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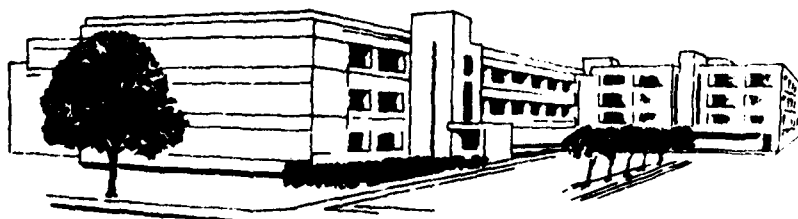
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Biological Research in Support of Project *MILES*--Lund *et al*

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determined for Nd:YAG lasers at pulse repetition frequencies (PRF) of 10 and 1000 Hz, for a frequency doubled Nd:YAG laser (532 nm) at a PRF of 10 Hz, for an Er:YLF laser (850 nm) at a PRF of 10 Hz, and for a GaAs laser (860 nm) at a PRF of 120 kHz. Exposure durations ranged from 20 ns (single pulse) to 1000 s, and the number of pulses per exposure ranged from 1 to 960,000. In all cases it was shown that the ED_{50} per pulse for N pulses equaled $N^{-1/4}$ times the ED_{50} for a single pulse. The ED_{50} s for the production of retinal lesions were determined for several wavelengths from 532 nm to 1330 nm. It was shown that the ED_{50} for Er:YLF laser irradiation at 850 nm was reduced when compared to the ED_{50} s for Ruby laser irradiation (694.3 nm) and Nd:YAG laser irradiation (1064 nm). An explanation was sought for a subtle retinal effect called "retinal clouding" induced by exposure to low level GaAs laser irradiation. Histopathological evaluation of exposed retinal tissue did not provide the explanation. Parallel experiments at other agencies did not confirm the LAIR observation of retinal clouding. The ocular effects were studied of lasers operating at infrared wavelengths of reduced ocular hazard. ED_{50} s for the production of corneal lesions were obtained for a Nd:YAG laser (1330 nm), an ER:glass laser (1540 nm), and a Ho:YLF laser (2060 nm). It was shown that the ocular damage threshold for lasers emitting at wavelengths greater than 1400 nm can be predicted from consideration of the optical absorption of physiologic saline.

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ABSTRACT

The MILES laser transmitter is a gallium arsenide (GaAs) laser system which emits pulse modulated radiation at a wavelength of 900 nm. The use of this device necessitates a high probability of intrabeam ocular exposure. An understanding of the ocular effects of the MILES laser is required so that its safe use can be assured. Because the MILES laser is a pulse modulated device, the additivity of effect for repetitive pulse exposure was evaluated. The ED₅₀s for the production of retinal lesions by repetitive pulse exposure were determined for Nd:YAG lasers at pulse repetition frequencies (PRF) of 10 and 1000 Hz, for a frequency doubled Nd:YAG laser (532 nm) at a PRF of 10 Hz, for an Er:YLF laser (850 nm) at a PRF of 10 Hz, and for a GaAs laser (860 nm) at a PRF of 120 kHz. Exposure durations ranged from 20 ns (single pulse) to 1000 s, and the number of pulses per exposure ranged from 1 to 960,000. In all cases it was shown that the ED₅₀ per pulse for N pulses equaled $N^{-1/4}$ times the ED₅₀ for a single pulse. The ED₅₀s for the production of retinal lesions were determined for several wavelengths from 532 nm to 1330 nm. It was shown that the ED₅₀ for Er:YLF laser irradiation at 850 nm was reduced when compared to the ED₅₀s for Ruby laser irradiation (694.3 nm) and Nd:YAG laser irradiation (1064 nm). An explanation was sought for a subtle retinal effect called "retinal clouding" induced by exposure to low level GaAs laser irradiation. Histopathological evaluation of exposed retinal tissue did not provide the explanation. Parallel experiments at other agencies did not confirm the LAIR observation of retinal clouding. The ocular effects were studied of lasers operating at infrared wavelengths of reduced ocular hazard. ED₅₀s for the production of corneal lesions were obtained for a Nd:YAG laser (1330 nm), an Er:glass laser (1540 nm), and a Ho:YLF laser (2060 nm). It was shown that the ocular damage threshold for lasers emitting at wavelengths greater than 1400 nm can be predicted from consideration of the optical absorption of physiologic saline.

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The MILES system incorporates the first military laser device designed with the intention of subjecting friendly personnel to laser irradiation. The use of this device in a training scenario will necessitate a high probability of intrabeam ocular exposure for a large number of trainees. Thus, the stringent requirement exists for a complete understanding of the ocular effects of the MILES laser transmitter so that its safe use can be assured.

The MILES laser transmitter is a gallium arsenide (GaAs) laser system with an emission wavelength of 900 nm. The output consists of a pulse amplitude and pulse interval modulated train of pulses at an average pulse repetition frequency (PRF) of 1632 Hz. The pulse duration is 60 ns. The effort to delineate the ocular hazard of this device has involved the study of several parameters affecting the interaction of laser radiation with ocular tissue (1). These parameters included wavelength, retinal image diameter, and exposure to repetitive pulses. The studies also included exposure of ocular tissue to prototype and engineering development versions of the MILES M-16 transmitter. The studies resulted in a better understanding of the dose required for creation of an ophthalmoscopically visible retinal lesion after irradiation by a laser operating in the MILES transmitter mode, and also resulted in a recommendation for alteration of the provisions of AR 40-46 (2) and TB MED 279 (3) which govern the maximum permissible exposure (MPE) to repetitive pulse laser irradiation (4). A disquieting result of these studies was the observation of a subtle retinal effect after exposure to GaAs laser irradiation at doses near the MPE. This retinal effect was termed "retinal clouding" (5).

Our studies indicated that the current safety standards might be too conservative when applied to the MILES laser transmitter, and that reevaluation of the standards was desirable. Consequently, the US Army Environmental Hygiene Agency provided a list of data that were required before such a reevaluation could be considered (6). The needed data were:

a. Threshold burn data from laser pulse trains lasting from 10 s to 1000 s at repetition rates from 1 Hz to 2000 Hz.

b. Ultrastructural damage data for very short pulse durations (i.e., less than 1 μ s for near infrared wavelengths.)

c. Threshold burn data from lasers closer to the GaAs wavelength for a variety of pulse rates and pulse train durations (i.e., PRF ranging from 1 Hz to 3000 Hz and pulse trains lasting from 1 s to 1000 s).

d. Data leading to an explanation of the "retinal clouding" effect from GaAs laser exposure.

An experimental program was designed to provide these data. The results are reported here. Also reported are data concerning the ocular effects of lasers operating in the infrared wavelength region of reduced ocular hazard. This report is presented in four sections.

- I - REPETITIVE PULSE LASERS
- II - WAVELENGTH EFFECTS
- III - LOW LEVEL EFFECTS
- IV - REDUCED OCULAR HAZARD LASERS

I - REPETITIVE PULSE LASERS

INTRODUCTION

Current safety standards provide for a decrease in the maximum permissible exposure (MPE) per pulse for exposure to repetitive pulse laser irradiation. For laser pulses of duration less than 10 μ s, the degree of decrease is obtained by multiplying the single pulse MPE by a correction factor, C_p . Presently, C_p is dependent only on the pulse repetition frequency (PRF), having a value of 1 at 1 Hz, decreasing to 0.06 at 1000 Hz, and remaining at 0.06 for all PRFs greater than 1000 Hz. Stuck et al (4) have provided evidence that, for a broad range of PRFs, C_p should not be a function of PRF, but should depend only on the number (N) of pulses in the exposure. They recommended a new relationship, $C_p = N^{-1/4}$, for the MPE derating factor for repetitive pulse exposure. This approach is attractive in that it is functionally identical to the computational method known as total on time pulse (TOTP) prescribed for determination of the MPE reduction factor for repetitive exposure to pulse durations greater than 10 μ s. The research reported here was performed to extend the data base necessary to determine the correct form of C_p .

PROCEDURE

Dose response data were obtained for exposure to repetitive pulse trains ranging in duration from 20 ns (single pulse) to 1000 s. The lasers used in these experiments were:

Laser	Wavelength	PRF	Pulse duration
Nd:YAG	1064 nm	10 Hz	20 ns
Nd:YAG	1064 nm	1000 Hz	180 ns
Nd:YAG	532 nm	10 Hz	140 ns
Er:YLF	850 nm	10 Hz	180 ns
GaAs	860 nm	120 kHz	500 ns

The 10 Hz Nd:YAG laser was a flashlamp pumped, pockel cell Q-switched device. The exit beam was nonuniform in cross section, therefore an external aperture was used to select a uniform portion of the beam. The transmitted beam was approximately gaussian with a beam divergence of 1 mr. The 1000 Hz Nd:YAG laser was a continuously pumped, acousto-optic Q-switched device. This laser operated in the TEM₀₀ mode, with a beam divergence of 0.8 mr. The frequency doubled Nd:YAG laser was also a continuously pumped acousto-optic Q-switched device with an intracavity frequency doubler. This laser operated in the TEM₀₀ mode with a beam divergence of 1 mr. The Er:YLF laser was a flashlamp-pumped, pockel cell Q-switched device operating in the TEM₀₀ mode. The beam divergence was 0.7 mr. Each of the lasers produced a beam diameter of 3 mm at the cornea. The GaAs laser was a

single diode operated at liquid nitrogen temperature (40°K). The characteristics of the GaAs laser are fully detailed in reference 27.

The exposure configuration was similar for all lasers (Figure 1). A dichroic beamsplitter having high reflectivity at the laser wavelength and high visual transmittance directed the laser beam into the eye of the monkey while permitting continuous viewing of the exposure site via fundus camera. The mirror and fundus camera were aligned so that the laser beam passed through the center of the ocular pupil and coincided with the camera crosshairs at the retina, thus facilitating selection and location of the exposure site. A constant proportion of the beam energy was diverted into a reference detector for dosimetry. The energy at this detector was correlated to the energy entering the eye by placing a calibrated EG&G 580 radiometer at the eye position and determining the ratio of the energy received by the two detectors. The exposure duration was controlled by an electronic shutter, and neutral density filters were used to attenuate the beam energy to the desired exposure level.

The animals used in these experiments were rhesus monkeys. The animals were anesthetized and the ocular pupils dilated. One eye per animal in 4 to 6 animals were exposed to determine each ED₅₀. For exposures of 10 s or longer, the eyes were immobilized by a retrobulbar injection of lidocaine. The eye was held open by a lid speculum during exposure, and corneal clarity maintained by periodic irrigation with normal saline. For exposure durations of 100 s or less, 25 to 36 exposures were placed in a rectangular array in the extramacular retina, including one row of marker burns for subsequent location. Only four 1000 s exposures were attempted at any one session because of difficulty in maintaining corneal clarity. The exposure sites were examined via ophthalmoscope 1 h after exposure. The criterion for retinal damage was the observation of a lesion at this examination. The data of 100 to 150 exposures were evaluated by probit analysis to determine the ED₅₀ for each exposure condition. The ED₅₀ is defined as that dose having a 50% probability of producing a criterion response.

