 0.5 μJ) the predicted ED_{50}. Pulse repetition rates, beam diameters, output energies, and position of the beam on the retinal surface were manipulated. In the single pulse mode, individual pulses averaged 15 nsec and when set in the multiple pulse mode, animals were normally presented a train of pulses with a pulse repetition frequency of 20 Hz within a variable exposure time interval of 50 to 250 msec. Exposures of different retinal diameters (<50 μ to greater than 800 μ) were also presented either on-axis (through the gap in a specified Landolt ring) or off-axis (displaced from the gap). Prior to and immediately following exposure acuity was measured using different viewing conditions (wavelength, luminance, contrast).

A 15 minute baseline acuity assessment preceded every exposure. If the level of pre-exposure acuity was within one standard deviation of that previously derived for this animal, then an exposure was made. If not, or if the session variability exceeded baseline variability, the exposure was aborted. Well trained animals routinely returned to their previous baseline acuity levels after exposure and maintained a consistent threshold during these test conditions. Immediately after exposure, postexposure acuity testing continued until either the animal's acuity fully recovered or until 30 minutes of time had past, whichever

occurred first. If recovery was not complete within the test session, additional daily postexposure measurements were made until the deficit recovered or stabilized. Following any long term shift in visual acuity, complete contrast and spectral sensitivity curves were derived for both the exposed and control eye. Additional exposures were made only after the animal's acuity had either stabilization or recovered.

Data analysis. Determination of the animal's baseline visual acuity and its changes over time following laser irradiation was analyzed in accordance with the statistics formulated by Dixon and Massey (1961) for the Up and Down Method. Average acuity was analyzed by determining the number of times each Landolt ring subtending a different visual angle was presented within the time period. Typically an overall pre-exposure average acuity was derived over a 15 to 20 minute period at the beginning of each exposure session. To determine any motivational or lingering exposure effects, the average pre-exposure acuity as well as degree of variability (number of different sized gaps represented) was compared to previous session baselines as well as to those from the animal's control eye. Postexposure acuity was analyzed in two minute intervals beginning immediately after the exposure. For each interval the percent deficit was derived by comparing the average acuity during this two minute period to the overall pre-exposure acuity derived for the animal immediately prior to exposure. In those cases were prolonged acuity changes were noted, no additional exposures were made and postexposure acuity was measured using different spectral and contrast conditions.

RESULTS

When either large (200 - 500 μ) diameter foveal exposures were presented for a brief period (single Q-switched pulse) or when small (50 -150) diameter foveal exposures were presented for relatively prolonged exposure periods using multiple Q-switched pulses (up to 250 msec) the immediate impact on visual acuity was relatively dramatic. These types of Nd/YAG exposures produced deficits reminiscent to those produced by short duration (50 to 100 msec) CW Argon and HeNe flashes and previously reported elsewhere (31). In these msec time domain exposures where full recovery was possible, immediately after exposure the animal's acuity typically decreased significantly (20 to 80% of pre-exposure acuity) and remained depressed for some time (4 to 20 minutes) before gradually recovering to its pre-exposure baseline. Both the size of the initial deficit as well as the total time for recovery was dependent upon the parameters of the exposure that included its energy density, spot diameter, duration, and position on the retina. For some exposure conditions defined as being within the transition zone between temporary and permanent effects, the initial deficits were as high as 80% and full recovery took as long as several days. Typically below the transitional zone, the magnitude of the initial deficit was largely dependent upon the size and location of the exposure site while the duration of the deficit was dependent upon exposure

energy. For energy densities near or within the transitional zone, the overall impact (size of initial deficit and time for recovery) of individual exposures gradually increased with repeated exposures even though these exposures were separated from each other by as much as several days. Often these cumulative effects produced permanent shifts in postexposure acuity that were only noted after the fourth or fifth exposure at a specific energy density.

When single Q-switched pulses of small diameters (50 to 150 μ) were presented, however, there was little obvious decrement in visual acuity at or below the ED_{50} level. Under these nsec time domain exposures, the animal was able to maintain a stable acuity after the exposure and throughout the post-exposure session. With larger diameter (>150 μ) exposures the adverse impact of single pulses on visual acuity was more evident and generally the same as the transient deficits produced by smaller diameter exposures presented either with CW irradiation (100 msec flashes) or with multiple Q-switched pulses in rapid succession of each other. With either type of condition, immediately after exposure, the animal's baseline acuity dropped and remained depressed for some time before postexposure acuity gradually began to return to its pre-exposure baseline. Both the magnitude and duration of the observed visual deficits were related to the amount of retinal area involved (exposure spot size) and to the number of Q-switched pulses presented. Increasing the power density of single Q-switched pulses for small diameter exposures produced little additional impact on the animal's derived acuity even for energy levels significantly above (10X to 100X) the ED_{50}. With larger diameter exposure sites, however, the energy of the pulses clearly influenced the duration of the deficit as well as the likelihood of full recovery within the remaining time of the test session. The impact of multiple exposures under this condition often became prolonged and sometimes permanent for Q-switched pulses above the ED_{50}. But unlike the msec time domain exposures, no transitional zone was found where cumulative effects could be noted for repeated exposures. Control trials in which low energy exposures were positioned as little as 1^0 off of the animal's point of central fixation dramatically reduced the overall adverse impact of laser irradiation. Measuring immediate postexposure acuity under different viewing conditions (high versus low contrast or achromatic versus chromatic) produced little relative difference in either the percent deficit or the duration of transient deficits and contributed little to a fuller understanding of the nature of these changes. In those exposures where permanent changes were noted, however, postexposure acuity was significantly different for different contrast, luminance, and chromatic targets and these types of long term changes did provide some discernment of the location and nature of the damage mechanism.

A comparison of the impact that retinal exposure position had on the ability of an animal to maintain a consistent acuity immediately after exposure is shown in the next series of figures. In these figures, as well as others to follow, the average postexposure acuity for each two minute interval is

plotted as a function of derived pre-exposure acuity and is displayed as a percent deficit. Even with relatively large diameter exposures (500 μ) the magnitude and duration of transient deficits to low level Q-switched exposures was small for single pulse exposures compared to those types of exposures when more pulses were presented. In these figures (Figures 4 A-D) the beam was positioned either coaxial with the gap in a threshold Landolt ring (on-axis) or positioned approximately one degree temporal to the gap (off-axis). When positioned within the critical feature (gap) of a threshold target, a foveal exposure would be expected as long as the animal maintained its central fixation while making the required discrimination. Positioning the beam away from the gap should expose areas of the retina outside the central fovea. In these figures the percent deficit in visual acuity was plotted as a function of time following laser irradiation. All exposures were Q-switched pulses of the same relative energy and only one set of pulses (exposure condition) was presented per session. In Figure 4A a single, low-level, Q-switched pulse was presented either on-axis or 1^0 off of the animal's fixation point. For the on-axis exposure, the animal's visual acuity decreased by approximately 15% during the first three minutes following irradiation before quickly returning to its pre-exposure baseline within 7 minutes of exposure. This visual deficit was rather minor and transient compared to those elicited by msec time domain flashes or multiple Q-switched pulses. Consistent with other examples of low level exposures (see Figures 4 B-D), immediately after the animal's postexposure acuity deficit recovered, the animal's acuity became temporarily enhanced for several minutes before gradually returning to its normal pre-exposure baseline. In this example, the animal's transient enhancement was approximately 20% better than its baseline, an increase in visual acuity to $1.44(\text{min of arc})^{-1}$ or a Snellen acuity of 20/14. This enhancement effect gradually began within eleven minutes of the exposure and lasted approximately eight minutes before the animal's acuity again stabilized at its pre-exposure level, some seventeen minutes after exposure. The off-axis exposure produced no immediate deficit or delayed enhancement in visual acuity.

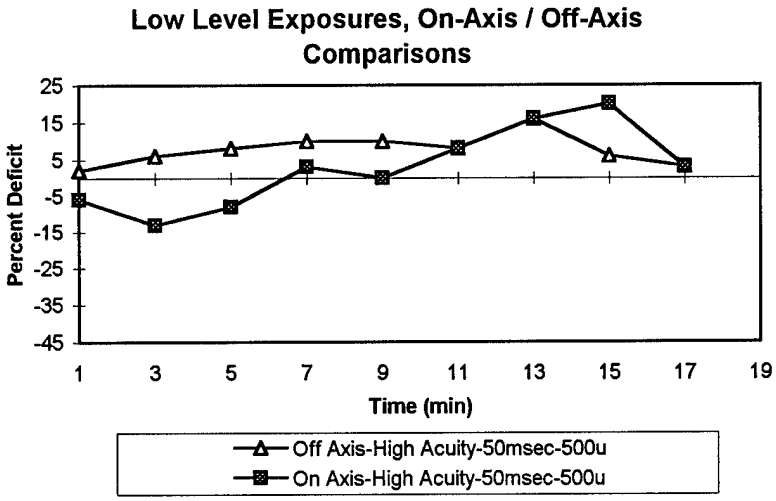

Figure 4 A. On- and off-axis exposures to single Q-switched pulses at energy levels below the transition zone for permanent deficits. One 532 nm Q-switched pulse from Nd/YAG laser was presented within a 50 msec exposure window either coaxial with or temporal to the gap in a threshold Landolt ring. The energy of the pulse was 0.1 μJ and the beam diameter on the retina was approximately 500 μ.

This animal was able to maintain its pre-exposure acuity level after exposure and, if anything, slightly improved during the course of the twenty minutes test session. For the most part, postexposure acuity was elevated by approximately 5% during the first thirteen 13 minutes after exposure. While minor, this shift was rather consistent and outside this animal's normal session variability. In Figure 4B, the same comparison of on- and off-axis exposures was made except in this example the number of Q-switched pulses presented was increased from one pulse to three pulses within a 150 msec exposure window. Again for the off-axis exposure, little if any deficit was noted during the twenty minute postexposure session but for the on-axis exposure an immediate and significant drop in visual acuity was noted. For the on-axis condition, the initial postexposure deficit was over 25% and the animal's acuity remained depressed for approximately seven minutes before returning to its pre-exposure acuity in nine minutes. Similar to the previous example (Figure 4A), the elicited visual deficit was followed by a brief, but significant enhancement in acuity that lasted several minutes before the animal's acuity stabilized at its pre-exposure level. The relative overall duration of these transient deficits and enhancements for on-axis exposures were the same for both the single and repetitive Q-switched pulse condition.

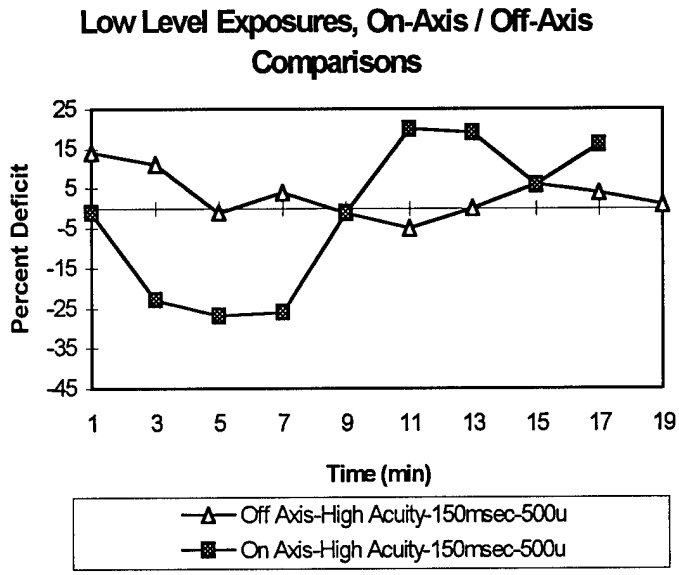

Figure 4 B. On- and off-axis exposures to multiple Q-switched pulses at energy levels below the transition zone for permanent deficits. Three 532 nm Q-switched pulses were presented within a 150 msec exposure window either coaxial with or temporal to the gap in a threshold Landolt ring. The energy of the pulse was 0.1 μJ and the beam diameter on the retina was approximately 500 μ.

Reminiscent of the recovery functions shown in the previous figures, on-axis exposures involving a greater number of Q-switched pulses presented within a narrow window of time produced even larger initial deficits although without significantly affecting the overall duration of the recovery function. With four Q-switched pulses (Figure 4C), for example, the initial deficit increased to over 40% (Snellen acuity of 20/28) and the animal's acuity remained depressed for approximately 10 minutes before gradually returning to its pre-exposure acuity level. Similar to the previous examples, the elicited visual deficit was again followed by a brief, but significant enhancement in acuity before it stabilized at its pre-exposure level. With five pulses (Figure 4 D), the initial deficit was closer to 45% of its pre-exposure level and reached its maximum within the first seven minutes following exposure before gradually returning to its

baseline within thirteen minutes. Again the animal demonstrated hyperacuity for the last four minutes of postexposure testing. The off-axis exposures for one, two, three, four, or five pulses were virtually identical to each other and showed no consistent or significant drop in acuity either during or immediately following laser exposures.