RESULTS

The ED_{50} and associated 95% confidence limits determined for ocular exposure to repetitive pulse laser irradiation are presented in Tables 1-5. In these tables, the following definitions apply:

PRF = pulse repetition frequency

t = duration of each pulse in the train

T = total exposure duration

N = number of pulses per exposure ($N = \text{PRF} \times T$)

ED_{50} = ED_{50} expressed as total intraocular energy (TIE) per exposure

ED_{50}/pulse = ED_{50} expressed as TIE/pulse

($ED_{50}/\text{pulse} = ED_{50}/N$)

95% limits = 95% confidence limits for the ED_{50}/pulse

TABLE 1

Nd:YAG - 1064 nm
PRF = 10 Hz t = 20 ns

T	N	ED_{50} (μJ)	ED_{50}/pulse (μJ)	95% limit
20 ns	1	99	99	83-120
1 s	10	389	39	32-47
10 s	100	3410	34	29-41
100 s	1000	18300	18	17-20
1000 s	10000	42800	4.3	2.9-6.4

TABLE 2

Nd:YAG - 1064 nm
PRF = 10 Hz t = 20 ns

T	N	ED_{50} (μJ)	ED_{50}/pulse (μJ)	95% limits
180 ns	1	136	136	107-173
2 ms	2	160	80	67-95
3 ms	3	153	51	40-65
6 ms	6	330	55	46-66
74 ms	74	1213	16	13-21
1 s	1000	10100	10	8.3-12
10 s	10000	115000	11	9.5-14
100 s	100000	330000	3.3	2.4-4.4

TABLE 3

Frequency Doubled Nd:YAG - 532 nm
PRF = 10 Hz $t = 140$ ns

T	N	ED ₅₀ (μ J)	ED ₅₀ /pulse (μ J)	95% limits
140 ns	1	2.8	2.8	2.5-3.2
1 s	10	16	1.6	1.3-2.0
10 s	100	107	1.1	0.8-1.5

TABLE 4

Er:YLF - 850 nm
PRF = 10 Hz $t = 180$ ns

T	N	ED ₅₀ (μ J)	ED ₅₀ /pulse (μ J)	95% limits
180 ns	1	12	12	9.5-15.1
1 s	10	59	5.9	4.7-7.5
10 s	100	270	2.7	2.0-3.5
100 s	1000	1200	1.2	0.8-1.7

TABLE 5

GaAs - 860 nm
PRF = 120 Hz $t = 500$ ns

T (s)	N	ED ₅₀ (mJ)	ED ₅₀ /pulse (μ J)
0.125	15000	7	0.46
0.5	60000	19	0.32
1.0	120000	39	0.33
8.0	960000	155	0.16

These data are shown in graphic form in Figures 3-4 which present the ED₅₀/pulse as a function of N.

DISCUSSION

Stuck et al (4) gathered from the literature all available ocular damage threshold data for repetitive pulse exposures. From these data, an empirical relationship was derived which equated the ED_{50} /pulse in a pulse train to the ED_{50} for a single pulse and the number of pulses in the pulse train. The relationship

$$ED_{50}/\text{pulse} = KN^{-1/4}$$

(where K is the ED_{50} for a single pulse of duration t) is valid for all of the repetitive pulse data examined. However, no data existed for large N or for long exposure durations. The experiment reported herein extended the data base to include data for long exposures and large N . It is evident that the empirical relationship continued to be valid for $T = 1000$ s and $N = 960000$ pulses.

It must be noted, however, that all the data used to derive the empirical relationship and all the repetitive pulse data reported herein were generated with the laser beam collimated to produce a minimal retinal irradiance diameter. Recently, Greiss et al (8) have reported data concerning the effects of ocular exposure to repetitive pulse Nd:YAG and frequency doubled Nd:YAG laser irradiation. Their data for minimal spot irradiation agree well with the data of this report. They also reported data for large retinal irradiation diameter exposure which show a different relationship between the ED_{50} /pulse and the number of pulses. Those data, in fact, indicate that the ED_{50} /pulse for large retinal irradiance diameter is a constant, independent of the number of pulses in the exposure. A second set of data for large retinal irradiance diameter exposure to repetitive pulse lasers has been reported by Walkenbach (9). His data, in direct contradiction to the data of Greiss et al (8), indicate that the ED_{50} /pulse equals $1/N$ times the ED_{50} for a single pulse. The large retinal spot dose response data are shown in Figure 5. It must be concluded that the pulse additivity effects for large retinal irradiance diameter exposure are as yet undetermined.

II - WAVELENGTH EFFECTS

INTRODUCTION

The MILES GaAs transmitter emits at 900 nm, a wavelength for which little bioeffects data exist. The 250 nm and 860 nm data presented in SECTION I of this report are the only available data concerning the ED_{50} for laser induced ocular damage between the wavelengths of 700 nm and 1000 nm. One is therefore compelled to estimate the ED_{50} for ocular damage at 900 nm by considering the data obtained at other wavelengths. For this purpose, dose response data for ocular exposure to laser irradiation have been obtained at wavelengths of 532 nm, 600 nm, 694 nm, 850 nm, 1064 nm, and 1330 nm. These data have a common genesis in that all were obtained for single short pulse exposure in the extramacular retina, all dosimetry and beam characterizations were performed by one individual, and all exposure placements and damage determinations were performed by one individual.

PROCEDURE

The 532 nm, 850 nm, and 1064 nm data are those ED_{50} s reported in SECTION I for single pulse exposure to the frequency doubled Nd:YAG, the Er:YLF, and the 1000 Hz Nd:YAG. The 694.3 nm data were obtained with a Q-switched ruby laser having a pulse duration of 20 ns. The details of that experiment are reported in reference 10. The 1330 nm data were obtained with a Nd:YAG laser modified to emit the 1319 and 1338 nm lines available from that material. The 650 μ s pulse duration of the 1330 nm laser was longer than for the other lasers employed herein. A full description of the 1330 nm Nd:YAG experiment is included in SECTION IV of this report. The 600 nm data were obtained with a flashlamp pumped Rhodamine 6G dye laser. The pulse duration of that laser was 400 ns, the beam divergence was 2.5 mr, and the beam diameter at the eye was 4 mm. The exposure configuration was essentially the same as that shown in Figure 1. Animal handling, exposure placement, and data collection and processing were as described in SECTION I.

RESULTS

Table 6 and Figure 6 present the data from these experiments.

TABLE 6
Wavelength Dependence of ED₅₀

Laser	Wavelength (nm)	Pulse Duration	ED ₅₀	95% limits
Nd:YAG	532	140 ns	2.8 μ J	2.5-3.1
R6G Dye	600	400 ns	5.2 μ J	4.3-6.2
RUBY	694.3	20 ns	17.5 μ J	...
Er:YLF	850	180 ns	12.0 μ J	9.5-15.1
Nd:YAG	1064	20 ns	99.0 μ J	83-120
Nd:YAG	1318&1338	650 μ s	356.0 mJ	323-392

DISCUSSION

It is evident that there is a dip in the ED₅₀ in the 800 to 900 nm region (Figure 6); that is, the ED₅₀ at 850 nm is lower than the expected value obtained by interpolation between 694.3 nm and 1064 nm. This dip is, however, based on a single data point, which leaves doubt about its validity. Two other sets of data exist which tend to confirm the decreased ED₅₀ near 850 nm. Ham et al (11) determined the ED₅₀ for retinal damage for exposure to narrow band filtered radiation from a xenon lamp at several wavelengths from 450 nm to 860 nm. The exposure duration for that experiment was 100 s, and the retinal irradiance diameter was 500 μ . These data are also shown on Figure 6. The ED₅₀s are considerably higher than those obtained for the laser exposures as would be expected because of the difference in exposure parameters. However, the data reported by Ham et al (11) do show a reduction of ED₅₀ at 860 nm, corresponding to the depression at 850 nm for the laser exposures. Another estimate of the ED₅₀ at 850 nm can be obtained from the 120 kHz GaAs data in Table 5. If

$$ED_{50}/\text{pulse} = ED_{50}(\text{single pulse}) \times N^{-1/4}$$

for those data, then the ED₅₀ for a single pulse must be 5 μ J. Again, this implies a reduced ED₅₀ at 860 nm. Verification of the wavelength dependence of ED₅₀ in this spectral region will require determination of the ED₅₀ at several wavelengths between 700 nm and 1000 nm.

The significance of the wavelength dependence of ED₅₀ is shown in Figure 7, which compares the bioeffects data to the MPE as provided by TB MED 279. TB MED 279 determines the MPE for wavelengths between 700 nm and 1060 nm by application of the factor C_A which is a straight line interpolation on a semilogarithmic scale. This wavelength dependency is compared to the ocular damage thresholds for 6943 nm, 850 nm, and 1060 nm (Figure 7). It can be seen that the

safety standard overestimates the damage threshold at 850 nm, that is, the ED_{50} at 850 nm is lower than predicted from the straight line interpolation from the ED_{50} at 6943 nm to the ED_{50} at 1060 nm. As a result, the safety margin at 850 nm is lower than that at 1060 nm by a factor of 3.

The preceding sections have described the additivity effects of repetitive pulse laser exposure and reported ocular damage threshold measurements for laser wavelengths near the GaAs laser emission wavelength. A relationship between the ED_{50} /pulse and the number of pulses in the exposure has been obtained and verified, resulting in a recommendation that TBMED 279 be modified by setting the repetitive pulse factor $C_p = N^{-1/4}$. It has been shown that TBMED 279 provides a reduced safety margin at 850nm as compared to the safety margin at 700 nm and 1060 nm. Figure 8 compares the emission energy of the MILES M-16 transmitter to pertinent biological data, to the MPE as determined from the current provisions of TBMED 279, and to the MPE as determined by setting $C_p = N^{-1/4}$. The MILES M-16 transmitter data points are the energy/near-miss-pulse for $N=132$ (single round) and for $N=720$ (full clip, automatic mode). The production model M-16 transmitters are reported to have greater pulse energy than the engineering development model evaluated at LAIR (12). In all cases, the pulse energy of the M-16 transmitter are at or above the MPE determined by either method. However, a safety margin of 40 is indicated between the MILES laser output and the best available ocular bioeffects data.

III-LOW LEVEL EFFECTS

INTRODUCTION

LAIR investigators reported the observation of a subtle retinal alteration after exposure to repetitive pulse GaAs laser irradiation at doses considerably below the estimated ED₅₀. These alterations, which were called "retinal clouding" (5), did not have the appearance of a typical retinal lesion, but rather created the impression of a slight difference of reflectivity at the exposure site. They were observed visually, via fundus camera or ophthalmoscope. All efforts to photograph the alterations, using standard color or monochrome film, fluorescein angiography, and spectrally resolved photography were negative. Visual observation of the alterations can be tenuous, as demonstrated in a blind experiment performed at LAIR. One investigator placed four GaAs laser exposures in a well-defined area of a clear rhesus retina, and carefully marked the exposure sites on a fundus photograph. He observed clouding at all four exposure sites. Three other observers were directed to the exposed area of the retina and given unmarked fundus photographs upon which to record their observations. None of these observers were able to locate correctly any of the exposure sites. When given the exact location of the exposures, one observer saw clouding at two of the sites. The other observers saw nothing. The 10 W MILES prototype laser was used in this experiment.

In a further effort to understand the nature of the retinal clouding phenomenon, histological evaluation of retinal tissue exposed to the GaAs laser was performed by using light and electron microscopy.

PROCEDURE

Rhesus monkeys were used in this experiment. The animals were anesthetized in preparation for the exposures and the pupils dilated. Marker lesions were placed in the retina with a Nd:YAG laser to facilitate location of the GaAs exposure sites. The laser source for the GaAs exposures was MILES ED M-16 transmitter SN 26. Each exposure consisted of repeated rounds with minimum delay between rounds, producing an essentially continuous pulse train. The number of rounds per exposure ranged from 10 to 100. The duration of a single round was about 0.5 s. Thus the exposure durations ranged from 5 s to 50 s. The animals were sacrificed two hours after exposure and both eyes enucleated. The eyes were fixed by immersion at room temperature in 3% glutaraldehyde in 0.1 M phosphate buffer. Processing of tissue for light and electron microscopy was done in the usual manner with embedding in epon/araldite.

RESULTS

During retinal tissue dissection, a block containing a 100 round exposure site was placed on edge and viewed in cross section. A noticeable opacity in the photoreceptor layer at the exposure site was observed. Subsequent light and electron microscopy did not show any obvious tissue or cellular morphological differences when compared to unexposed control tissue. This opacity could have been due to differences in the density of tissue fluids at the exposed site with no detectable cellular alterations at these levels of investigation. Light photomicrographs showed no significant differences between exposed and control areas for all samples of tissue. Electron microscopy showed no discernible cell or organelle changes at the exposure sites. Preparation and fixation artifacts, such as vacuoles in the pigment epithelium and swollen mitochondria, were seen in samples from both exposed and unexposed areas. Mitochondria in cone inner segments appeared to have been more fixation sensitive than those in neighboring rod inner segments. Figures 9-18 show representative electron photomicrographs of exposed and normal retinal tissue.

DISCUSSION

The results of light and electron microscope histology performed at LAIR, disclosed that no significant differences between the exposed and control areas of retina after exposure to the MILES V-16 transmitter. At the exposure levels obtained from this device, no ultrastructural alterations were produced in the retina.

In pursuit of confirmation of retinal clouding, experiments were performed at USAFSAM by Zuclich et al (13) and at the Virginia Commonwealth University (VCU) by Ham et al (11) which approximate the conditions producing retinal clouding at LAIR. The parameters of each exposure configuration used are given in Tables 7-9. The following definitions apply.

- PRF = pulse repetition frequency
- t = duration of each pulse in the pulse train
- Q = energy of each pulse in the train
- P_p = peak power of a pulse
- P_a = average power of the pulse train
- Θ = divergence angle of the laser beam
- D = dimension of the retinal irradiance area
- T = total duration of the exposure

TABLE 7

MILES ED M-16 Transmitters

Agency:	LAIR	LAIR	USAFSAM
Device:	SN49	SN26	SN11
<i>Characteristics:</i>			
Wavelength	900 nm	894 nm	900 nm
PRF	1632 Hz	1632 Hz	1632 Hz
t	60 ns	60 ns	150 ns
Q	0.083 μ J	0.070 μ J	0.078 μ J
P _p	1.38 W	1.17 W	0.52 W
P _a	0.135 mW	0.114 mW	0.125 mW
O	0.2x2 mr	0.2x1.8 mr	0.3x2.2 mr
D	2.7x27 μ	2.7x24 μ	4x30 μ
T	2-30 s	30-600 s	1-750 s

TABLE 8

Pulsed GaAs

Agency:	LAIR	VCU
Device:	1W MILES prototype	RCA SG-2007
<i>Characteristics:</i>		
Wavelength	899 nm	904 nm
PRF	1600 Hz	1700 Hz
t	112 ns	100 ns
Q	0.021 μ J	1.08 μ J
P _p	0.18 W	10.8 W
P _a	0.034 mW	1.84 mW
O	2x2.2mr	6x40 mr
D	27x29 μ	81x545 μ
T	1-90 s	10-1000 s

TABLE 9

GaAlAs Lasers

Agency:	LAIR	VCU	VCU
Device:	LDL LCW-10	RCA C30127	RCA C30127
<i>Characteristics:</i>			
Wavelength	883 nm	820 nm	820 nm
PRF	...	...	1600 Hz
t	continuous	continuous	100 ns
Q	...	...	4 μ J
P _p	...	...	40 W
P _a	10 mW	7.1 mW	6.4 mW
O	0.65x4.8 mr	8.7x58 mr	8.7x58 mr
D	8.8x65 μ	117x780 μ	117x780 μ
T	30 s	8 ms-1000 s	8 ms-1000 s
ED ₅₀	7.7 mW		

Zuclich et al (13) irradiated the eyes of 12 rhesus monkeys and 2 cynomolgus monkeys for a total of several hundred exposures in the macular and extramacular retina. They examined the retinas at 1, 24, 48, 72, and 120 h after exposure. No visible evidence of retinal alteration was seen at any examination. One animal was sacrificed to study the exposure sites by light microscopy. No morphology was seen. The USAFSAM experiment (13) differed from the LAIR experiment in one respect. At LAIR, the retina was continuously observed during the exposures. At USAFSAM the retina was not observed during the exposures.

Ham et al (11) irradiated a total of 14 rhesus monkeys to the laser devices tabulated above. Half the eyes in each experiment were exposed with the fundus camera illumination light on and half with the light off. They examined the retinas at 1, 24, and 48 h after exposure. No retinal alterations were seen at any examination. No histopathology was attempted. The significant factor in the VCU experiment was the use of a large retinal irradiance area which reduced the retinal irradiance. Even though their pulsed GaAs laser produced higher average power, because of the retinal irradiance area difference, the retinal irradiance produced was less than obtained with the 1 W MILES prototype. It should be noted that, had they collimated the pulsed GaAlAs laser beam for minimal retinal spot size, they would undoubtedly have produced frank retinal lesions for the longer exposure times with the pulse energy available.

IV - REDUCED OCULAR HAZARD LASERS

INTRODUCTION

The Army has a strong interest in the development of lasers presenting a reduced ocular hazard for training purposes. In the visible and near infrared region of the spectrum, collimated laser radiation is transmitted by the ocular media and focused to a small area on the retina. Consequently, the retinal irradiance is several orders of magnitude greater than that incident on the cornea, and the total intraocular energy required to produce a retinal lesion is small. In the spectral region near and beyond 1400 nm, the outer ocular structures begin to absorb incident radiation. As the laser beam passes from the cornea to the retina, energy is lost because the tissues of the eye absorb the laser radiation, reducing the total energy reaching the retina. The irradiance at the retina is less than that at the cornea despite the fact that the irradiance diameter is smaller at the retina. For equal incident energy, the corneal irradiance is much less than the visible wavelength retinal irradiance. Lasers that operate in the spectral region of high pre-retinal ocular absorption present a reduced ocular hazard. The ED₅₀ for ocular damage was determined for three lasers which emit in the infrared region of high ocular absorbance. These were a Ho:YLF laser emitting at 2060 nm, a Er:Glass laser emitting at 1540 nm, and a Nd:YAG laser emitting simultaneously at 1313 nm and 1338 nm.

PROCEDURE

Corneal damage thresholds were determined for the following laser wavelengths and exposure durations:

Laser	Wavelength	Exposure duration
Nd:YAG	1318&1338 nm	250 μ s
Er:Glass	1540 nm	930 μ s
Ho:YLF	2060 nm	100 μ s
Ho:YLF	2060 nm	42 ns

These experiments are detailed in reference 14. A system for determination of corneal damage thresholds was assembled which provided for dosimetry and beam attenuation and focusing to produce the required corneal irradiance (Figure 19). The beam profile at the corneal plane was measured to allow computation of the peak corneal irradiance. The damage criterion was the presence of corneal alteration visible via slit lamp biomicroscope 1 h after exposure.

The retinal damage threshold for the Nd:YAG laser emitting at 1318 and 1338 nm was determined. The ocular absorption for these wavelengths provides significant attenuation of radiation reaching the retina. For small corneal beam diameters, the corneal damage

threshold is reached at total intraocular energy well below that required to produce retinal alteration. By expanding the diameter of the beam at the cornea, sufficient total intraocular energy can be introduced to damage the retina without exceeding the corneal damage threshold. The laser used in this experiment was a pulsed Nd:YAG laser having resonator mirrors designed to suppress 1064 nm oscillation and allow emission in the 1330 nm complex. The laser emitted simultaneously at 1318 nm and 1338 nm with 40% of the output energy at 1318 nm and 60% of the output energy at 1338 nm. No emission was observed at 1358 nm. The pulse duration was 650 μ s, which was required to generate sufficient output energy. The exposure configuration of Figure 1 as described in SECTION I was used. A Laser Precision joulemeter was used for dosimetry. The beam divergence was 2.3 mr, and the beam diameter at the cornea was 5.5 mm.

Rhesus monkeys were tranquilized and anesthetized. The ocular pupils were dilated to allow biomicroscopic and funduscopic evaluation. The outer ocular structures (cornea, aqueous, lens, and vitreous) were examined before and after exposure via slit lamp biomicroscope. Retinal exposures were evaluated via direct ophthalmoscope. Body temperature of the subject was maintained with a thermal blanket. The eyelid was held open by a lid speculum, and the cornea periodically irrigated with physiological saline to maintain clarity. Two to 12 exposures were placed in each eye. The criterion for damage was the presence of a visible alteration 1 hr after exposure. The ED₅₀ and associated confidence interval were determined by probit analysis.

RESULTS

The ED₅₀s for production of corneal lesions are presented in Table 10.

TABLE 10
Corneal Damage Thresholds

Laser	Wavelength (nm)	Exposure duration	Irradiance diameter (mm)	ED ₅₀ (J/cm ²)
Nd:YAG	1318&1338	250 μ s	0.4	45
Er:Glass	1540	930 μ s	1.0	9.6
Ho:YLF	2060	100 μ s	1.8	2.9
Ho:YLF	2060	42 ns	0.32	5.2

The ED₅₀ for the production of retinal lesions with the Nd:YAG laser at 1318 and 1338 nm was 356 mJ total intraocular energy.