The impact that the position of the exposure on retina has on postexposure acuity appears independent of the exposure time domain. Using msec time domain exposures we have demonstrated a similar decrease in effect as the exposure site is positioned further away from an animal's point of central fixation. For example, in Figure 5 a series of recovery functions from four different 100 msec exposures is shown where the exposure position relative to the animal's fixation point varied from on-axis to as much as 6^0 off-axis. Somewhat independent of their actual position on the retina, these longer duration CW

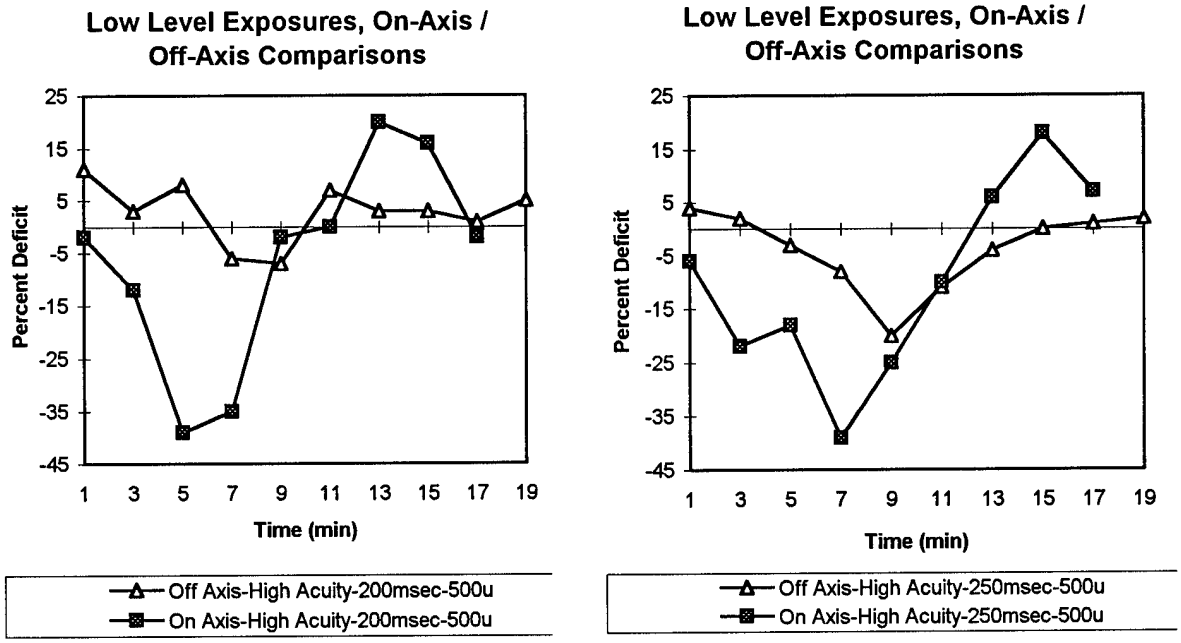

Figure 4 C and D. On- and off-axis exposures to low level, multiple Q-switched pulses at energy levels below the transition zone for permanent deficits. Repetitive, 532 nm Q-switched pulses were presented within either a 200 msec (Figure 4C) or 250 msec (Figure 4D) exposure window either coaxial with or temporal to the gap in a threshold Landolt ring. The energy of each exposure was 0.1 μJ and the beam diameter on the retina was approximately 500 μ.

exposures also involved a larger retinal region than the previous Q-switched pulses. Continuous and random eye movements during the exposure period even when the animal was fixating on the visual target resulted in a larger area of involvement when msec time as opposed to nsec time domain exposures were made. With even multiple Q-switched pulses, presented for the same time msec period, only two, 15 nsec pulses would normally be delivered, thus reducing the actual time in which eye movements could spread the exposure across the retinal mosaic. In Figure 5 an animal was exposed to a series of different

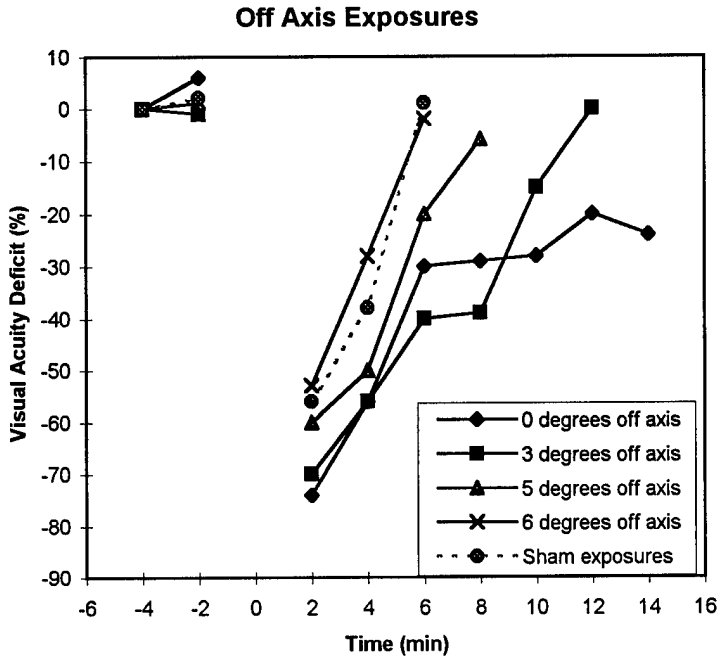

Figure 5. Recovery functions following different CW exposures at various eccentricities. This animal was exposed to single, 100 msec, 647 nm flashes that varied in position on the retina. Postexposure acuity was measured using targets on a achromatic background. The energy of the exposure was below the transitional zone between temporary and permanent effects. The degrees off axis represent the extent to which the beam was positioned temporal to the gap in a threshold Landolt ring

exposures positioned varying distances away from the point of central fixation. Again only one exposure was presented per session. The sham exposure represents the control where no exposure was made but where the discriminanda size was shifted to the approximate level that an on-axis exposure could first be visible. This curve thus represents the time in which it takes for a subject using our tracking technique to return to baseline without making any discrimination errors. The recovery functions for exposures of 5^0 and 6^0 degrees off-axis were virtually identical to that observed in the sham condition. With a 3^0 off-axis exposure, recovery was delayed by approximately six minutes and for an on-axis exposure recover in visual acuity was not complete within the fourteen minutes postexposure session. Follow-up postexposure testing in this animal revealed no long lasting deficit or lingering effects from these or other exposures at this power density.

Again using msec time domain exposures we have demonstrated the effects that variations in exposure duration can have on the duration of the recovery function when minimal diameter spots (< 50 μ) are employed. In Figure 6 the individual recovery functions are shown for four different duration exposures ranging from 19 to 103 msec. As the figure shows, recovery to flashes of 19 msec and 50 msec are almost immediate (within 4 to 8 minutes) and represent the recovery times not significantly different from the sham condition shown in the previous figure. For longer or repeated exposures using either CW lasers or multiple pulses from a Q-switched energy source, however, the duration of the recovery function for minimal diameters spots was similar to those observed when larger diameter exposures were administered. It would appear from this data that the consequence of one longer, 103 msec flash was slightly greater than two 50 msec flashes presented two minutes apart. Such might be the case if eye movements alone were the prevailing catalyst for this type of an effect.

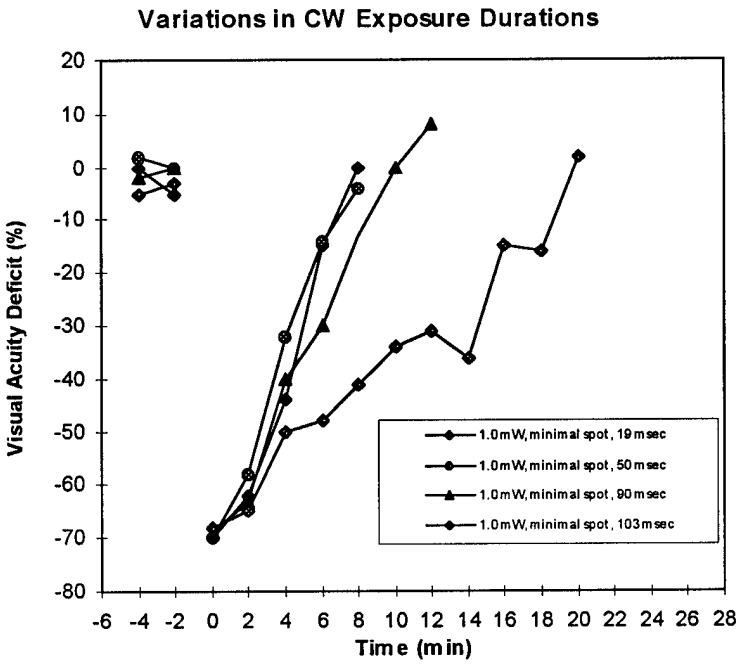

Figure 6. Effects of exposure duration on postexposure visual acuity for msec time domain exposures. The individual recovery functions were derived for one animal exposed repeatedly to 1.0 mW flashes of Argon (514.5 nm) light. Each flash produced approximately a 50 μ spot on the central fovea. Each data point represents means of several exposure sessions. The duration of the retinal exposures was produced by a programmable electronic shutter whose pulse duration was measured and by a standard oscilloscope.

The influence that the acuity task had on delineating the magnitude and the duration of any elicited transient deficit is shown in the next two figures (Figures 7A and 7B) for low level laser irradiation. In each of these figures the animal's pre- and post-exposure acuity was measured using either a high luminance background (high acuity) or a low luminance background (low acuity) against darkened visual targets. Typically an animal's pre-exposure acuity in the high acuity (high luminance) condition was approximately 1.2 $(\text{min of arc})^{-1}$ or a Snellen acuity of 20/17 while pre-exposure acuity derived under the low acuity (low luminance) condition was approximately 0.65 $(\text{min of arc})^{-1}$ or a Snellen acuity of 20/31. Our animals' pre-exposure acuity varied little from session to session and was extremely consistent within a testing session when no exposure was made. Shown in Figure 7A were the deficits observed using different contrast targets when a single, 15 nsec Q-switched pulse was presented within a 50 msec window after the animal correctly detected a threshold Landolt ring. For this single pulse exposure condition (7A), visual acuity for either the high or the low acuity criterion shifted little after exposure relative to its pre-exposure level. The maximum shift in either direction, deficit or enhancement, was less than 15% and all changes were normally fully recovered within fifteen to twenty minutes of exposure. In Figure 7B, the animal's postexposure acuity following a series of 5 to 6 Q-switched pulses presented within a single 250 msec window is shown. In this example, the animal's acuity dropped approximately 40% within the first six minutes after exposure and remained depressed for approximately six minutes before gradually recovering to its pre-exposure level in approximately fourteen minutes. Little relative difference was noted in either the magnitude or the duration of the deficit when using targets of differing luminance backgrounds or contrast. Similar results demonstrating consistent deficits for both high and low luminance targets were observed for other exposure conditions where spot size and the number of pulses

were varied. On the other hand, the magnitude of the deficit and its duration did vary according to the exposure conditions (energy, position, size, and duration) employed. Reminiscent of previous recovery

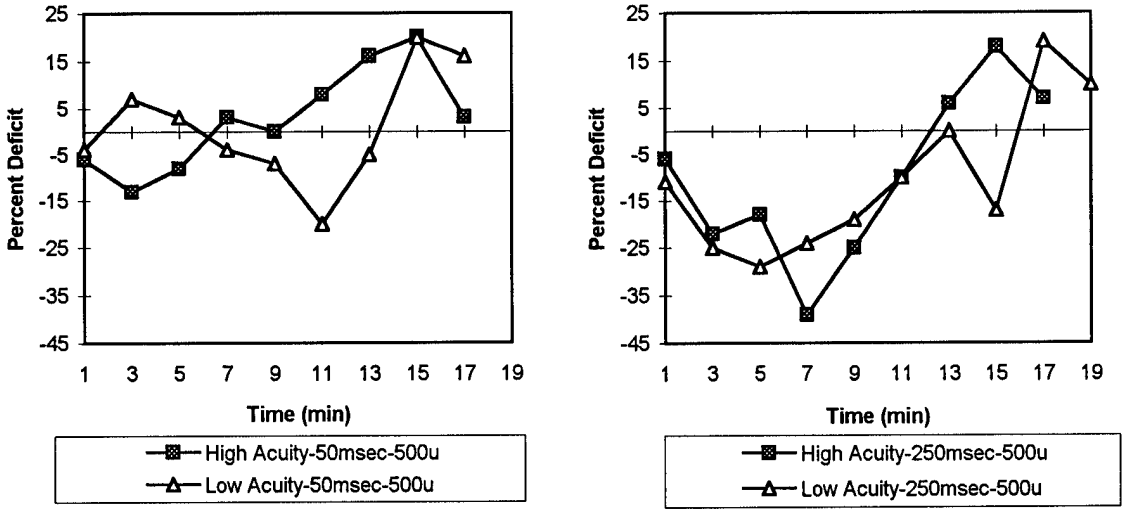

Figure 7 A and B. Effects of high and low luminance targets on postexposure acuity. In these figures, the animal was exposed to either a single Q-switched pulse (A) or to 5 Q-switched pulses within a 250 msec window (B). The energy per pulse was 0.1 μJ presented coaxial with the gap in a specified Landolt ring (on-axis). Each pulse produced an exposure diameter of approximately 500 μ on the retina. Postexposure acuity was measured for 20 minutes after each exposure using different targets projected onto white light backgrounds of two different luminances. The differences in luminance density between the high and low background was 3.0 log units. Each data point represents the mean visual deficit during a two minute sampling period.

functions shown for low energy exposures was the presence of a "rebound" or "enhancement" in acuity during the later stages of the recovery. This effect also occurred somewhat equally when tested with either high or low luminance targets.

Generally, the recovery functions for repeated exposures using the same conditions (either exposure or performance) were remarkably similar especially when large diameter spots and multiple Q-switched pulses were presented. When single Q-switched exposures were used and/or when the diameter of the exposure on the retina was minimal (< 50 μ), the elicited deficit was smaller and more variability existed across exposure sessions and between animals. This increased within subject variability observed likely represents the degree to which the exposure was centered on the fovea and the extent to which surrounding foveal regions were still functional. The between animal variability likely also represents the degree to which different animals employ different strategies to detect threshold targets after exposure especially when off-axis fixations are required. As expected, deriving postexposure acuity functions using percent change from pre-exposure acuity rather than absolute acuity reduced considerably the between subject variability. In spite of generally higher energy densities for Q-switched pulses, more variable recovery functions were noted in this study using nsec time domain exposures than in previous

studies with lower energy CW laser exposures in the msec time domain. The majority of exposures in this study, however, involved smaller diameter spots and briefer duration exposures which could easily explain the increased variability noted. In Figure 8A and B an average recovery function derived for one animal from four separate exposure sessions is shown for both high and low acuity criterion. No statistically significant difference was found between the two recovery functions. For each criterion, the animal's visual acuity decreased rather significantly within seven to ten minutes after exposure and remained depressed for the next twenty minutes before gradually returning to its pre-exposure level within thirty five minutes of exposure. In the recovery functions shown in Figure 8 the initial visual deficit appeared to occur earlier during the postexposure period when high acuity criteria as opposed to low acuity criteria were used. However, in the next figures (Figure 9A and B) no significant differences were found between the time course of the initial deficit and acuity criterion employed.