The ocular response to the Ho:YLF and Er:Glass lasers was confined to the cornea. The diameter and depth of the lesions were both dose and wavelength dependent. As the dose increased, the lesion diameter increased. Erbium lesions in cross section were conical in shape and varied in depth from $1/2$ to full corneal thickness. Holmium lesions involved only the upper $1/8$ to $1/4$ of the corneal thickness. For both the erbium and holmium laser exposures, the transition from no observed lesion to a high probability of observing a lesion required little change of dose. Exposure to the 1318 and 1338 nm neodymium laser where the beam was focused to a corneal irradiance diameter of 0.4 mm were full corneal thickness. The "track" or scar through the cornea was slightly tapered. When the corneal irradiance diameter was expanded to 5.5 mm for the retinal studies, no alteration of cornea or lens was observed.

DISCUSSION

The retinal ED_{50} for exposure to the 1318 and 1338 nm Nd:YAG laser lines is over 3000 times that for exposure to the 1064 nm Nd:YAG laser line. The transmission of the pre-retinal ocular media in rhesus monkey is 65% at 1064 nm and 2.1% for combined 1318 and 1338 nm at the ratio used in this experiment. Absorption in the retina and choroid is approximately 2 times greater at 1064 nm than at 1318 nm. Thus one would expect on the basis of ocular absorption, that the ratios of ED_{50} s would be approximately 60. Possible explanations for the discrepancy between theory and data include scattering in the ocular media and differences in retinal spot size due to laser beam divergence and chromatic aberration of the eye.

The corneal irradiance for production of a corneal lesion for combined 1318 and 1338 nm irradiation is 45 J/cm^2 . The corneal irradiance for production of a retinal lesion, obtained by assuming the total intraocular energy required to produce a retinal lesion is uniformly distributed over a 7 mm aperture at the cornea, is 0.93 J/cm^2 . The primary site for ocular damage at 1318 and 1338 nm is therefore the retina. The safety margin afforded by this laser is nonetheless, 3 orders of magnitude greater than that afforded by the 1064 nm laser line.

The corneal response resulting from exposure to laser irradiation is considered to be a result of temperature elevation of the tissue. Sufficient energy is absorbed in a finite volume to result in a localized temperature rise that produces coagulation or opacification of the tissue. When ED_{50} data for various laser lines are compared, the wavelength dependence of the corneal damage threshold is apparent. Inherent to this dependence is the wavelength dependence of the relative absorption of the cornea. Table 11 presents selected ED_{50} data for pulsed exposure to several infrared laser lines. These data are plotted in Figure 20. The curve represents the penetration depth for 95% absorption of

incident radiation in physiological saline. Physiological saline matches well the transmission of the ocular media for wavelengths longer than 1000 nm.

TABLE 11
Corneal Damage Thresholds

Laser	Wavelength (nm)	Exposure duration	Irradiance diameter (mm)	ED ₅₀ (J/cm ²)
Nd:YAG	1318-1338	250 μ s	0.40	45
Er:Glass	1540	50 ns	1	21 ^c
		930 μ s	1	9.6
Ho:YLF	2060	42 μ s	0.32	5.2
		100 μ s	1.8	2.9
HFF ^a	2600-2900	45 ns	0.82	0.156 ^d
DFB ^b	3600-3900	100 ns	0.96	0.377 ^d
CO ₂	10600	100 ns	2	0.350 ^e

^amultiline hydrogen fluoride

^bmultiline deuterium fluoride

^cLund et al, reference 15

^dDunsky and Egbert, reference 16

^eStuck, unpublished data, 1980

Let x_1 be the depth at which 95% of the incident radiation is absorbed. The x_1 is obtained from the equation $I/I_0 = e^{-ax}$ by letting I/I_0 equal 0.05 and solving for x . I_0 is the incident intensity, I is the transmitted radiation, and a is the absorption coefficient of saline. The volume in which the radiation is absorbed is equal to Ax_1 where A is the cross section area of the incident beam. If Q is the absorbed energy, then the absorbed energy/unit volume is Q/Ax_1 . Assuming the absorbed energy per unit volume required to produce corneal damage is independent of wavelength, we can set $Q/Ax_1 = k$, a constant, at threshold. Therefore the irradiance Q/A equals kx_1 . There is a direct correlation between the damage threshold and the penetration depth for absorption of a given fraction of the incident radiation. Figure 20 clearly shows this relationship. The right and left scales on this figure are arbitrarily positioned with respect to each other. A better fit to the bioeffects data could be obtained by adjustment of the 95% absorption depth scale.

The close correlation between the bioeffects data and the curve derived from the absorption of physiological saline apparently provides a means of assessing the hazard of any proposed laser emitting at a wavelength greater than 1400 nm. However, care must be exercised in such predictions. Lower absorption, which presents the highest corneal ED₅₀, can allow sufficient energy to reach the retina to produce damage. This is demonstrated by the 1330 nm Nd:YAG laser which produces retinal damage at lower corneal irradiance than is

required to produce corneal alteration. In theory it is possible to predict the ocular absorption at which the transition from corneal to retinal alteration occurs. In practice, it is difficult to make an accurate prediction because of the uncertainties of ocular transmission measurements. One other consideration must be made in choosing a laser. Those wavelengths presenting higher corneal damage thresholds generally alter deeper layers of the cornea, resulting in a permanent scar. Those wavelengths having lower damage thresholds generally produce only superficial damage which heals with no residual alteration of the cornea.

CONCLUSIONS

This research has extended the data base necessary to formulate laser safety standards. The data reported herein suggest that there is reason to reevaluate those provisions of TBMED 279 which determine the MPE for exposure to repetitive pulse lasers emitting pulses shorter than 10 μ s and the MPE for lasers emitting at wavelengths longer than 1400 nm. The data also indicate a discrepancy between the MPE and the bioeffects data between 700 nm and 1100 nm. While the bioeffects data verify that the MILES laser output is well below the ED_{50} for production of a retinal lesion, our failure to resolve the question of retinal clouding leaves some doubt about the safe use of this device.

RECOMMENDATIONS

We recommend that the provisions of TBMED 279 be reevaluated. This reevaluation should consider our findings that the bioeffects data are more accurately reflected by the MPE when $C_p = t^{-1/4}$ for repetitive pulse exposure and when the MPE for laser wavelengths longer than 1400 nm are correlated to the absorption spectrum of physiologic saline.

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LEGEND OF FIGURES

FIGURE 1. Laser exposure system for study of retinal effects.

FIGURE 2. Dependence of the ED_{50} (TIE/pulse) on the number of pulses in the exposure for 10 Hz and 1000 Hz Nd:YAG laser irradiation of rhesus monkey retina.

FIGURE 3. Dependence of the ED_{50} (TIE/pulse) on the number of pulses in the exposure for 10 Hz frequency doubled Nd:YAG laser irradiation of rhesus monkey retina.

FIGURE 4. Dependence of the ED_{50} (TIE/pulse) on the number of pulses in the exposure for 10 Hz Er:YLF and 120 kHz GaAs laser irradiation of rhesus monkey retina.

FIGURE 5. Dependence of the ED_{50} (TIE/pulse) on the number of pulses in the exposure for large retinal irradiance diameter irradiation of rhesus monkey retina.

FIGURE 6. Dependence of the ED_{50} on wavelength for exposure of rhesus monkey retina to short pulse laser irradiation and to 100 s filtered xenon lamp irradiation.

FIGURE 7. ED_{50} for retinal exposure of rhesus monkey retina to 6943 nm, 850 nm, and 1064 nm laser irradiation compared to the MPE derived from TBMED 279.

FIGURE 8. The TIE delivered by the MILES M-16 transmitter compared to current bioeffects data and compared to the MPE computed both by the methods of TBMED 279 and by setting $C_p = N^{-1/4}$.

FIGURE 9. Fifty exposure site in extramacular area showing pigment epithelium and photoreceptor outer segments. Some vacuoles are evident in pigment epithelium cells but most cytoplasmic organelles remain normal in appearance. Photoreceptor outer segments (OS) appear to be normal.

FIGURE 10. Same exposure site as FIGURE 9, showing cone and rod inner segments. Mitochondria of the cone inner segments (CIS) are much more swollen than those in rod inner segments (RIS). These changes are apparently fixation related.

FIGURE 11. One hundred exposure site in lower macular area, showing pigment epithelium. Some vacuoles appear in the pigment epithelium cells but the rest of the cell contents are normal. Melanin granules appear to be normal.

APPENDIX

FIGURE 12. Same exposure site as FIGURE 11, showing photoreceptor outer segments (OS). OS appear to be normal in arrangement.

FIGURE 13. Same exposure site as FIGURE 12, showing cone and rod inner segments. Cone inner segment (CIS) mitochondria appear to be much more swollen than neighboring rod inner segment (RIS) mitochondria. This change is fixation related.

FIGURE 14. Fifty exposure site in upper macular area, showing pigment epithelium (PE) and photoreceptor outer segments (OS). Pigment epithelium melanin granules, and other cell contents appear normal except for vacuoles which are the result of osmotic effects. Outer segments appear normal in lamellae arrangement.

FIGURE 15. Same exposure site as FIGURE 14, showing rod and cone outer and inner segments. Rod (RIS) and cone inner segments (CIS) show the same mitochondrial differences as described in the previous micrographs. Outer segments show twisting and folding which is also seen in control samples.

FIGURE 16. Control area from lower macular area of unexposed eye showing pigment epithelium and outer segments. Pigment epithelium (PE) cells are normal in appearance except for the previously described vacuoles and photoreceptor outer segments appear quite normal in arrangement.

FIGURE 17. Control area from the nonexposed eye from lower macular area showing pigment epithelium (PE) and outer segments (OS). PE cells are normal in appearance except for the previously described vacuoles and photoreceptor outer segments appear quite normal in arrangement.

FIGURE 18. Same control area as FIGURE 16, showing cone inner and outer segments with mitochondrial swelling which is also seen in tissue samples from the exposed eye. Outer segments appear to have a normal lamellar arrangement and there is some twisting and folding of the outer segments.

FIGURE 19. Exposure system for study of laser induced corneal effects.

FIGURE 20. Ocular damage thresholds for exposure to infrared lasers. These data show a close correspondence to the curve representing the penetration depth for 95% absorption of incident radiation in physiologic saline.