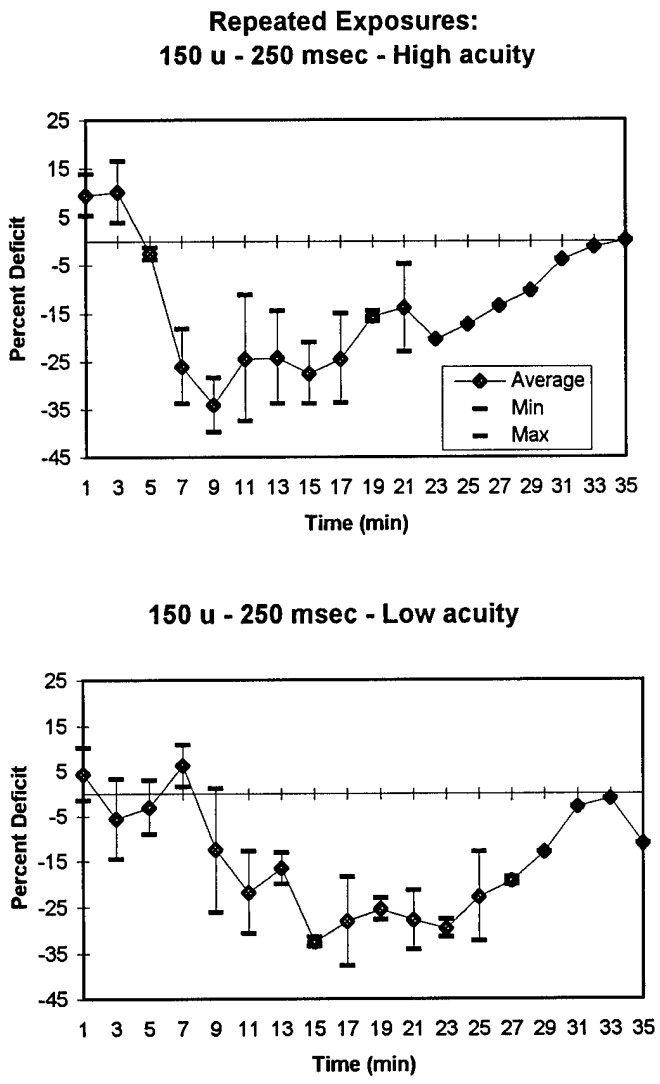

Figure 8 A and B. Average recovery functions derived for different luminance backgrounds after low-level, multiple pulse exposures (small spot size). In this figure a comparison of the recovery functions of one animal is shown for both high (A) and low acuity (B) criteria. This animal was exposed to five Q-switched pulses presented within a 250 msec window. Only one set of 532 nm pulses (exposure) were presented per session (day) and each recovery function shown here represents the average of four separate exposure sessions. The vertical error bars through each data point represent the range of acuity variability observed for the four separate exposure sessions presented. Overall, a random design of eight different diameter spots and five different pulses trains were presented. In this figure the retinal spot size was 150 μ and the energy per pulse was 0.1 μJ. In all cases the animal's visual acuity returned to its pre-exposure baseline within the test session and no long term shift in postexposure acuity was noted on subsequent test days.

In Figures 9A and B the diameter of the exposure on the retina was increased from 150 μ to 200 μ while the number of pulses was decreased from five Q-switched pulses presented within a 250 msec exposure window to four pulses presented within a 200 msec window. In spite of these changes in exposure parameters both

the magnitude of the initial deficit and time for full recovery for each derived recovery function did not change significantly from those recovery functions previous shown. For the high acuity criterion (Figure 9A), postexposure acuity dropped to 25% of its pre-exposure level in approximately 7 minutes after exposure. During the next 14 minutes the animal's acuity gradually improved and eventually returned and stabilized at its pre-exposure baseline. For the low acuity criteria (Figure 9B) neither the initial deficit nor the size of the maximum deficit was as large as that shown for the high acuity criterion but here again the immediate deficit in visual acuity stabilized in approximately 7 minutes before finally returning to its pre-exposure baseline within 17 minutes of exposure. The variability in results across different exposure sessions was actually quite small as represented by the error bars in each of these figures. Each of these curves represent the average of four separate exposure sessions. Similar results were also observed with other spot sizes and number of Q-switched pulses at this energy level.

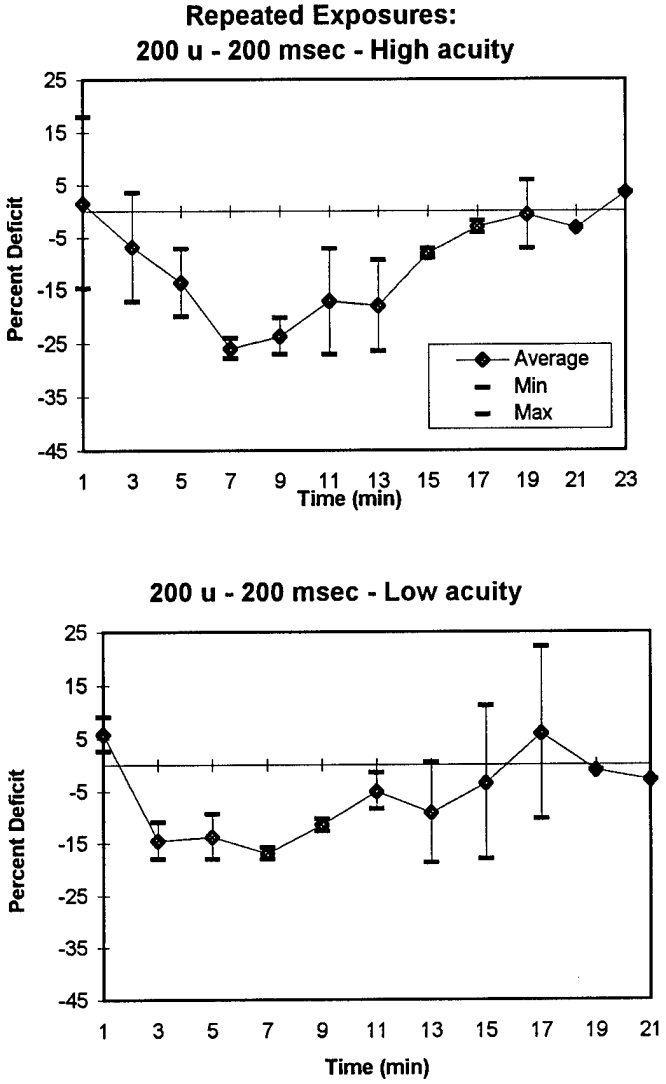

Figure 9 A and B. Average recovery functions derived for different luminance backgrounds after low-level, multiple pulse exposures (large spot size). In this figure a comparison of the recovery functions of one animal is shown for both high acuity (A) and low acuity (B) criteria. This animal was exposed to four Q-switched pulses from a Nd/YAG laser. All four pulses were presented within a 200 msec exposure window. Each recovery function represents the average of four separate exposure sessions and the error bars represent the range of variability of acuity during these four separate exposures. In this figure the retinal spot was 200 μ and the energy per pulse was 0.1 μJ. In all exposures the animal's visual acuity returned to its pre-exposure baseline within the test session and no long term shift in postexposure acuity was noted on subsequent test days. A random design of eight different diameter spots and five different pulses trains were presented.

Differences in the diameter of the laser exposure on the retina did have an impact on the likelihood

observing a deficit and on the magnitude of any observable acuity shift produced. As previously reported, for very small diameter, Q-switched pulses the deficits observed were often very small and transient in spite of the fact that they were presented on-axis. This minimal consequence was most evident when only one or two nsec pulses were presented. When larger spot sizes were employed, larger and more sustainable visual deficits were elicited. The comparison of deficits produced by two different spot sizes is shown in Figure 10. In this figure the animal was exposed on two separate occasions to two Q-switched pulses of low energy light that generated either a 100μ or 400μ diameter spot on the retina. These exposures were presented co-axial with the gaps in threshold Landolt rings and postexposure visual acuity was measured using high luminance targets. With either diameter exposure there was a significant decrease in the animal's visual acuity immediately after the exposure. For the 100 μ diameter exposure, the initial visual deficit leveled off after 4 minutes and remained at this depressed level for approximately 12 minutes before gradually returning to its pre-exposure level in 16 minutes. The average deficit that was sustained during the initial phase of the recovery was 15%. For the 400 μ diameter exposure the animal's visual acuity also immediately

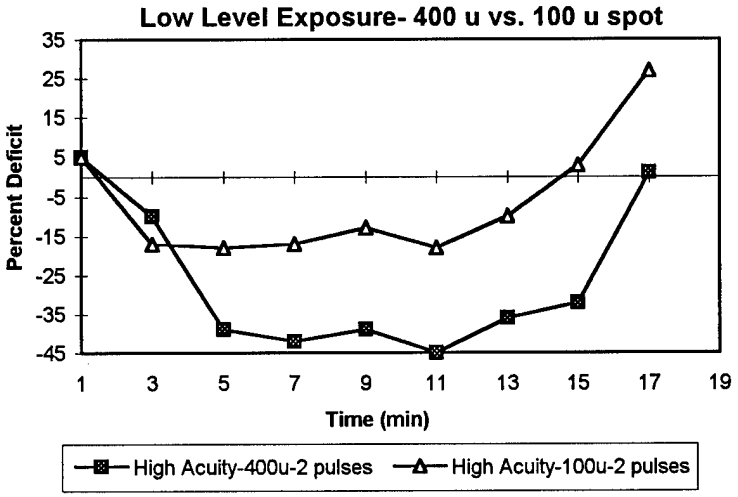

Figure 10. Comparison of spot sizes on the magnitude and duration of the visual deficit. Two, low energy, Q-switched pulses were presented. Each pulse produced either a 100 μ or 400 μ diameter spot on the retina. The beam was presented on-axis and only one exposure (two pulses) was presented per day. Acuity was measured using high luminance targets.

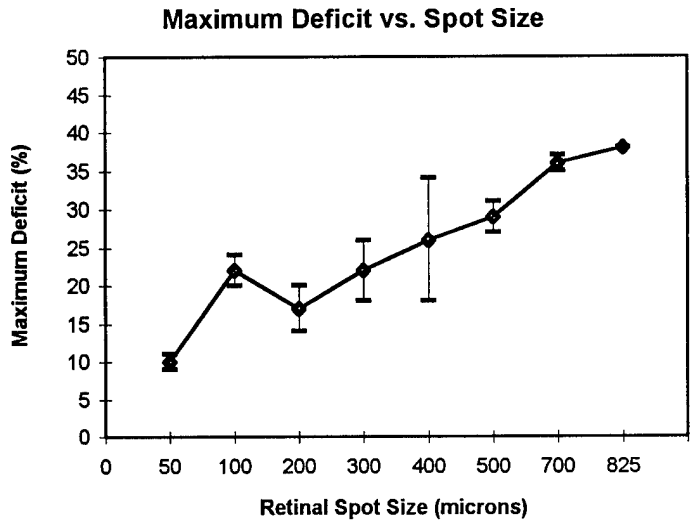

Figure 11. Effects of retinal spot size on the magnitude of the maximum deficit. This subject was exposed daily to a single, 3 μJ, Q-switched from a Nd/YAG laser. All exposures were presented on-axis. Acuity was measured using high contrast, achromatic targets. Each data point represents the mean of five different exposures and the vertical bars represents the range of deficits observed for each spot size.

dropped and within 6 minutes had reached a maximum deficit of 45%. The animal's deficit remained at this acuity level for approximately 12 minutes before the visual deficit gradually returned to its pre-exposure baseline in 18 minutes. The time course of the recovery curves for these two different exposures was remarkably similar and were different only in the degree of the initial deficit.

A direct comparison of the size of the initial acuity deficit with eight different retinal spot sizes is shown in Figure 11. For relatively small diameter exposures (50 μ) little or no deficit was observable using our behavioral paradigm, but as the spot diameter increased, an almost monotonic relationship developed between the magnitude of the maximum deficit and retinal spot size. In this example the animal was exposed to only a single, 15 nsec pulse for each exposure diameter which virtually eliminated any impact that either voluntary or involuntary eye movements might have on the actual size of the retinal irradiation. The calculated diameter of the exposure site on the fovea varied from approximately 50 μ to 825 μ. The largest diameter spots employed likely irradiated the animal's entire fovea and produced a significant loss in photopic acuity that peaked at about 45% of the animal's pre-exposure acuity level. For smaller areas of retinal involvement the deficit was proportionally smaller. Overall, little variability was observed between exposures of the same diameters and a random design of different spot sizes was presented over different test sessions. A somewhat heightened deficit was observed for spot diameters of 100 μ in comparison to spot diameters of 50 μ and 200 μ.

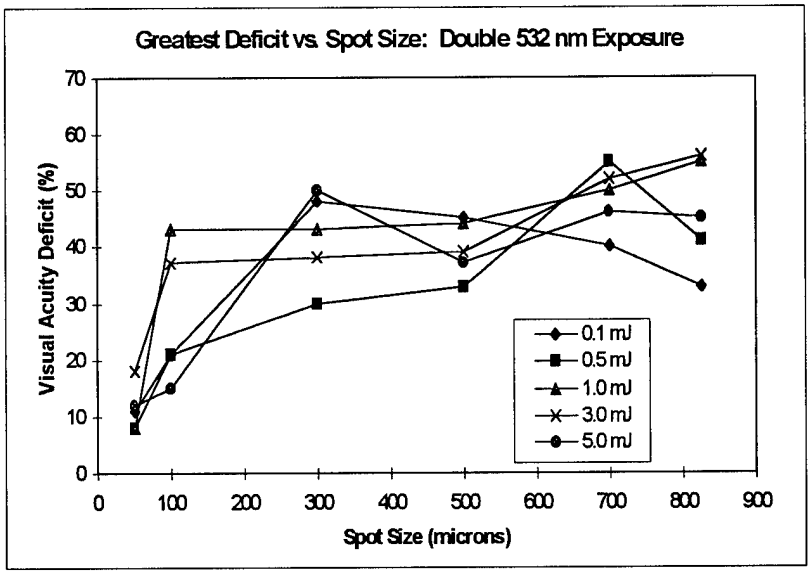

Figure 12. Maximum deficit in visual acuity for different diameter spots of varying energy densities. This subject was exposed daily to two Q-switched pulses within a 100 msec window from a Nd/YAG laser. For each diameter exposure, the pair of 532 nm pulses varied in energy density from 0.1 μJ to 5.0 μJ. Acuity was measured using high contrast, achromatic targets.