APPENDIX (continued)

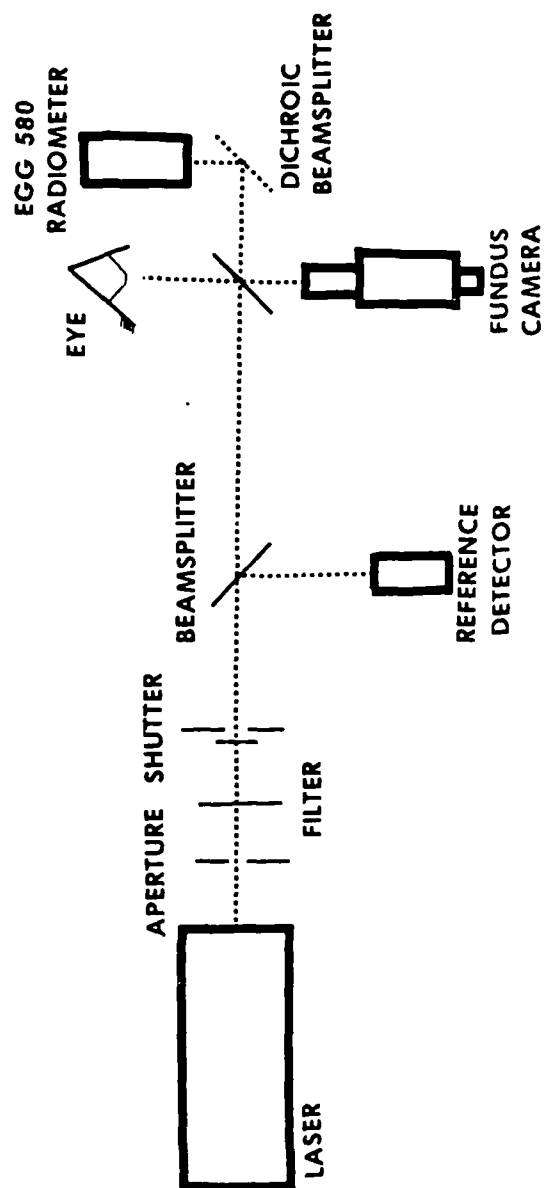


Figure 1. Laser exposure system for study of retinal effects.

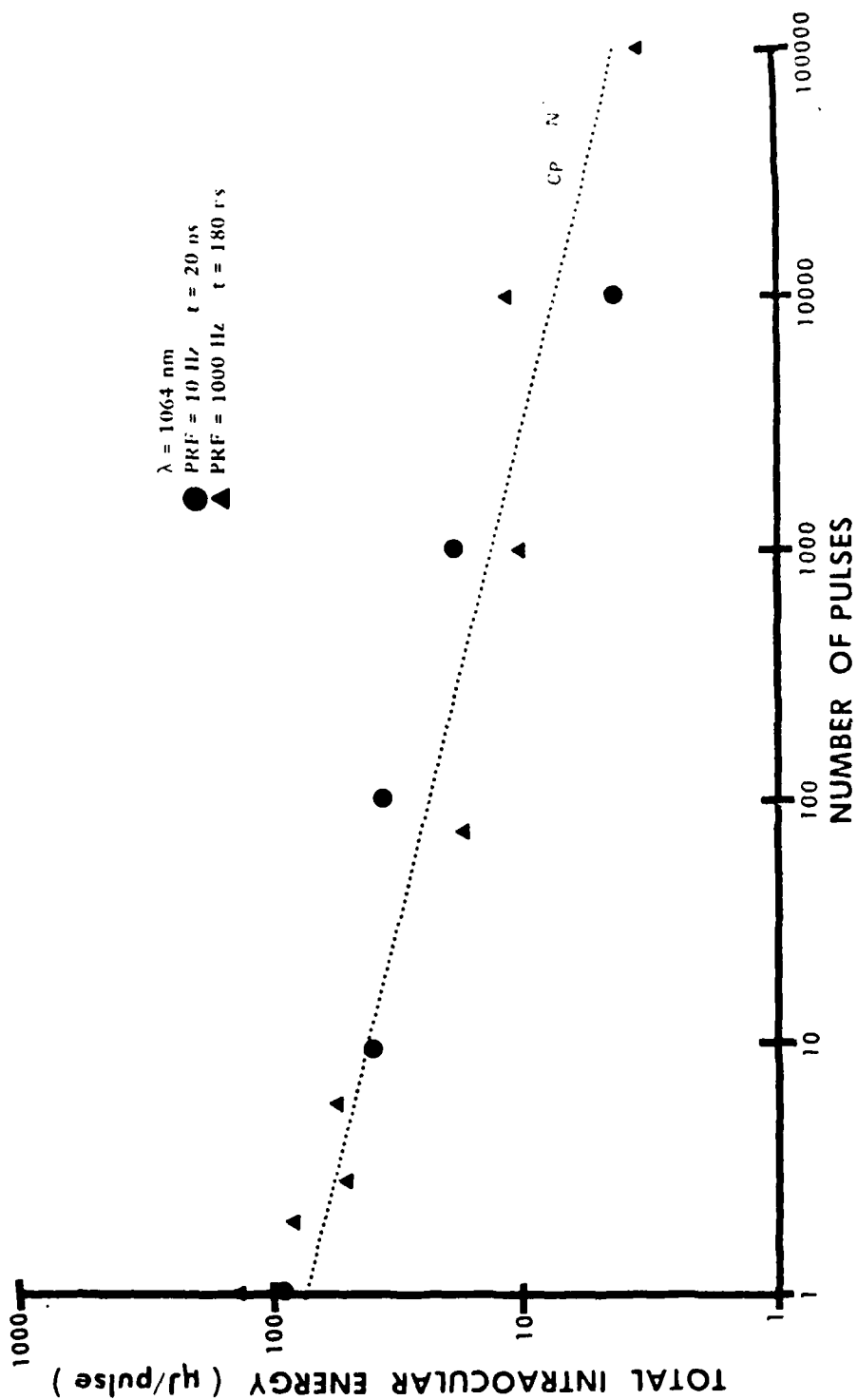


Figure 2. Dependence of the ED_{50} (TIE/pulse) on the number of pulses in the exposure for 10 Hz and 1000 Hz Nd:YAG laser irradiation of rhesus monkey retina.

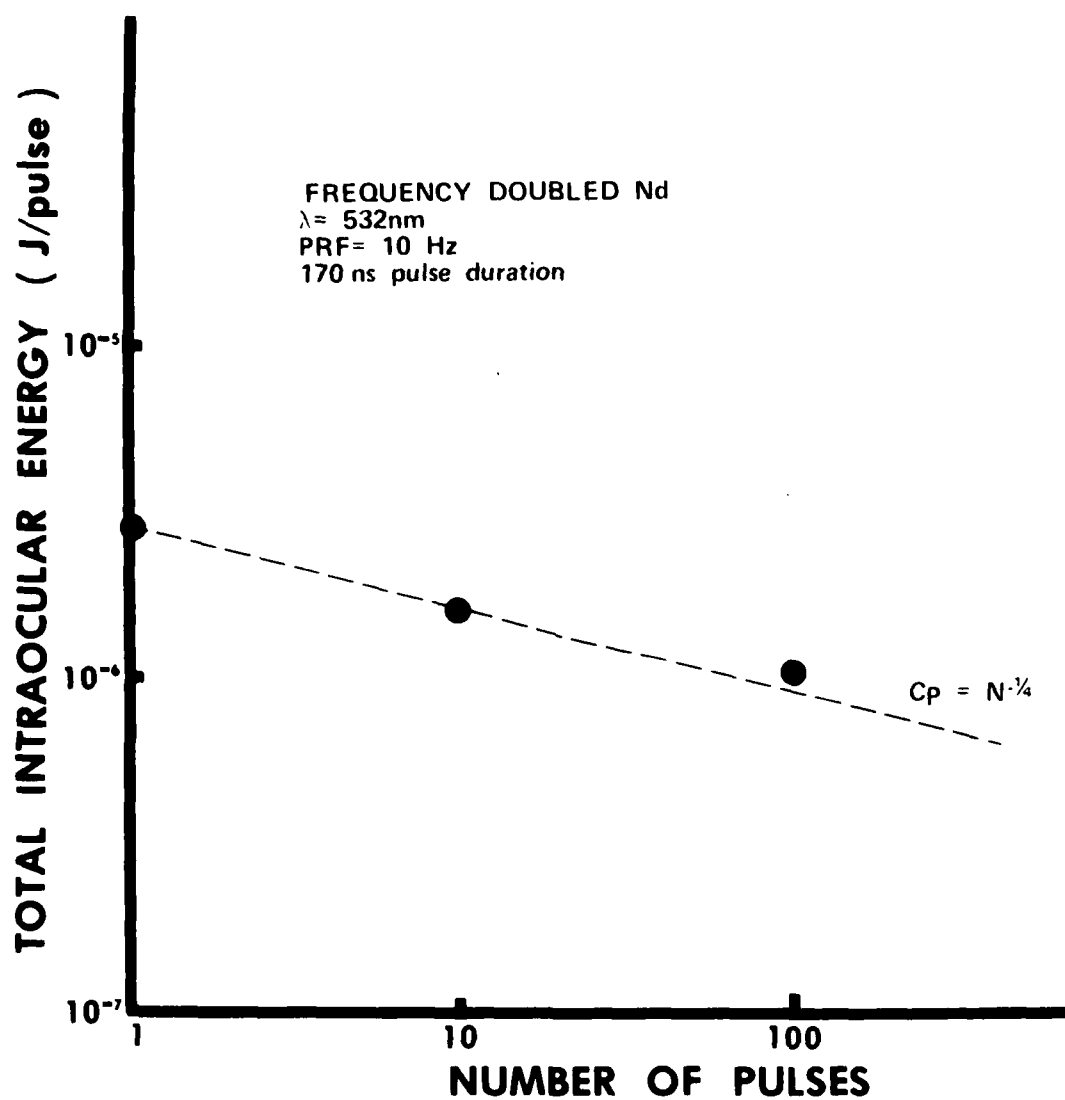


Figure 3. Dependence of the ED_{50} (TIE/pulse) on the number of pulses in the exposure for 10 Hz frequency doubled Nd:YAG laser irradiation of rhesus monkey retina.