Increasing the number of Q-switched pulses presented within a 100 msec exposure window reduced the overall impact that retinal spot size had on determining the magnitude of the initial deficit. In Figure 12 a similar comparison of the impact that retinal spot size had on the maximum of the initial acuity deficit is shown. In this figure, however, two rather than one Q-switched pulse per exposure is shown. The magnitude of the maximum deficit varied from less than 10% to greater than 50% of its pre-exposure level. In this example, the energy per pulse was also varied from 0.1μJ to

5.0μJ for the six different spot diameters employed. Under these exposure conditions the energy per pulse had little impact on the magnitude of the initial deficit especially when very small diameter exposures were used. For example, when 50 μ spots sizes were employed the initial deficit was quite small (less than 10%) and varied little regardless of the energy of the pulses. Increasing spot diameters to 100 μ or more, however, significantly changed the magnitude of the maximum deficit. Overall the magnitude of the maximum deficit varied from 10% to greater than 50% of its pre-exposure level. However, little systematic change in the magnitude of the initial deficit was observed for spot sizes that varied as much as 600 microns from each other. In this figure individual curves represent different energies per pulse for varying spot sizes. For the energy densities used in this example little trend could be observed for the different energy pulses. Typically, the maximum deficit was observed within the first five to eight minutes after exposure and full recovery was complete within thirty to forty minutes of exposure. No long term shift in acuity was observed for any of the exposures used to produce the data in this figure.

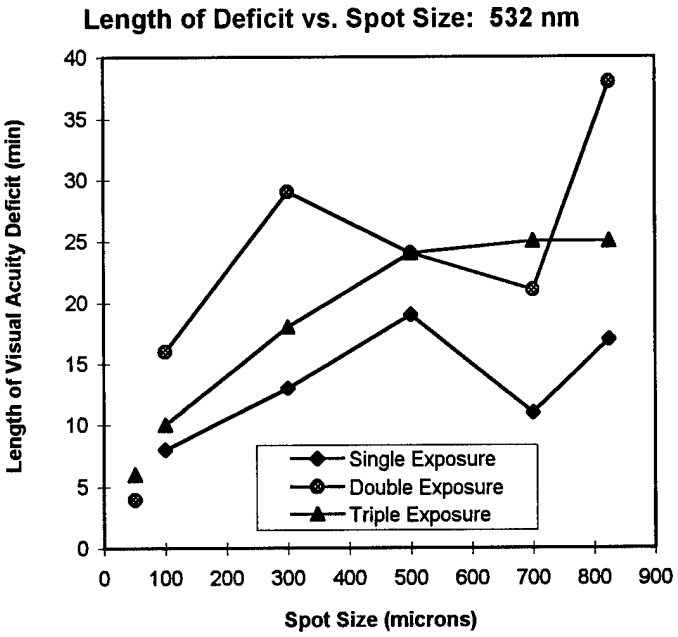

Figure 13. Duration of the visual deficit for single, double, and triple Q-switched pulses. This animal received only one exposure per day and that exposure varied in either in the number of Q-switched pulses presented or in the size of the irradiation on the retinal surface. The diameter of the on-axis exposure varied from less than 50μ to 825μ. The energy of these pulses were several log units below the ED_{50} and averaged 0.01 μJ per pulse. Postexposure acuity was measured using a high acuity criterion and the duration of the visual deficit was defined as the total time from exposure to the animal's return to its pre-exposure baseline.

As might be expected, the magnitude of the initial deficit was related not only to the area of retinal involvement but it was also related to the total time for recovery. Figure 13 demonstrates the length of the time required for full recovery following single, double, and triple Q-switched pulses of different retinal spot diameters. All exposures were below the ED_{50} level and were presented on-axis. This figure shows that the length of recovery following a single Q-switched pulse was considerable shorter than that following either a double or triple exposure regardless of the diameter of the spot(s) on the retina. For this subject, a single, minimal diameter (<50μ) Q-switched pulse produced no significant shift in postexposure acuity and was not included on this graph. For the multiple pulse condition (2 or 3 Q-switched pulses),

only a minor shift in postexposure acuity was noted for the smallest of exposure sites and the deficit quickly ended within 5 minutes of exposure. As the size of the exposure on the retina increased from 100 μ to greater than 800 μ, not only did the size of the maximum deficit increase, as previously shown, but also the duration of the visual deficit increased from five minutes to almost forty minutes. For all pulse conditions, larger diameter exposures produced more consistent and sustained deficits than those for small diameter exposures. The relationship between the two and three pulse condition was complex with often the double pulse condition producing a larger deficit than the triple pulse condition.

Variations in the energy per pulse had some impact on the nature of the visual deficit but these differences were only evident for relatively large spot sizes. Single Q-switched pulses of minimal spot size (<50 μ) produced little observable change in postexposure acuity even for high energy exposures at or slightly above the ED_{50}. Increasing the area of retinal involvement by increasing the spot size and/or by increasing the number of presented Q-switched pulses in a moving eye, however, did produce immediate but still transient changes in the animal's postexposure acuity. In the next two figures the recovery functions for relatively large diameter exposures (500μ) are shown for two different energy levels: 1.0 μJ (ED_{50} for small spot exposures) and 0.1 μJ (one log unit below the ED_{50}). In Figure 14, the animal was exposed on two separate sessions to a single Q-switched pulse at both of these energy levels. In Figure 15, the same animal under the same exposure conditions was exposed to three rather than two Q-switched pulses within a 150 msec time interval at these same energy levels. All exposures were presented on-axis and the animal's postexposure acuity was measured using high luminance targets. When exposed to a single, low level Q-switched pulse, the animal's postexposure acuity dropped only slightly for a brief period before quickly returning to its pre-exposure level within approximately eight minutes. This curve demonstrates little initial impact of this exposure on the ability of the animal to maintain a consistent postexposure

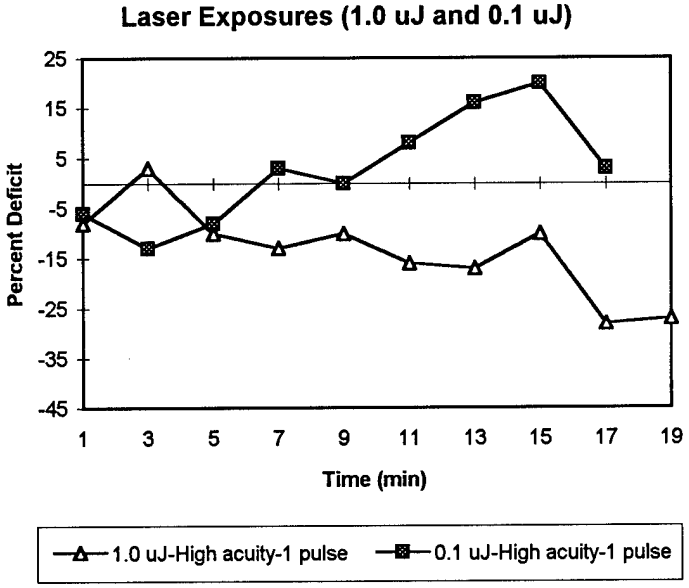

Figure 14. Single Q-switched pulse exposure at two different energy levels. A single pulse at either 1.0 μJ or 0.1 μJ was presented. Both exposures were made on-axis and each exposure produced a retinal spot size of 500 μ. Post exposure acuity was measured using high luminance target (high acuity criterion).

threshold comparable to its pre-exposure level. However, during the later portions of the test session the animal demonstrated the same type of enhancement in visual performance that had been noted previously for those exposures where an immediate deficit was observed. In this example, the initial deficit elicited was less than 15% (Snellen acuity of 20/20) and was very transient in nature. The enhancement in postexposure acuity, on the other hand, was somewhat more pronounced and less transient in nature although by the end of the twenty minute test session, the animal's postexposure acuity had returned to its pre-exposure baseline. At the higher energy level (1.0 μJ), the initial deficit was not remarkable during its early stages especially compared to previously reported initial deficits but as time passed the animal demonstrated a gradual but significant drop in visual acuity that lasted for the duration of the test session. Within the twenty minute postexposure session, visual acuity had dropped by approximately 25% and no recovery or enhancement effect was noted. The next day the animal's acuity had returned to its pre-exposure baseline level and in the days that followed no permanent deficit was noted. No additional exposures were presented to this animal during this period.

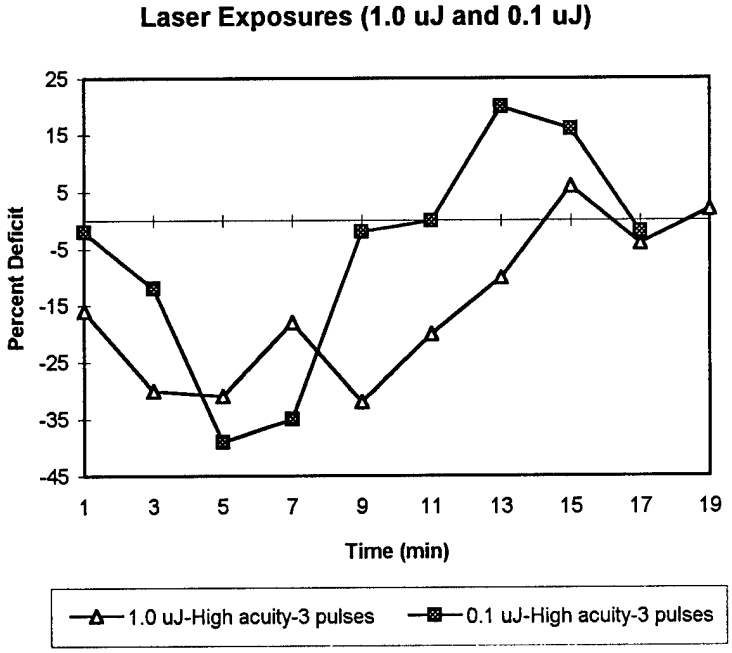

Figure 15. Three Q-switched pulses at two different energy levels. Three pulses at 1.0 μJ and 0.1μJ were presented within a 150 msec window. Both the high and low energy exposures were made on-axis and the exposure produced a retinal spot of 500 μ. Postexposure acuity was measured using high luminance targets.

Larger, more consistent and prolonged visual deficits were observed for minimal spot diameters of higher energy density when the number of individual pulses presented. Shown in Figure 16 are the recovery curves following two different energy exposures presented to the same animal over the course of several different sessions. In Figure 16A, four Q-switched pulses were presented within a 200 msec exposure window. Each pulse had an energy density of 0.5 μJ and produced a retinal spot diameter of approximately 50 μ. The actual size of the exposure site, however, was significantly larger due to involuntary and on-going voluntary eye movements. The total area of exposure could have varied from 50 μ, assuming total overlap to greater than 100 μ in diameter, assuming little retinal overlap in individual

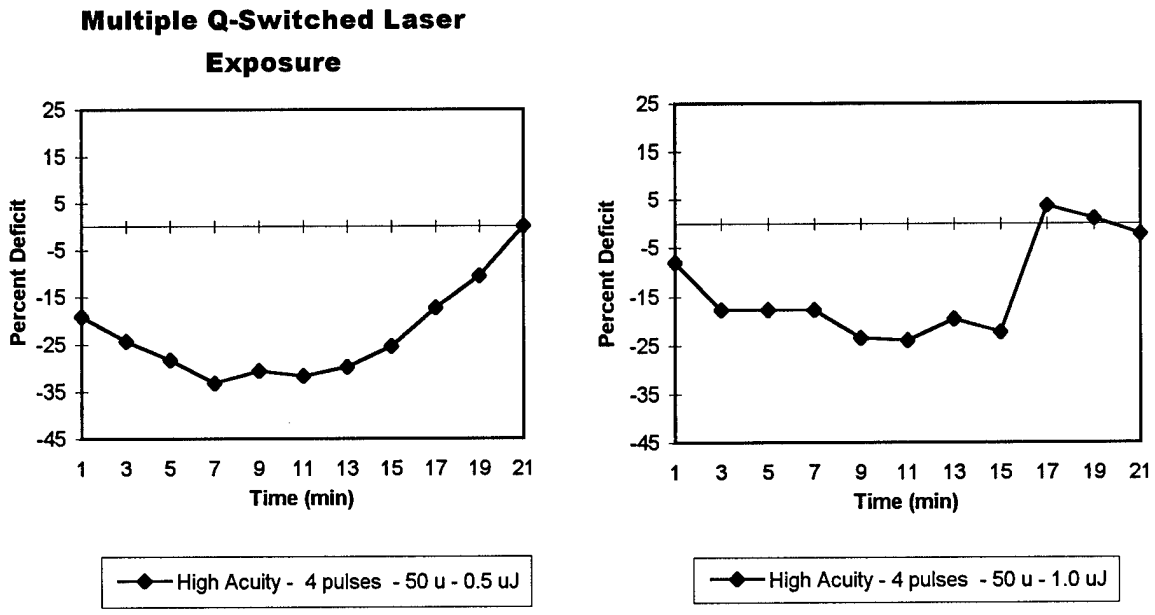

Figure 16 A and B. Multiple Q-switched pulses (4) at two different energy levels. On separate exposure sessions this animal was exposed to 4 Q-switched pulses from a ND/YAG laser. All four pulses were presented within a 200 msec exposure window and were presented on-axis. The energy density of each pulse was the same but was different for the two different exposures. In the left hand figure (A) the animal was exposed to a series of 0.5 μJ pulses while in the right hand figure (B) the energy density per pulse was 1.0 μJ. All pulses presented a 50 μ diameter spot on the retina. Postexposure acuity was measured using high luminance (high acuity criterion) targets.

pulses. The total energy presented was slightly below the ED_{50} for this exposure condition. Immediately after exposure, this animal's visual acuity dropped to 35% of its pre-exposure acuity and remained at this depressed level for approximately 15 minutes before gradually returning to its pre-exposure level within the 20 minutes. Increasing the energy density per pulse to 1.0 μJ produced a similar recovery function. In this case, however, the animal's pre-exposure acuity decreased by as much as 25% during the first 15 minutes after the exposure and within 17 minutes the animal's acuity had returned to its pre-exposure level. In both of these exposures the animal's long term acuity remained unaffected by these exposures even though their energy densities were at or near the ED_{50}. Additional exposures were not made on subsequent days and typically after exposures of this magnitude the animal's baseline acuity was followed for several days before any additional exposures were made. In the examples given here, the animal's postexposure baseline remained consistent with that derived prior to any exposure and was also consistent with the baseline established in this animal's control (unexposed) eye. With higher energy pulses or with pulses that exposed a greater overall area of the fovea (larger spot diameters), some increased variability in acuity was noted in subsequent test sessions even though the animal's average acuity approximated its pre-exposure level. Within days, however, these slight variability differences disappeared and the animal appeared fully recovered from the exposure.