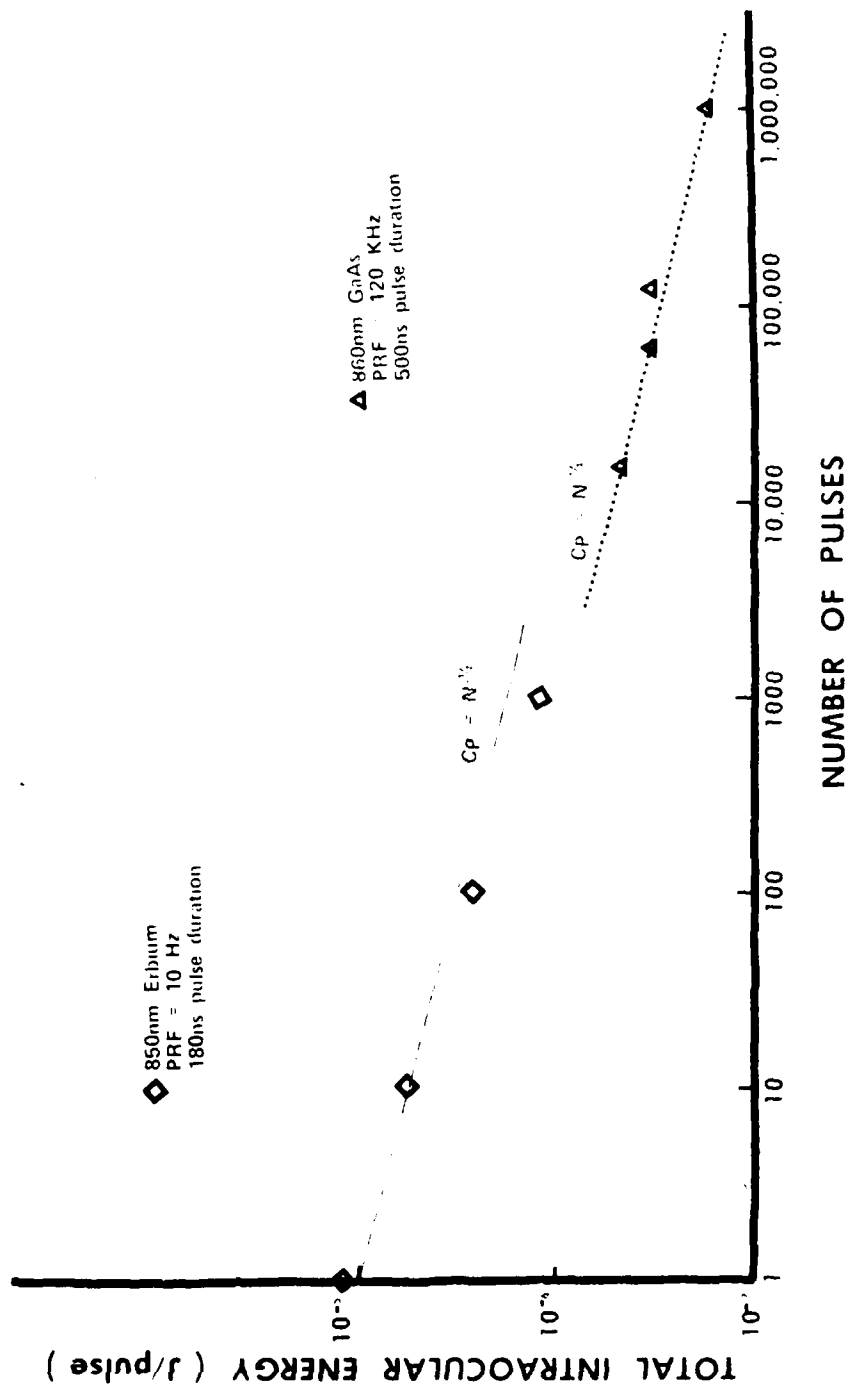


Figure 4. Dependence of the ED_{50} (TIE/pulse) on the number of pulses in the exposure for 10 Hz Er:YLF and 120 kHz GaAs laser irradiation of rhesus monkey retina.

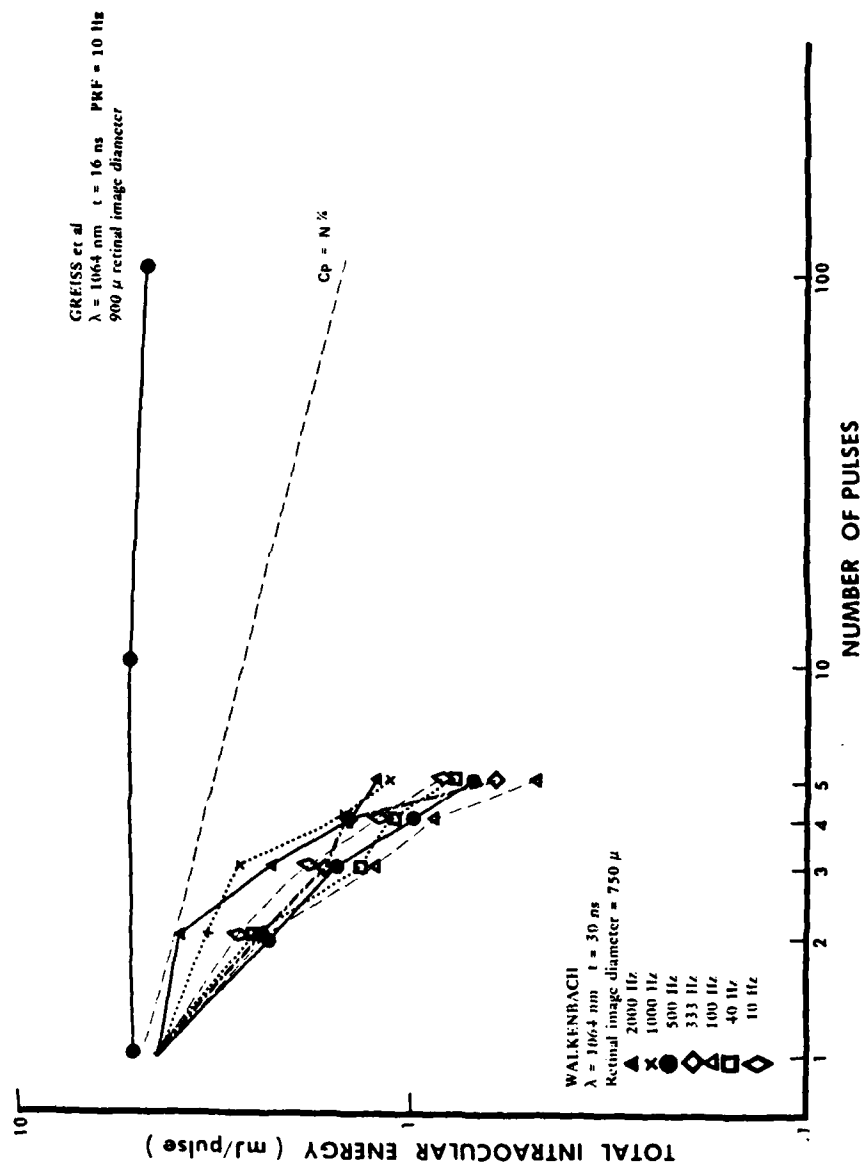


Figure 5. Dependence of the $ED_{50}(\text{TIE/pulse})$ on the number of pulses in the exposure for large retinal irradiance diameter irradiation of rhesus monkey retina.

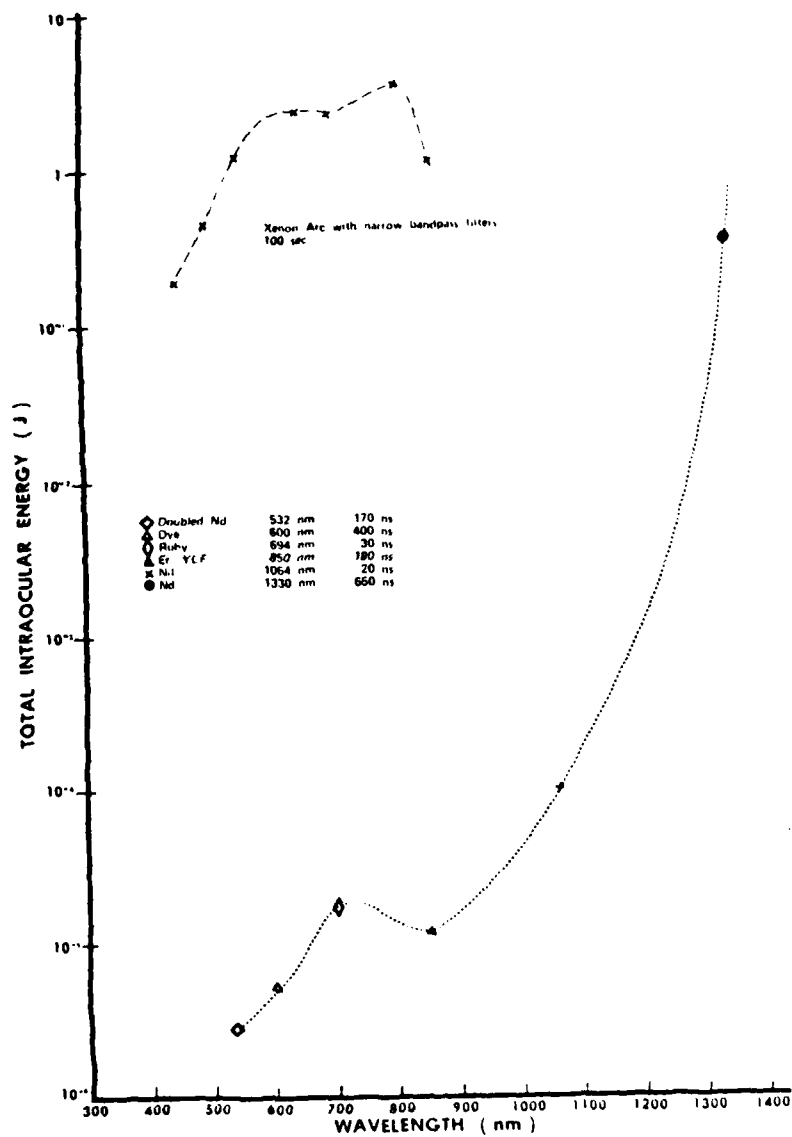


Figure 6. Dependence of the ED_{50} on wavelength for exposure of rhesus monkey retina to short pulse laser irradiation and to 100 s filtered xenon lamp irradiation.

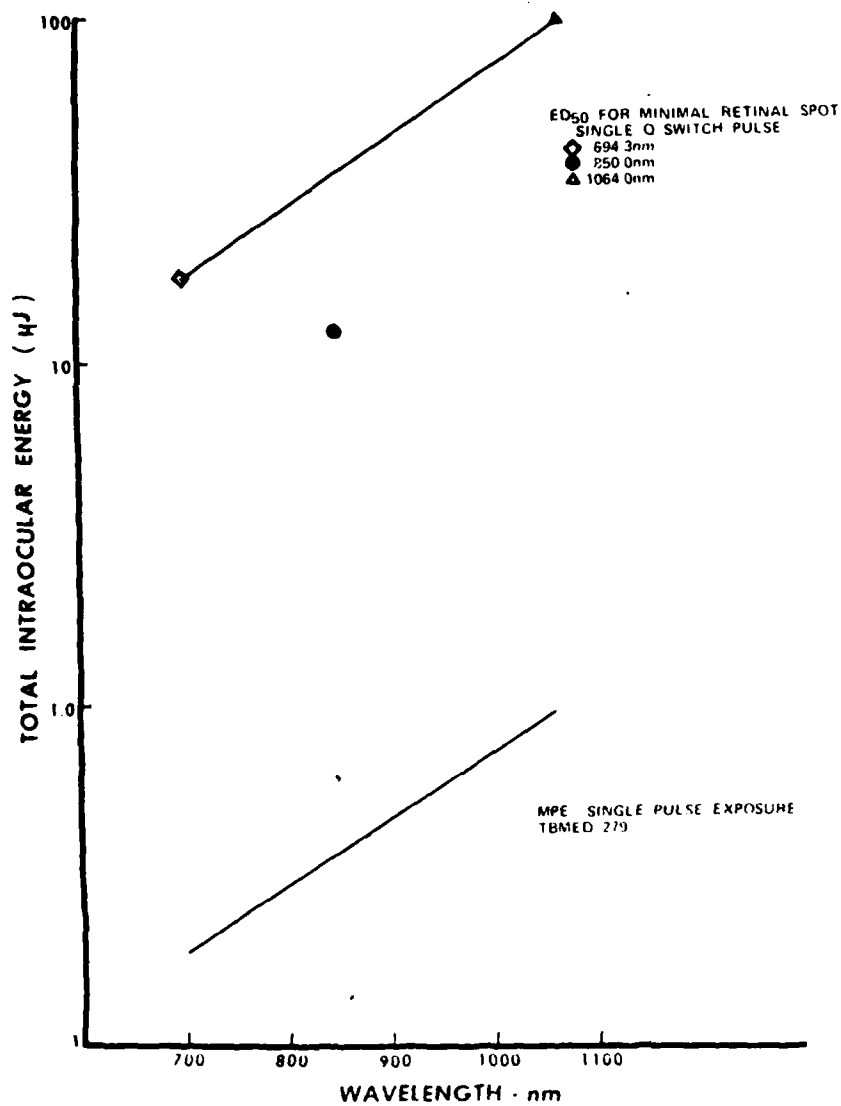


Figure 7. ED₅₀ for retinal exposure of rhesus monkey retina to 694.3nm, and 1064nm laser irradiation compared to the MPE derived from TBMED 279.