As previously shown, variations in the number pulses, the energy per pulse or the area of involvement (spot diameter) produced no significant lingering effects beyond the actual exposure session for those exposures at or below the MPE. The impact of each exposure appeared independent of previous exposures and there were considerable similarities in recovery for each exposure in terms of the magnitude of the initial deficit and the time required for full recovery. At the transitional zone between temporary and permanent visual loss, however, the impact that any one exposure had on the recovery from another exposure became dependent upon both the energy of the exposure and the number and sequence of previous high energy exposures. As individual exposures approached the transition zone between temporary and permanent visual loss there were predictable variations in the recovery functions for successive exposure. This cumulative effect on the nature of the recovery occurred in spite of the fact that individual exposures were separated from each other by at least 24 hours and often recovery to the previous exposure appeared complete within its immediate 30 minute postexposure session. Typically, in the transition zone, successive exposures produced only slight variations in the size of the initial deficit but there were significant differences in the time for full recovery for each exposure. In some cases recovery appeared complete within 30 to 45 minutes after exposure but 24 hours later there were slight depressions in baseline acuity normally associated with increased variability in the animal's ability to maintain a stable baseline. In Figures 17 and 19 the differential effects of successive exposures are shown for two animals exposed to 50 μJ and 100μ uJ pulses. Each animal was exposed to only one 15 nsec pulse per day, and following the first several exposures at these energy levels recovery was complete within a matter of minutes following the initial transient deficit. In the case of the 50 μJ exposures (Figure 17), no prolonged effect beyond the initial transient deficit was noted 24 hours later for the first three exposures. The maximum initial deficit elicited by these exposures was approximately 70% and acuity

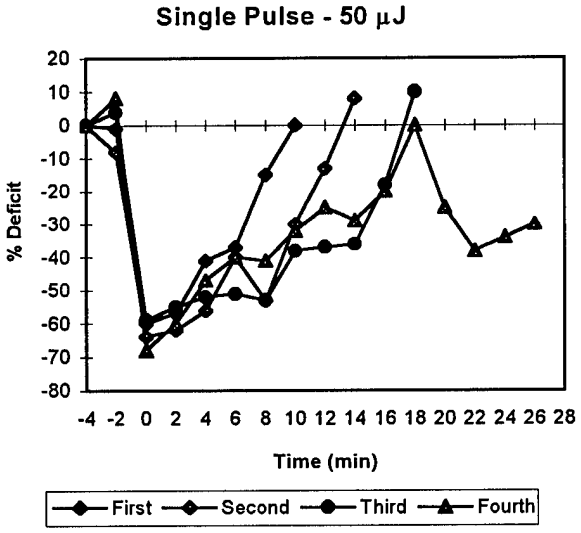

Figure 17. Changes in visual acuity following four, separate 50 μJ exposures. This animal was exposed over several weeks to high level, 532 nm light from a Nd/YAG laser. Each exposure was single Q-switched pulse that was represented on-axis and created a 250 μ diameter spot on the retina. Only one exposure was made per session and postexposure acuity was measured using high luminance (high acuity criterion) targets. Postexposure acuity was plotted against the animal's pre-exposure baseline.

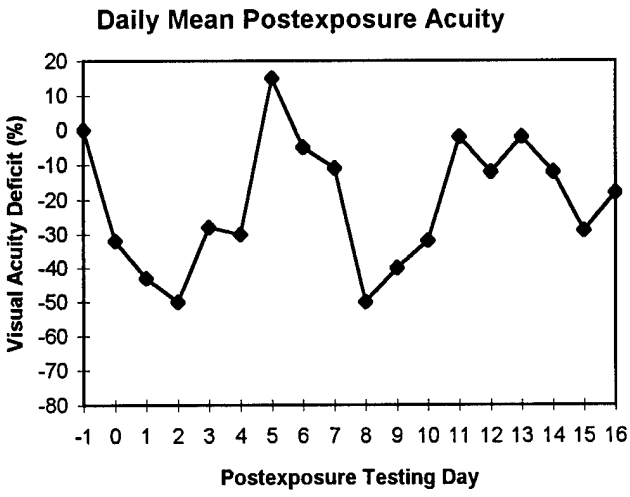

Figure 18. Mean daily postexposure acuity following multiple 50μJ exposures. This animal was exposed to four separate 50 μJ, 532 nm, Q-switched pulses. Each pulse was separated from the other by at least several days. Following each exposure, postexposure testing continued until a stable baseline was again established consistent with this animal's pre-exposure acuity level. Once a stable baseline was established, the animal was re-exposed to another 50 μ pulse and postexposure testing continued until the animal had apparently recovered from that exposure. This figure demonstrates the day to day changes in baseline acuity over a 16 days period following the fourth 50 μJ pulse. Each data point represents the average deficit derived from a minimum of 30-45 minutes of testing.

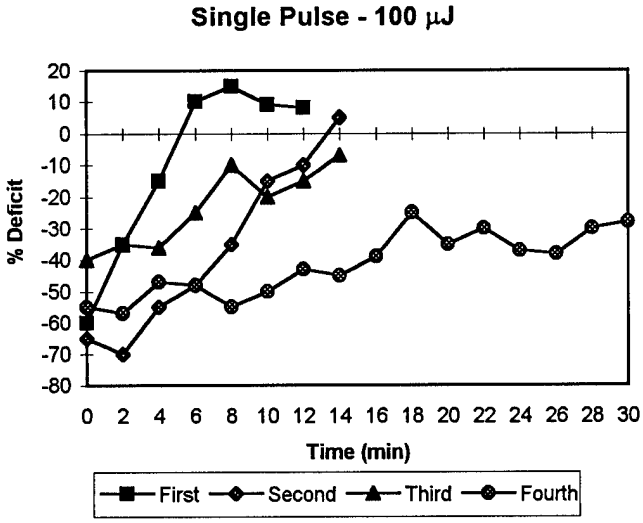

Figure 19. Changes in visual acuity immediately following four, separate 100 μJ exposures. This animal was exposed over a several weeks to high level, 532 nm light from a Nd/YAG laser. Each exposure was single Q-switched pulse that represented on-axis and created a 250 μ diameter spot on the retina. Only one exposure was made per session and postexposure acuity was measured using high luminance (high acuity criterion) targets. Postexposure acuity was plotted against the animal's pre-exposure baseline.

began to improve almost immediately after this rather large initial shift. For the first exposure the animal's postexposure acuity returned to its pre-exposure baseline level in approximately 10 minutes, for the second exposure the total time for recovery increased to 14 minutes, and for the third exposure more than 18 minutes was required. For the fourth exposure, the animal's acuity again returned to its baseline within 18 minutes but the animal was unable to maintain this baseline level and its acuity again dropped and leveled off at approximately 35% of its pre-exposure level. Full recovery did not occur within the next 30 minutes and this animal's postexposure acuity on subsequent days appeared unusually inconsistent both within and between test sessions. This animal received no additional exposures and his postexposure acuity baseline remained somewhat depressed over the next six months. During this period this animal failed to consistently maintain a postexposure baseline in his exposed eye.

The actual daily average post-exposure acuity for this animal following a fourth single 50 μJ pulse is shown in Figure 18. This animal's postexposure acuity to various background targets was followed over the next several weeks. Figure 18 demonstrates this animal's day to day baseline variability. As shown this animal's

average daily postexposure acuity varied considerably from day to day, varying from an average deficit of greater than 50% on one day to an actual acuity enhancement of 15% on another day. Overall, the animal's acuity during this 16 day period averaged nearly 25% below its previous consistent baseline. Several other animals exposed in a similar manner did not show as great a day- to-day variation as is shown in this example but instead their acuity remained more consistently depressed for several days after exposure before any significant recovery occurred. All animals exposed to single, 50 μJ pulses ultimately regained their acuity to a level consistent with both their control eye and their pre-exposure baseline. Often, however, it took several months before this recovery occurred.

Similar to the exposure paradigm shown in Figure 17, Figure 19 demonstrates changes in an animal's immediate postexposure acuity following four separate 100 μJ pulses. Again, each exposure consisted of a single Q-switched pulse that was positioned co-axial with the gap in a threshold Landolt ring and presented immediately after the animal had correctly detected the target. Only one Q-switched pulse was presented per exposure session and only after the animal had established a stable pre-exposure baseline. In contrast to the exposure paradigm for the 50 μJ pulse each 100 μJ pulse was presented at least five weeks apart. In the interim period between exposures (see Figure 20) average daily postexposure baselines were measured.

At this high energy level animals typically had considerable difficulty fully recovering from the exposure during the normal 30 minute postexposure session. In Figure 19, similar to the recovery functions shown in Figure 17, the animal appeared to regain its pre-exposure acuity baseline for the first three exposures within 15 to 20 minutes of exposure. But unlike the recovery to 50 μJ pulses this animal exposed to 100 μJ pulses was unable to maintain its pre-exposure baseline in subsequent daily postexposure testing in spite of the fact that no additional exposures were made. Postexposure testing continued for this animal for 5 weeks before re-exposure and this process was repeated five times until the animal ultimately failed to recover to its pre-exposure baseline during the actual 30 minute exposure

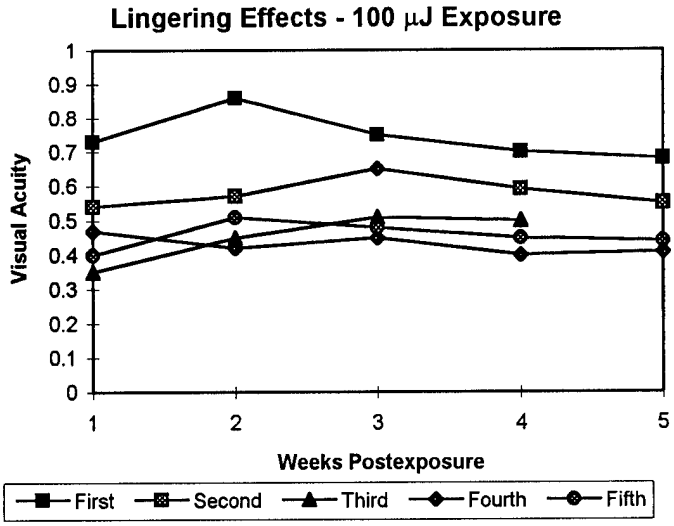

Figure 20. Mean weekly postexposure acuity following each of five 100 μJ pulses. Each curve represents the average weekly acuity measured daily. Visual acuity was derived under high luminance conditions and no laser exposures were made during each of the five week postexposure periods shown above.

session. For example, after the first exposure the animal appeared to fully recover within six minutes but in the days that followed this animal demonstrated a subtle but consistent depression in its baseline acuity as shown in Figure 20. Several months later, however, this animal's baseline shift had completely stabilized at a level just slight below his pre-exposure baseline. At this point the animal was exposed to a second, 100 μJ pulse and again appeared to return to its newly established but reduced baseline in approximately 14 minutes. After 24 hours the animal's baseline acuity level in the exposed eye again shifted from 0.75 (min of arc)$^{-1}$ to 0.6 (min of arc)$^{-1}$ This new baseline level was followed for another five weeks before a third exposure was made. The immediate deficit produced by a third exposure was similar to those of the first two exposures and again the animal appeared to quickly recover to its previous stabilized baseline in approximately fifteen minutes. After another five week delay the animal was exposed to a fourth, 100 μJ pulse and following this exposure the animal was unable to regain its previous stabilized acuity within the thirty minute test session. After still another delay of five weeks this animal was exposed to a fifth 100 μJ pulse (not shown). The reaction to this exposure was somewhat similar to that of the fourth in that the animal was unable to regain its immediate pre-exposure during the 30 minute postexposure session.

The lingering effects following each of the five separate 100 μJ pulses is shown in Figure 20. In this figure the average weekly baseline acuity for a five week period after each 100 μJ exposure is shown. This data represents postexposure acuity over a five month period. In each case, with each successive exposure, the animal's baseline acuity shifted downward representing a growing visual deficit following each exposure. Typically for the first few postexposure days the animal had difficulty maintaining a stable baseline. With time the animal's baseline stabilized but at a reduced level.