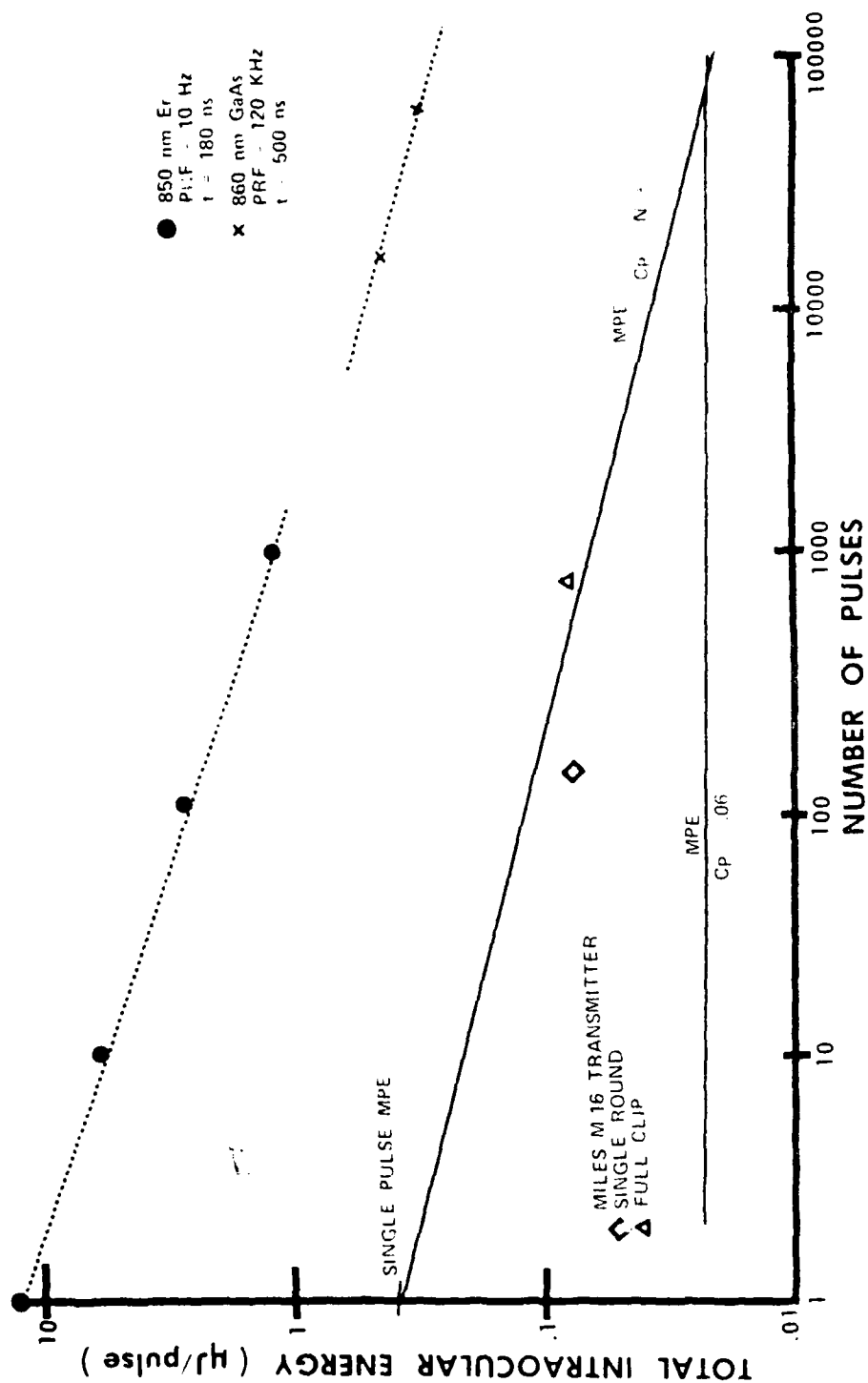


Figure 8. The TIE delivered by the MILES M-16 transmitter compared to current bioeffects data and compared to the methods of TBMED 279 and by setting $C_p = N^{-1/4}$.



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Figure 10 Same exposure site as *Figure 9*, showing cone and rod inner segments. Mitochondria of the cone inner segments (CIS) are much more swollen than those of rod inner segments (RIS). These changes are apparent x 7500 magnification.