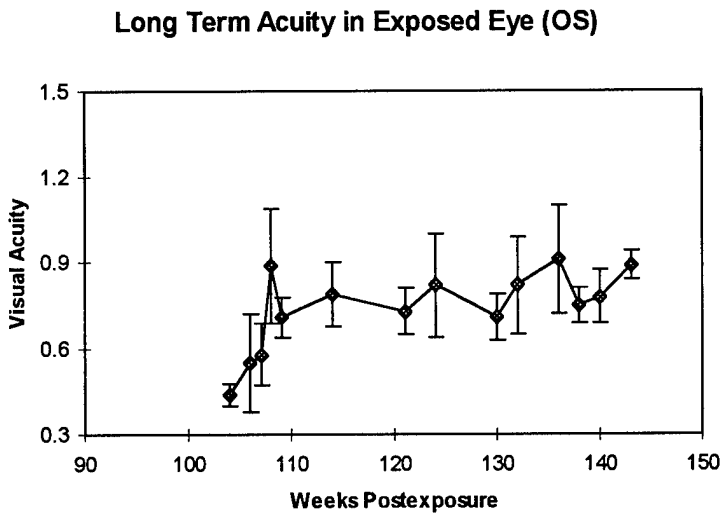

Figure 21. Long term postexposure changes following high energy exposure. Average weekly visual acuity for one animal exposed to five, separate 100 μJ pulses is shown. All exposures were presented on-axis. The vertical lines in this figure represent daily and weekly variability. Each data point represented mean weekly acuity in term of visual acuity (min of arc)$^{-1}$. In this figure visual acuity was measured using high luminance, achromatic targets (high acuity criterion).

Long term changes in visual acuity were followed in this animal after the fifth 100 μJ, Q-switched pulse. Figure 21

shows the gradual change in acuity over a period of several years following the last laser exposure that this animal received. More than three years later this animal's acuity of 0.9 (min of arc)$^{-1}$ was still depressed from its original pre-exposure baseline of 1.45 (min of arc)$^{-1}$. This decline represents an almost 40% deficit that was maintained in the exposed eye throughout this time period. No similar shift in acuity was noted in this animal's control eye. This animal's postexposure acuity was measured using both achromatic and chromatic targets.

Complete spectral acuity curves were also derived for this subject's control and exposed eyes using both high (photopic)and low (scotopic) luminance conditions. Figure 22 represents the spectral acuity curves for the exposed and control eye using a high acuity criterion. Actually this animal's baseline acuity in the exposed eye relative to the control eye improved when chromatic, rather than achromatic, targets were used to tract visual acuity. Using achromatic targets this animal's maximum acuity in the control eye was 1.4 (min of arc)$^{-1}$ and 0.9 (min of arc)$^{-1}$ in the exposed eye while chromatic acuity in the exposed eye was 0.8 (min of arc)$^{-1}$ and 1.1 (min of arc)$^{-1}$ in the control eye. For the exposed eye, the shape of its spectral acuity curve was somewhat flat across the entire visible spectrum For the control eye, this animal's spectral acuity peaked between 480 and 520 nm. Overall the two spectral curves for the control and exposed eyes overlapped considerably except in the short wavelength region of the spectrum where the short wavelength sensitivity in the exposed eye was approximately 30% reduced from that of the unexposed eye. Not shown here are the spectral acuity curves for low acuity criterion (low luminance conditions). Under these luminance levels, the spectral curves for the control eye was also flat across most of the visible spectrum and in that extent were similar to the curve shown here for the exposed eye. The spectral curve for the exposed eye under these reduced luminance conditions (low acuity criterion) was greatly depressed and the criterion difficult to derive at the spectral extremes leaving measurements available only for mid-spectrum background targets.

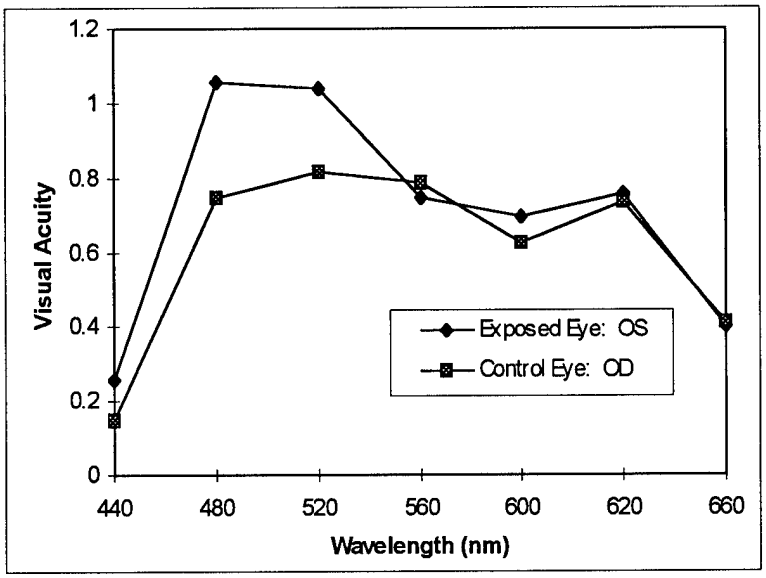

Figure 22. Postexposure spectral acuity. Acuity was measured using different chromatic backgrounds all equated for equal energy. The diamonds represent the spectral acuity of the exposed eye (OS) and the squares (OD) the control. Each data point represents the mean acuity for this spectral background test over a period of approximately one month.

Ophthalmoscopy was performed on several animals exposed to laser irradiation under this project. The procedures used to produce these fundus photographs were developed at the Division of Ocular Hazards, USAMRD-BAFA, TX and performed in our laboratories under joint efforts between our staff and the staff at Brooks AFB. Fundoscopic examination and photographs of our animals was completed after the termination of a series of laser exposures in our animals and in two cases after significant, permanent visual deficits were produced. In Figure 23 a fundus photograph is shown of an animal that had received extensive on-axis and off-axis laser exposures over a period of several years. This animal has a significant visual loss in the exposed eye that varies from an average acuity of 0.75 (min of arc)$^{-1}$ to an acuity of 0.5 (min of arc)$^{-1}$ depending upon the acuity task and time since last exposed. This animal's postexposure acuity data is shown in Figures 19-21. Nearly ten years ago this animal was exposed to low level CW Argon irradiation on an almost daily basis. These exposures produced both wide field and punctate irradiation but all exposures were significantly below those levels that were known to produce morphological damage. No long term acuity deficits resulted from these exposures. More recently this same animal was exposed to a series of on-axis, 532 nm, Q-switched pulses that produced minimal diameter retinal spots (<50 μ). These latter exposures consisted of single and double pulses at power densities above the ED_{50} (100 μJ). Individual exposure sessions were separated in time from each other by days and/or weeks depending upon the specific exposure paradigm employed. The fundus photographs of this animal's eye shows distinct retinal pathology broadly spread out throughout the macular region. The pattern of pathology suggests repeated damage from individual laser pulses whose position varied across the central portion of this animal's eye.

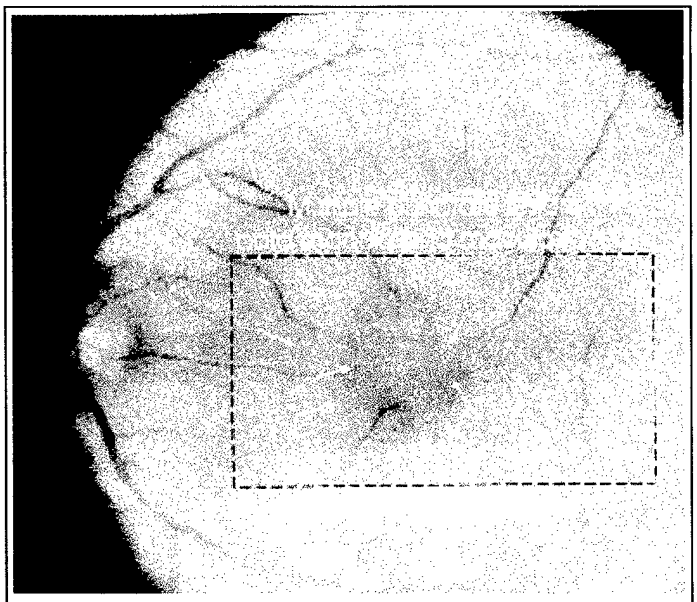

Figure 23. Fundus photograph of the OS eye of an animal repeatedly exposed to both CW Argon and Q-switched, Nd/YAG pulses. This animal's last laser exposure was approximately 10 years prior to when this photograph was taken although the animal's acuity in this eye up until the time of this photograph remained depressed over this prolonged period of time. The arrows on this photograph indicate the various positions within the macula where pathology appears to exist. This animal demonstrates extensive pathology throughout the macula including the central fovea.

Fundus photographs of another eye is shown in Figure 24. This animal's eye was exposed more recently to on-axis, high energy Q-switched pulses. The energy of each exposure varied from 0.1 to 5 μJ

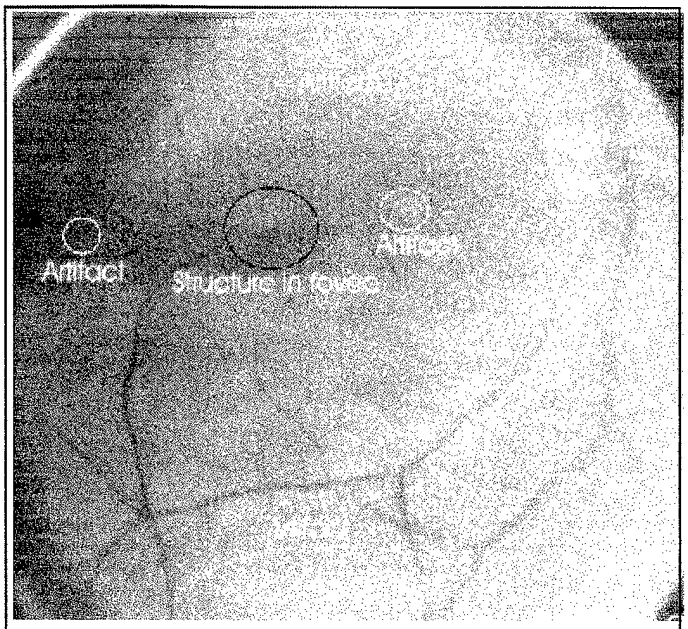

Figure 24. Fundus photograph of the OD eye of an animal repeatedly exposed to both on- and off-axis, Q-switched, Nd/YAG pulses. This animal was exposed almost daily to a variety of on- and off-axis pulses of relatively low energy (0.1 μJ) up until the time immediately before these photographs were taken. The majority of exposures presented were on-axis and each pulse subtended a retinal spot size of 50 to 825 μ. A circle around the fovea indicates are area where pathology is believed to exist.

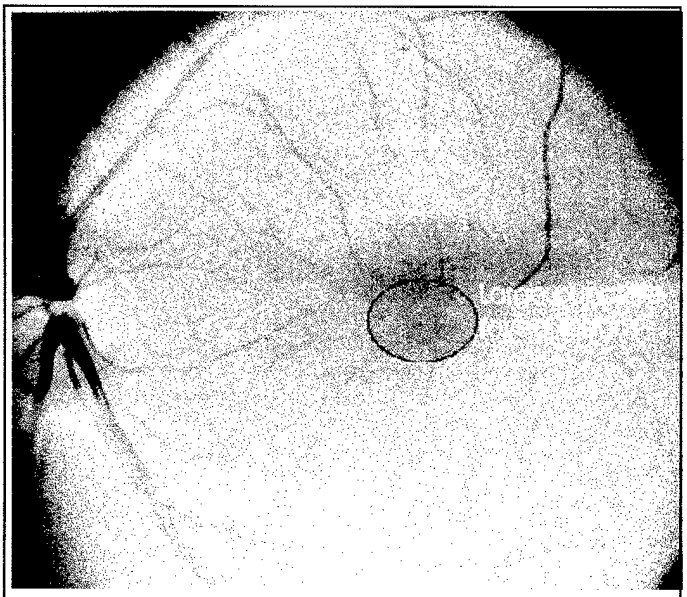

Figure 25. Fundus photograph of the OD eye of an animal repeatedly exposed to off-axis, Q-switched, Nd/YAG pulses. All exposures were presented within a year of the fundus photograph. Single and multiple 532 nm Q-switched pulses were presented 1o temporal the animal's point of central fixation. A red circle around the fovea indicates the area of maximum pathology.

and varied in spot diameter from less than 50 μ to greater than 800 μ. centered on the fovea. The number of pulses per exposure varied from one pulse per session to six pulses per session. This animal also received a series of daily off-axis exposures to 532 nm pulses that were positioned 1° temporal to the critical feature in threshold Landolt rings that the subject was correctly detecting. The energy of these Q-switched pulses was 0.1 μJ and each pulse produced a 500 μ spot on the retina. The energy levels that this animal regularly received were just below the MPE for the single pulse condition. These exposures produced transient shifts in the animal's postexposure acuity that did not result in any significant, long lasting acuity deficit. Immediately prior to these fundus photographs, the animal was able to maintain a 0.9 (min of arc)$^{-1}$ acuity under maximum photopic conditions. This acuity level was slight below the 1.0 to 1.33 (min of arc)$^{-1}$ maximum acuity normally observed in this species but was rather consistently maintained in this animal both prior to and after Q-switched laser exposures. The pathology of this eye was more concentrated in the fovea than that shown in the previous figure. This foveal pathology might explain the somewhat reduced acuity in this eye and might be the cumulative result of both low level Argon exposures and Q-switched

Nd/YAG pulses presented repeatedly over a period of nearly six years.

In the next fundus photograph (Figure 25) an animal was exposed to a series of low level (0.1 J) pulses presented off-axis approximately 1° temporal to the point of this animal's central fixation. This animal received no on-axis exposures but each off-axis exposure produced a rather large spot (500) within the macular region. This animal also received up to four Q-switched pulses within a 200 msec exposure window which could have spread the actual exposure site over an area larger than any single pulse could produce. There is pathology in this animal's exposed eye extending mostly temporal to nasal in the macula. This type of damage is consistent with repetitive off-axis exposures. This animal's acuity in the exposed eye was slightly less than normal although often erratic but following laser exposure postexposure acuity always returned to its pre-exposure baseline. When exposed to single or multiple pulses, this animal's baseline acuity normally decreased by 20 to 45% depending upon the number of Q-switched pulses presented.

DISCUSSION

The visual deficits elicited by Q-switched pulses that are reported in this report are consistent with the notion that the experimental paradigm we developed to expose awake, task-oriented animals actually produced reliable placements of the laser exposures onto the retina. Movement of the laser beam by as little as one degree from its coaxial position within the gap in a threshold Landolt ring had a significant impact on immediate postexposure acuity. Only those exposures that were presented coaxial with the critical feature of the discriminanda produced long lasting conspicuous acuity deficits. Single exposures presented off-axis produced little or no observable visual deficit as might be expected in an animal with an intact, functional central fovea. The visual task used in this study required that the subject fixate centrally on a small, spatially isolated portion of the visual field. Laser irradiation of this highly sensitive region should either temporarily or permanently alter the ability of the subject to accurately process spatially detailed incoming light images isolated on this area. On the other hand, laser irradiation of surrounding regions outside the fovea might well produce significant temporary and even permanent morphological damage but not lead to photopic acuity changes since fovea would still be intact and able to process high resolution targets. In tracking immediate postexposure acuity, variations in the overall luminance, contrast, and/or color of the target backgrounds were manipulated but these changes did not prevent the animal from still successfully discriminating targets using unexposed foveal regions or other unexposed peripheral regions that would still be functional.

Exposure of wide regions of either the animal's fovea or macula by either large diameter spots or repetitive, small diameter pulses lead to immediate and often sustained loss of visual acuity. The nature and duration of these elicited deficits indicate that our training paradigm maintained the animal's ongoing vigil to the visual task throughout the postexposure session in spite of either transient or permanent retinal changes of that normally allow an animal to easily complete a visual discrimination. Typically, immediately after exposure the animal's visual acuity dropped to a maximum deficit that remained depressed for several minutes before gradually returning to it pre-exposure level. The magnitude of the initial deficit appeared related to the area of retinal involvement while the duration for full recovery was more dependent upon the energy rather than size of the exposure.

Consistent with the nature of our task exposure to single, Q-switched pulses of minimal spot diameters produced little or no acuity deficits. Irradiation of very small foveal regions (<50 μ) would not be expected to disrupt enough photoreceptors and/or neural pathways in any one region to seriously limit the processing of incoming visual information. Even for energy densities significantly above the ED_{50}, multiple pulses presented either over several exposure sessions or within the same exposure session would be necessary to produce damage in a large enough region to alter an animal's ongoing photopic acuity. The only exception might be transient changes that could result from exposures which were powerful enough to induce retinal bleeding. Blood can cloud the vitreous and obstruct the pathway of reflected light as it travels through the ocular media. At energy levels near the ED_{50}, both single and multiple Q-switched pulses did temporarily impede the ability of the animal to consistently maintain a baseline photopic acuity. While large diameter exposures and more pulses per exposure produced larger and more sustainable visual deficits, it was only the combination of these factors that elicited a permanent deficit in visual acuity. A relatively wide range of different retinal spot sizes (50 μ to 825 μ) were employed in this study and these variations in the size of the exposure did produce initial deficits of varying degrees. Typically, the larger the spot size, the greater the initial deficit and, to some extent, the longer the time required for full recovery. The same relationship was generally true for the number of Q-switched pulses. Single, 15 nsec pulses normally had only a minimal impact on the ability of the animal to maintain its pre-exposure baseline unless the spot size was large (greater than 150 μ). These brief exposures would allow a highly motivated observer the ability to "look" around the affected regions and still maintain maximum visual performance. Consistency, however, might be a problem, and we did observe with single Q-switched pulses subtle changes in discrimination errors (false positives and misses) and in response times that were not characteristic for the subject. This was especially the case when intense but extremely small, punctate exposures were made within the fovea. Bleeding and involuntary eye movements possibly affected the

ability of even highly motivated animals to consistently maintain the discriminanda on functional rather than irradiated or clouded regions of the fovea. Multiple Q-switched pulses even for these small spot sizes, on the other hand, typically elicited more sizable initial deficits that required longer recovery times. Larger diameter multiple pulses produced even larger visual deficits and required more time for full recovery.

Increasing the power density of individual pulses generally produced longer recovery times, and in some cases, produced prolonged deficits that extended beyond the 30 minute test session. Multiple Q-switched pulses at energy levels 10X below the ED_{50} produced only transient deficits in immediate postexposure acuity. These deficits were reminiscent of those deficits that we observed for long duration exposures (msec time domain) below the ED_{50} or for Q-switched pulses (nsec time domain) above the ED_{50} where neuropathological effects would be expected. However, if the area of retinal exposure was small (50 -100 μ) due to either the number of pulses presented and/or the diameter of the exposure sight, little change was noted to either the animal's immediate or long term postexposure visual acuity regardless of the exposure energy used. Even for initial exposures at energy levels that were significantly above the ED_{50} (10X to 100X), remarkably little decrement in visual acuity was often noted. In several cases single Q-switched pulses of larger retinal diameter (>100 μ) produced more pronounced visual deficits similar in nature to the transient deficits produced by large diameter, longer duration (either msec CW exposures or multiple nsec Q-switched pulses). When significant areas of the fovea were exposed, an immediate drop in baseline photopic acuity resulted and what followed was a gradual recovery that often lasted 45 minutes or longer. Both the magnitude and duration of the observed visual deficits were related to the amount of retinal area involved (exposure spot size) and to the number of Q-switched pulses presented.

With larger spot sizes, the exposure energy clearly influenced the duration of the initial deficit as well as the likelihood of full recovery within the remaining time of the test session. The impact of multiple exposures under this condition often became prolonged and sometimes permanent for Q-switched pulses above the ED_{50}. Unlike msec time domain exposures, no similar cumulative effect has been noted for repeated nsec time domain exposures at energy levels significantly below the ED_{50}. The lack of any corresponding cumulative impact for Q-switched pulses is noteworthy. While high energy exposures often produced transient acuity shifts, our results suggest that for the smallest diameter and shortest duration exposures, the functional criterion may be limited in defining a permanent effect even when minimal neuropathy may be present. We have noted, however, significant initial effects and possibly subtle longer term changes in discrimination errors especially when multiple punctate exposures within the fovea are made. These less conspicuous effects could possibly reflect more global dysfunction when briefly presented discriminable targets fall on "altered" retinal regions. The consequences of repeated exposures

within these transitional energy zones may appear particularly important in understanding these changes. The demonstration of any transitional zone between temporary and permanent functional changes for nsec time domain exposures similar to that found for msec time domain exposures would suggest the possibility of increased susceptibility of exposed tissue to permanent damage, especially in those situations in which brief, but repeated low level energy exposures may occur.

The transient effects observed in this study at energy levels below the ED_{50} and below those that might cause edema suggest that single, isolated Q-switched pulses can have a significant impact on an animal's immediate postexposure acuity even if the consequence is not permanent. The time course of these transients effects suggest reversible receptor or photochemical alterations that may bypass the normal time parameters of visual adaptation. Still unresolved is the possibility that repeated nsec time domain exposures within the same retinal region might ultimately become additive and eventually produce permanent functional changes similar to those that we have demonstrated exist for msec time domain exposures. If this were true, over time these transient visual deficit might blossom into a significant permanent functional loss with minimal initial warning. Such changes would likely not be immediately apparent through ophthalmoscopy but might be observed if visual functioning was carefully tracked.

The energy required to produce a threshold functional deficit for the nonhuman retina in the msec time domain (CW exposures) approximated damage thresholds using morphological criteria and in some cases, especially when using repeated exposures or large spot sizes, was somewhat lower than that found using nonfunctional criteria (30-32). Pathology thresholds for nsec time domain exposures is even lower than for msec time domain exposures and may be the result of higher peak powers produced by these briefer pulses (33). Such concentrations of energy can create, in addition to a thermal component, acoustic damage when it interacts with the retina. In comparison to longer duration exposures, this acoustic or mechanical insult may be sufficient to rupture tissue membranes at much lower energy levels than is possible in the msec time domain. In relation to the function of retinal tissue, Q-switched pulses are deposited within the neural layers of the retina before photoreceptors are normally able to respond. This rapid delivery of light energy could temporarily short circuit the full response of the photoreceptor system and bypass its normal adaptation function. However, because the pulse is still sufficient to cause morphological damage, alterations in permanent visual function might still occur. Because of both its limited temporal and spatial domains, repeated nsec exposures may be required to influence large enough areas necessary to produce a significant overall functional effect.

In previously reported studies using msec time domain exposures (32) larger spot sizes were normally employed and were made even larger due to the impact that involuntary eye movements had on smearing these exposures across even larger retinal regions. Independent of the differences in exposure

energies used, the immediate and often transient acuity deficits that resulted from msec time domain exposures were larger than those shown here using nsec time domain exposures. Given the differences in spatial characteristics of these two types of exposure, repeated exposures over different sessions would more likely irradiate the same retinal regions when large diameter, longer duration (msec time domain) exposures are used. With minimal diameter Q-switched pulses of limited spatial extent, repeated exposures in either the same or different exposure sessions would have a much lower likelihood of exposing the same retinal region. Thus, the lack of any cumulative impact observed in this study at energy densities below the ED_{50} for nsec time domain exposures, but not for the msec time domain exposures, could be explained on the basis of non-overlapping sites and not strictly differences in the delivery of energy over time.

In our previous studies using msec time domain exposures permanent acuity deficits were noted following repetitive exposures at energies below the MPE (34). Recent ophthalmoscopy on one animal suggest that these types of cumulative functional deficits even at levels below the MPE can be associated with distinct pathology in the eye. While in the current study no similar cumulative functional effect was noted for low energy Q-switched pulses a distinct cumulative behavioral effect for small spot exposures was evident for energy densities above the MPE. Similar to lower energy and longer time domain exposures, repetitive high energy Q-switched pulses produced longer and longer recovery times until evidentially a permanent functional deficit was observed. Unlike the msec time domain exposures, however, the size of the initial deficit with repeated exposures did not significantly change when high energy nsec time domain exposures were made. This suggests that even small-diameter, high-energy, Q-switched pulses can produce a significant dazzle effect independent of any permanent change that it might produce. These results may be consistent to other functional studies using slightly different exposure conditions. For example, it has been demonstrated that repeated extended source exposures slightly above the MPE for a single extended source exposure, induce a bullseye maculopathy (35) which imaged confocally and these results suggested a primary or secondary retinal nerve fiber defect (36). However, in this case no permanent loss in high contrast grating acuity was observed. Visual targets in that study did not exceed 20/40 Snellen acuity. The present investigation used Landolt ring targets and animals normally achieved photopic acuity levels better than 20/15. Hence, this study now extends the methodology and data to reveal how repeated exposures to laser irradiation impact high contrast, high resolution visual targets.

Of particular interest in the current study was the consistent temporarily enhancement in acuity (hyperacuity) that followed predictable acuity deficit produced by low energy Q-switched exposures. Hyperacuity was routinely observed following either single or multiple, 0.1 μJ, Q-switched pulses and like

the preceding acuity deficit, this enhancement was also not sustainable. The cause of this hyperacuity is difficult to discern, but it might be significant that it was only obvious with on-axis exposures and with low energy exposures that produced small and transient deficits. A similar enhancement effect might not be expected in the off-axis exposure where the neural networking between cells is different. Exposing the fovea to intense light might eventually disinhibit the areas within and around the central fovea by fatiguing the retina's lateral inhibition mechanisms. The sensitivities and recovery times for this neural inhibitory mechanism and that of the photochemical process in the receptor cell could be different and could possibly account for this apparent enhancement (37).

At the onset of this effort, several hypotheses were made and are now empirically supported. First, light-induced damage to the retina not only disrupts retinal physiology but also function. The type and magnitude of the functional alteration appears related to the location and degree of the retinal insult. Structural damage to photoreceptors should affect an organism's fine resolution capability through changes in the organism's inherent color, brightness, and contrast sensitivities. These changes should be especially distinct if foveal areas are involved. Damage to areas outside the fovea may disrupt scotopic and peripheral vision, but would not be easily detected unless more complex visual field testing are performed. Using our performance paradigm, only foveal damage would disrupt photopic acuity although scattered damage throughout the parafoveal region should increase within session variability. Typically we have defined these parafoveal and peripheral exposures as misses; in reality the animal's retina was likely exposed but not in the region where photopic acuity would be altered. Our off-axis exposures that produced only limited acuity changes support this notion. Second, the size of the retinal area irradiated should directly impact the magnitude of the observed visual deficit. As previously stated, irradiation of very small regions of the fovea still permits a highly motivated observer to develop alternative viewing strategies that could effectively allow him/her to "look" around isolated dysfunctional regions and maintain a high acuity criterion. Larger spot sizes or multiple exposures within the same region would make this strategy less effective. Also, exposing larger retinal zones increase the probability of a "successful" foveal exposure since they irradiate a larger retinal region and therefore increase the probability that at least some portion of the central fovea will be involved. Exposing the animal to a single pulse (nsec duration) of relatively small spot diameter (less than 100 microns) evokes only a small lesion even at the highest power densities and therefore elicits only minimal acuity shifts that might appear transient in nature. Edema, bleeding and other damage and repair mechanisms are often delayed and thus their impact would not be immediately obvious.