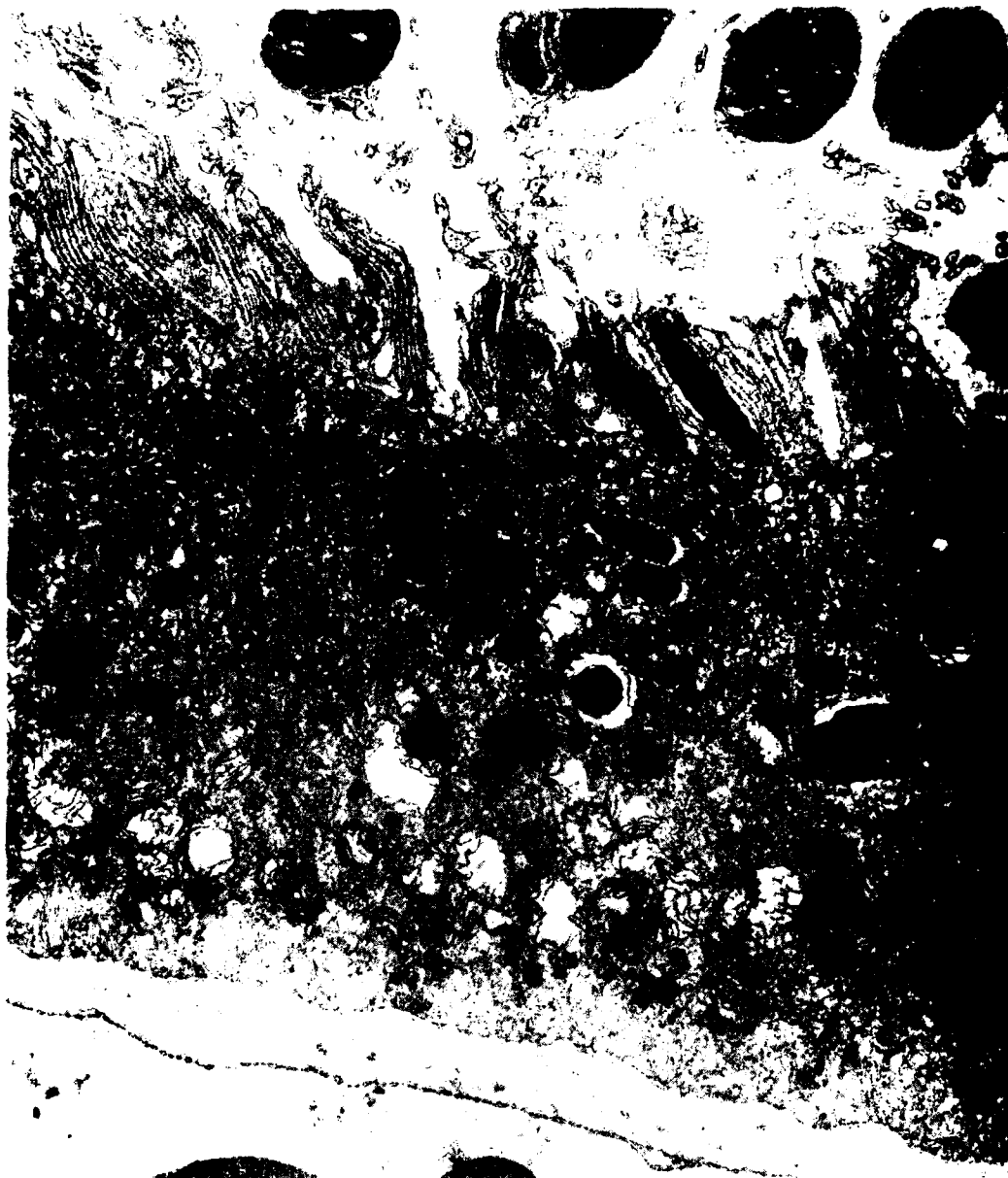


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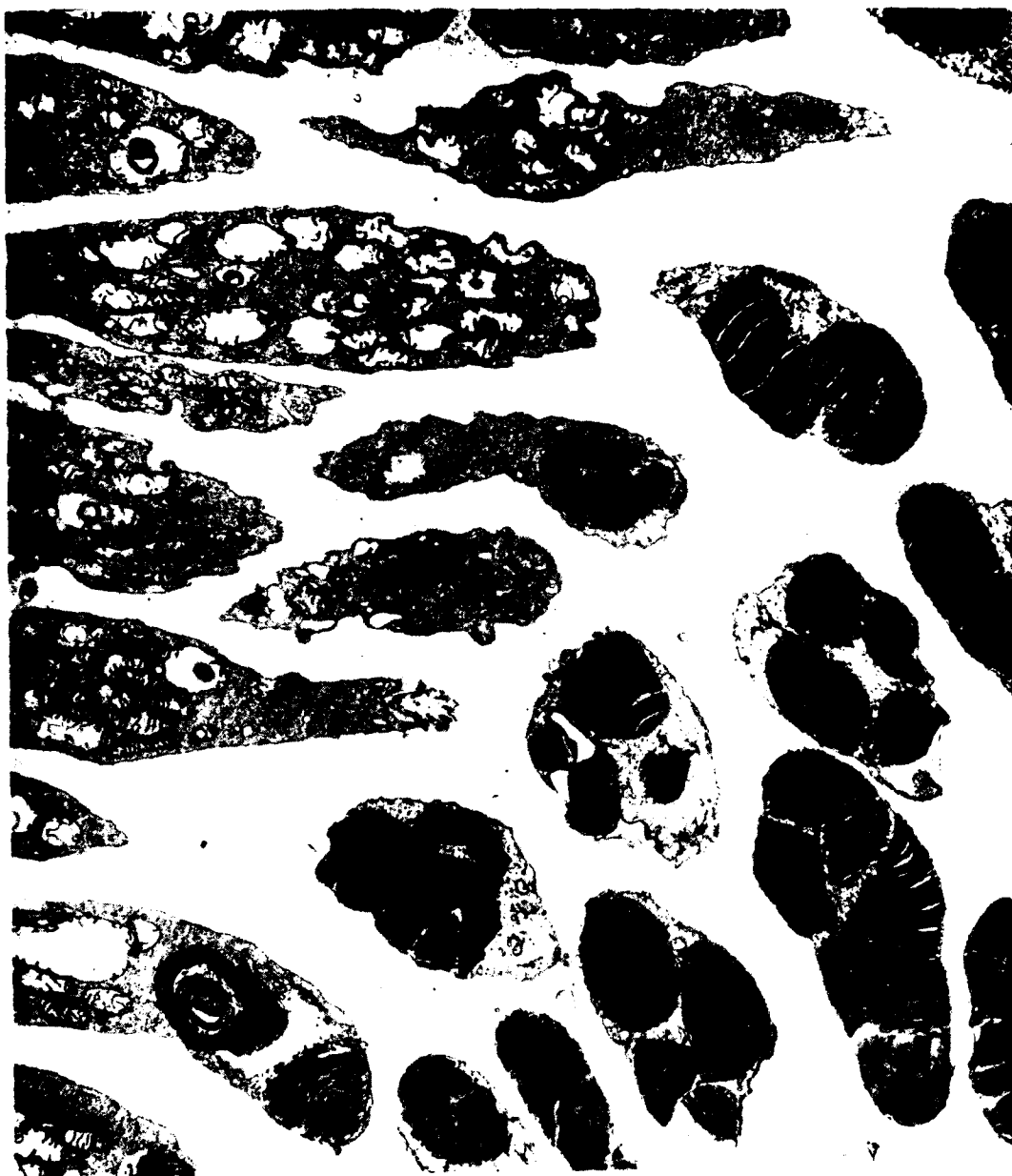


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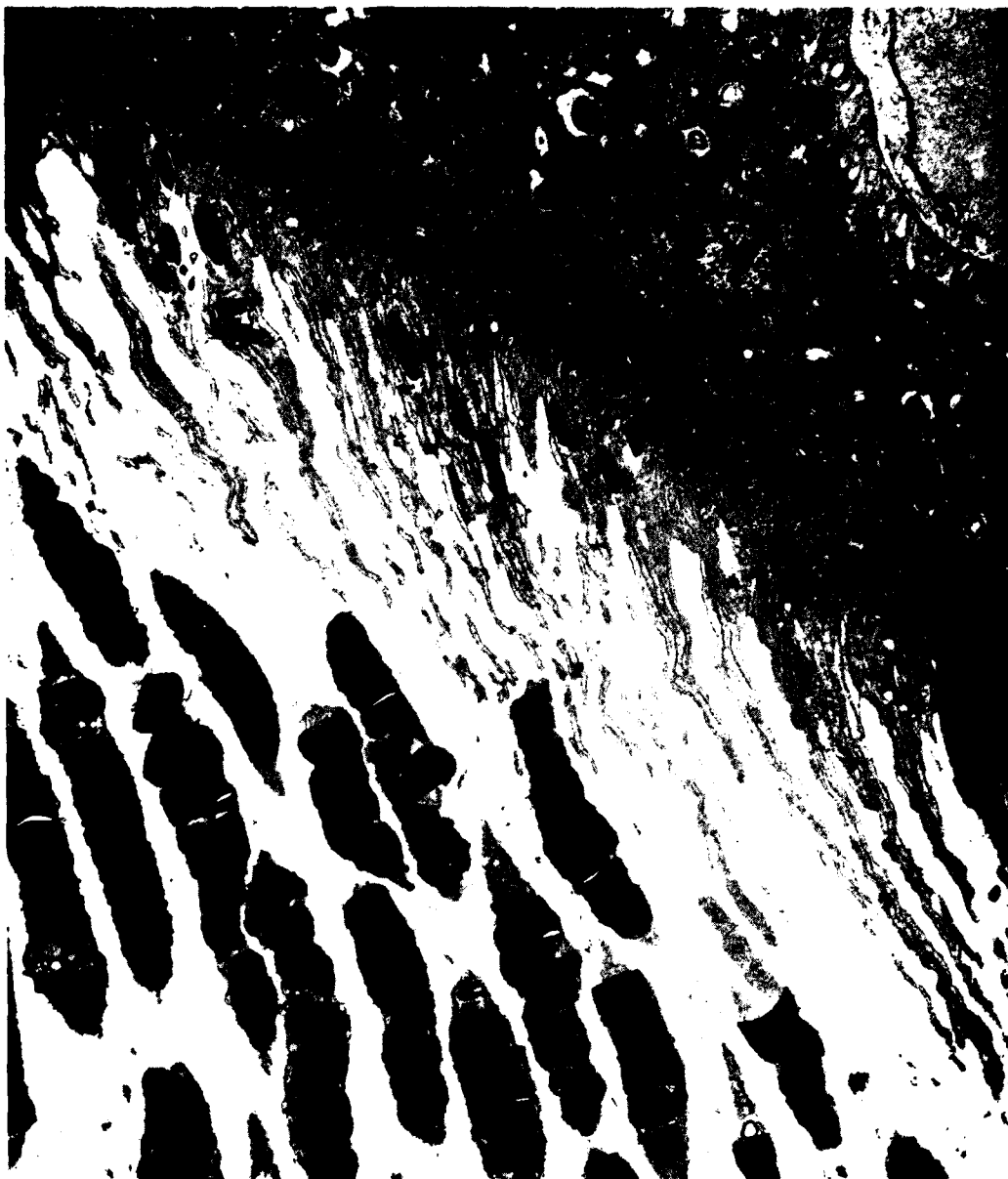


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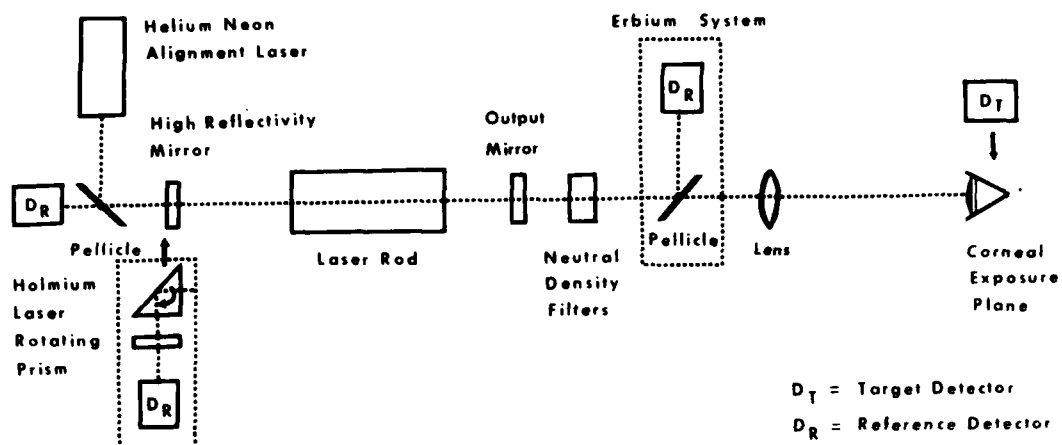


Figure 19. Exposure system for study of laser induced corneal effects.

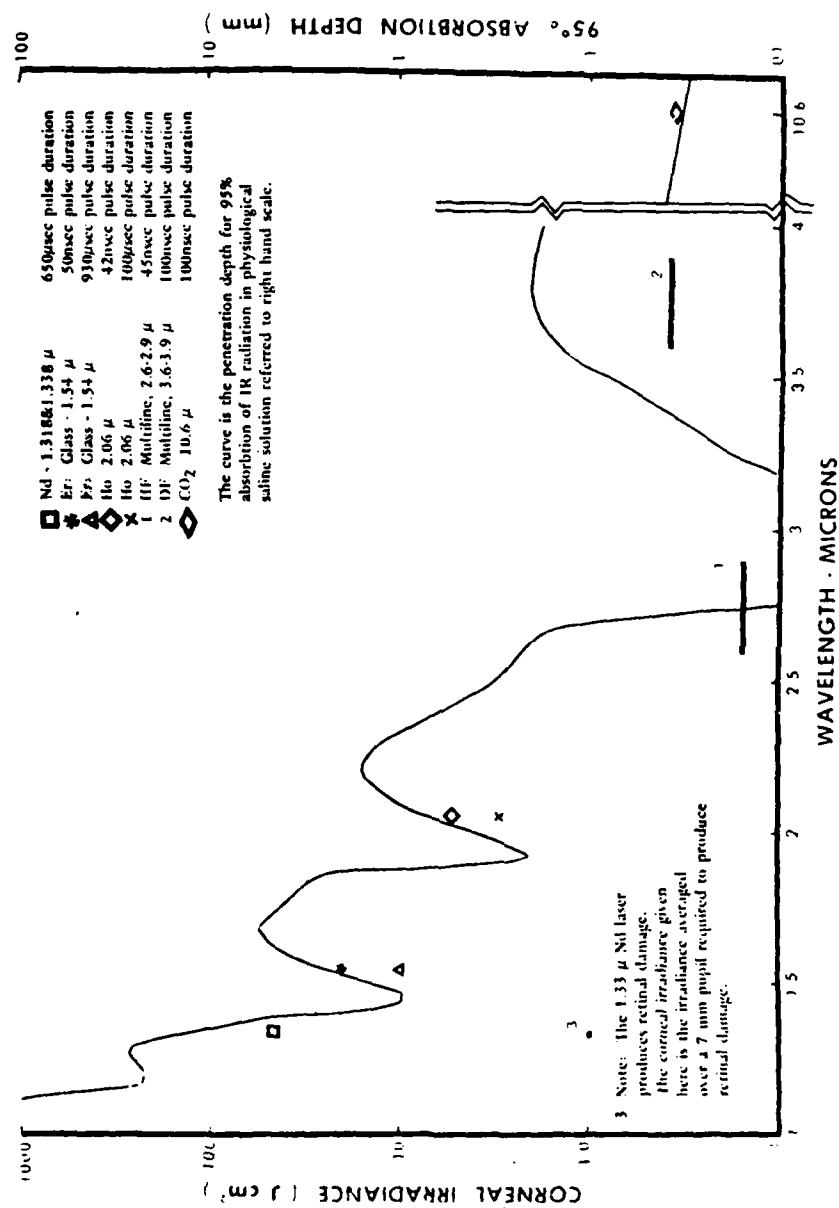


Figure 20. Ocular damage thresholds for exposure to infrared lasers. These data show a close correspondence to the curve representing the penetration depth for 95% absorption of incident radiation in physiologic saline.

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