Somewhat unexpected was the lack of consistent and large scale deficits when relatively large diameter (100 - 500 μ) single Q-switched pulses were presented. These very brief exposures produced

only small observable deficits for both high or low acuity criterion. It is likely, however, that exposures of this brief duration (15 nsec), did not allow for involuntary eye movements to produce enough "smearing" of the exposure and therefore increased the probability that the image was not consistently centered within the fovea. Hence, below the $ED_{50,}$ this paradigm appeared unable to fully delineate transient acuity deficits in spite of the fact that some temporary or even semi-permanent damage might have occurred. Using more spatially complex targets or more sensitive measures of contrast sensitivity and/or color vision in future studies could delineate subtle functional changes not observed in the current study. Repetitive Q-switched pulses, on the other hand, were shown to summate their individual effects and create significant transient shifts in immediate postexposure acuity even for those energy levels significantly below the MPE. Fewer, larger diameter exposures should produce the same overall effect as would longer duration, single exposures from a CW laser. Furthermore, repeated low energy exposures within the same retinal region even if delayed by hours or days may increase the long-term susceptibility of that particular tissue to insult. If the nature of nsec exposures are consistent with those observed for msec exposures, these individual exposures can be presented beyond the time needed for full functional recovery to any one exposure. In both nsec and msec exposures, we have noted within the transitional zone that repetitive exposures which initially produce only minimal baseline shifts can increase the variability of the animal's postexposure acuity. This more erratic behavior was normally temporary, lasting only several days or weeks and might be the result of ongoing repair mechanisms within the affected tissue. With time, variability should decrease and acuity improve as the repair mechanisms proceed, as surrounding unaltered photoreceptors migrate into the area now devoid of active photoreceptors, and/or as the animal learns to compensate by improving its fixation ability to stabilize the critical features of the target on unaltered portions of the retina.

Shifts in postexposure acuity noted in this study also could be explained by an initial edema within or surrounding the exposed tissue. Swelling of the retina tissue would alter photoreceptor orientation, spacing, and possibly impact neural functioning. These changes could clearly impact the ability of exposed animals to resolve spatial detail. If swelling occurred, the initial acuity deficit would be expected to grow in time, stabilize, and possibly then decrease depending upon the time course of the edema. Combined with ocular clouding due to even minor hemorrhages that could develop from low energy exposures, transient acuity deficits could also have resulted from increased light scatter that created a blurred image within an otherwise intact neural encoding system. As the hemorrhage dissipated over time, acuity would have then returned to normal. These optical changes in image clarity should be more transient than those caused by encoding problems associated with photoreceptor repair.

Even more immediate and transient postexposure acuity changes could be explained by a dazzle effect. Its time course could correspond to the normal regeneration of pigments or could be prolonged depending upon any reversible actinic insult that might also accompany the exposure. Psychological variables associated with even temporary blindness might also adversely impact the organism's normal viewing and decision making strategies. Changes in the ratio of false alarms to correct detection and misses to correct rejections might signal shifts in the organism's confidence level and strategies employed to complete the task. Ultimately, however, in forced-choice tasks where there is a high payoff for positive performance, observers should develop strategies to maximize their perceived rewards. Following laser exposure such strategies should involve altered points of fixation to maximize the use of retinal regions with the highest ongoing sensitivities. Our data clearly support the notion that our animals did engage in defensive behaviors that maximized their existing visual sensitivities since their visual acuity did not drop to zero after exposure but rather quickly stabilized at new levels consistent with the resolution power of the parafovea.

The purpose of this study has been to simulate laser exposures that may be encountered in the field and predict the type of visual performance changes that a solider might experience which could impact the successful completion of a mission. This study has been unique in its ability to generate immediate postexposure visual performance. The paradigm permits the opportunity to examine both short and long term shifts in acuity at and below the ED_{50}. This information may be of significance in training soldiers how to minimize the impact of potentially damaging light. The problems associated with ocular damage on the battlefield clearly extend beyond treatment intervention and should include training strategies for off-axis viewing that might minimize foveal damage and maximize postexposure performance necessary for the successful completion of a visually guided mission. These strategies are important not only for those with pathology but also for those who might be only temporarily disabled by laser irradiation.

Our data may help to further delineate the impact of dazzle, changes in the integration of neural retinal circuits, minute enzyme changes within irradiated tissue, and changes in ocular opacity that might not otherwise be evident with traditional ophthalmoscopic examination. In addition a functional approach to laser safety similar to that used in the current study might be useful in developing visual displays to counter the immediate loss in acuity following exposure. This data should not be inconsistent with the morphological data but may, at time, reveal more subtle effects that could equally degrade visual performance.

Although there already has been extensive research in this area, there is still much more to be accomplished not only to protect human observers from accidental exposures but to prevent

underutilization of lasers because of unrealistic restrictions placed upon their use. Of particular concern remains the adverse consequences produced by repetitive pulses and variations in exposure wavelengths. Equally important is a further elaboration of postexposure visual performance changes using more spatially complex visual tasks that more closely approximate the type of viewing situations that are of military relevance. The typical strategies employed by exposed subjects to compensate for any real or simulated loss in visual functioning could have important training significance for the soldier. Our data continues to support the value of a functional approach in developing more realistic safety standards for viewing laser light. While there are clear differences between the recovery from Q-switched and CW laser exposures, especially within the transitional zone between temporarily and permanent visual loss, the current study demonstrates that flash effects may be produced by low level Q-switched pulses even at levels where no tissue damage or edema would be expected. These results suggest, in addition to tissue damage, important photochemical and neural processes may also play a role in developing safety standards and guidelines for those individuals working around lasers either in the laboratory, in training, or in the workplace.

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Appendix A

List of Publications / Meeting Abstracts

Zwick, H., Robbins, D.O., Reynolds, S.B., Lund, D.J., Schuschereba, S.T., Long, R.C. and Nawim, M. Effects of small spot foveal exposure on spatial vision and ERG spectral sensitivity. in *Colour Vision Deficiencies X* edited by Drum, B., Moreland, J.D., and Serra, A. Kluwer Academic Publishers, Dordrecht, 581-597 (1991).

Zwick, H., Gagliano, D.A., Gunzenhauser, J., and Robbins, D.O. Spatial Visual Function Loss in Accidental Human Laser Exposure. *Neuroscience Abstracts*. (1992)

Zwick, H., Gagliano, D.A., Gunzenhauser, J., and Robbins, D.O. *Spatial visual function loss in accidental human laser exposure*. Paper presented at the Annual Meetings of the Society for Neuroscience, Los Angeles, CA, October 1992.

Gunzenhauser, J., Zwick, H. Molchany, J., and Robbins, D.O. *Comparison of visual recognition thresholds for normal and degraded images*. Paper presented at the Annual Meetings of the Association for Research in Vision and Ophthalmology, Sarasota, FL, May 1992.

Robbins, D.O. and Zwick, H. Subthreshold functional additivity occurring at the transition zone between temporary and permanent laser-induced visual loss. *Laser-Inflicted Eye Injuries: Epidemiology, Prevention, and Treatment, SPIE, 2674* 44-52 (1996)

Robbins, D.O. and Zwick, H. Subthreshold functional additivity occurring at the transition zone between temporary and permanent laser-induced visual loss. Paper presented at the SPIE International Society for Optical Engineering, San Jose, CA January 1996.

Robbins, D.O. Zwick, H., Bearden, B.D., Evans, B.S., and Stuck, B.E. Visual Acuity Changes in Rhesus Following Low Level Q-Switched Exposures. *Laser and Nonchoerent Light Ocular Effects: Epidemiology, Prevention, and Treatment. SPIE, BiOS '97* (1997)

Robbins, D.O. Zwick, H., Bearden, B.D., Evans, B.S., and Stuck, B.E. Visual Acuity Changes in Rhesus Following Low Level Q-Switched Exposures. Paper presented at the SPIE International Society for Optical Engineering, San Jose, CA January 1997.

Robbins, D.O., Zwick, H., Jacobsen, D.R., Evans, B.S., and Stuck, B.E. Spatial and Temporal Effects of Q-Switched Pulse Exposures on Visual Acuity. Paper presented at the Association for Research in Vision and Ophthalmology (ARVO) annual meetings, Fort Lauderdale, FL May 1997.

Appendix B

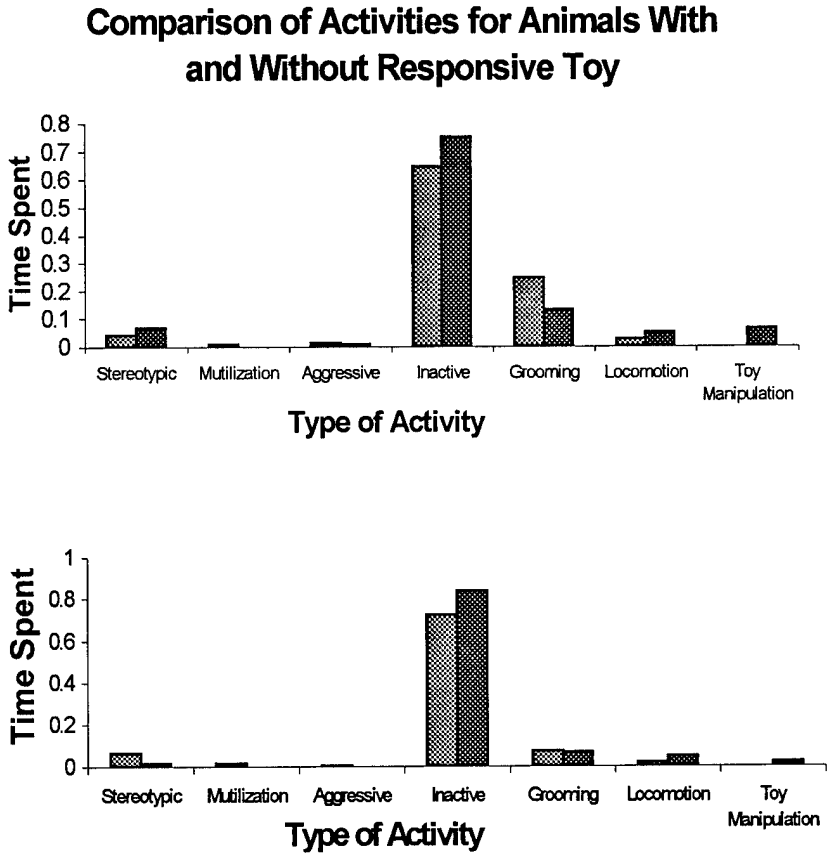
Personnel

Name	Title	Dates of Employment
David O. Robbins, Ph.D.	Principle Investigator	9 /92 - 8/97
Thomas L. Dillman, Ph.D.	Research Physicist	9/92 - 7/97
Brenda S. Evans, D.V.M.	Associate Research Director	11/92 - 7/97
Ronald Bell, D.V.M., M.S.	Attending Veterinarian	9/92 - 7/97
Bradley Bearden, B.A.	Research Assistant	8/96 - 8/97
David R. Jacobsen, B.A.	Research Assistant	
John Wiebe	Animal Caretaker	9/92 - 8/93
Natasha Shah	Animal Caretaker	9/92 - 5/93
Marie Wiebe	Animal Caretaker	9/92 - 8/97
Robert Fryer	Animal Caretaker	8/93 - 5/94
Bradley Bearden	Animal Caretaker	10/95 - 8/96
Nicole Detling	Animal Caretaker	8/96 - 7/97
Sonya M. Kahlenberg	Animal Caretaker	9/96 - 7/97

Appendix C

Animal Enrichment

Consistent with current USDA regulations (Authority: 7 U.S.C. 2131-2157; 7 CFR 2.17, 2.51, and 371.2g) and federal and local IACUC specifications on primate enrichment, all animals were assessed on a daily basis as to their psychological well being and every attempt was made to provide these animals with an enriching experience while housed in our laboratory. As required, an enrichment protocol was been established for each animal and a daily record maintained of the animal's exposure and reaction to various enrichment activities. Quantitative analyses of the animals' responses to enrichment activities were made from videotape recordings to further evaluate the appropriateness of each activity for each animal. A variety of enrichment activities were established and they included: TV viewing, videotapes of nature scenes, music, food puzzles, interactive play toys, ropes, mirrors, sticks, foraging for food, and frequent human interactions. Time budgets were established for each animal and each animal's behavior was divided into thirteen different categories: foraging, grooming, inactive, TV Viewing, locomotion, stereotypic, aggressive, sexual, consumption, vocalization, self aggressive, manipulation of feces and miscellaneous. These thirteen behaviors were summarized into two categories described as positive and negative behaviors. The impact of different enrichment activities was analyzed in terms of their ability to reduce negative behaviors and to increase the variety and duration of positive behaviors. We also assessed the degree to which various toys, some which that were responsive to the animal's manipulations, impacted the rate at which an animal's interest in a particular toy changed over time. Interest was defined as the total time in which the animal spent holding and/or manipulating a specific object. Typically animals habituated rapidly to novel devices placed within their cage even though some animals often became possessive of specific toys or small objects and would become aggressive if these items were removed from the cage. In the later case these animals would handle the objects only when a stranger entered the room or when an animal caretaker attempted to remove the objects. Typical time budget records that were kept for our animals are shown in Figures 26A and 26B for two animals. In this example, each animal was given a commercially available infant's interactive toy. Pushing different buttons on the face of the toy resulted in music and/or flashing. One toy was made inoperative and given to one of the two animals. The other operative toy was placed on the side of a second animal's cage, clearly in view for the animal with the inoperative toy. In Figure 26A, the responsive toy was given to an animal named Sid and both Sid and Jim's behavior measured over time. Neither animal spent a significant amount of time manipulating either toy in spite of numerous attempts to reposition the toys on the animals' cages, and for the most part both animals were largely inactive during the two hour test period. In Figure



Figures 26A and B. Comparison of Activities for Animals With and Without Responsive Toys. In Figure 26A an animal named Jim was given a unresponsive toy while another animal, Sid, was given the same toy but one that responded with lights and sounds to his touching specific buttons on the face of the toy. The darker bars represent the different activities of Sid over a two hour sampling period. The lighter bars represent the analysis of the same activities for Jim over the same time period. Both animals could see and hear each other and the other's toy. In Figure 26B the same two animals were observed but this time Jim had the responsive toy and Sid the unresponsive one.

26B, the toys were switched (operative vs. inoperative) and again little difference was observed between behaviors of the two animals. Similar data was collected for other animals using different infant toys and times of presentation. Overall those enrichment objects that were the most primitive in nature often captured the curiosity of the animal more than those were more elaborate and/or marketed for humans. A stick, piece of rope, piece of tape were more effective in reducing negative behaviors than a TV, food puzzle, or battery powered toys.