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BIOLOGICAL APPLICATIONS AND EFFECTS OF OPTICAL MASERS

MIDTERM REPORT

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Threshold radiant exposures for retinal damage in 3 macaque monkeys are given for exposures of 0.5, 0.125 and 0.01 seconds duration to laser wavelengths 514.5 and 488 nm. Intravitreal injections of 5 X 10-5 gm of Cu-Zn Sod were toxic to cornea, lens and retina of the rhesus monkey after a radiant exposure of 33 J/cm² of 440 nm light. No further experiments with SOD are contemplated. Similar experiments with catalase will be tried during the first quarter of of the second contract year. The effects of oxygen on retinal toxicity during exposure to wavelengths 540, 640 and 840 nm were delayed by the untimely death of Dr. Millen, our consultant on anesthesiology and oxygen administration. Arrangements have been made to activate this program during the second contract year. Threshold data on 40 microsecond pulse trains cannot be obtained until the acoustic modulator can be incorporated into the Ar-Kr laser which was used during the contract year to produce exposures less than 1 second to 514.5 and 488 nm laser lines. Data on PRF's of 10 and 100 KHz and 1, 10 and 20 MHz will be obtained during the second contract year. The long-term experiment on cataractogenesis on 2 rhesus monkeys exposed to a near UV spectrum (330-420 nm) has been completed. No cataracts were detected probably (cont.)

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19. because of the long latency period for cataract in the rhesus monkey and also because wavelengths above 330 nm are less effective than the UV spectrum between 300 and 325 nm in producing lens opacities.

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.

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__X__ In conducting research using animals, The investigator(s) adhered to the "Guide for the care and use of Laboratory Animals," prepared by the committee on care and use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (NIH 78-23, Revised 1978).

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William T. Ham, Jr. 9/29/88

PI Signature Date

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3. INTRODUCTION:

The research proposal leading to Contract DAMD 17-87-C-7186 entitled "Biological Applications and Effects of Optical Masers" was submitted January 15, 1986 but was not funded until September 1, 1987. While the award was signed on August 25, 1987 we did not have funds or salaries available until November 1, 1987. The research protocol is a natural "follow-up" of our Annual/Final report for the period March 16, 1982-October 15, 1986.

In this Annual/Final report light toxicity in the macaque retina as a function of wavelength was described in detail[1,2]. In particular, wavelengths ranging from 1064 nm to 325 nm were studied using rhesus monkeys. The corneal power required to produce a minimal lesion in 1000 s increased by three orders of magnitude in going from 441 nm to 1064 nm. Furthermore, the type of lesion produced by 441 nm was entirely different from that produced by 1064 nm. The latter was a retinal burn whose image diameter was smaller than the exposed site and at a temperature rise of 23°C, whereas the lesion produced with 441 nm occured with negligble temperature rise (< 0.1°C) and the lesion appeared two days after exposure and was full size. This was clear evidence that some type or types of actinic or photochemical reaction(s) were produced by short wavelength light.

Histologically as well as morphologically, minimal burn lesions differed markedly from minimal blue light lesions.[3] When thermal lesions were examined by light microscopy at 24 to 48 hours postexposure it was found that many of the photoreceptor cells had been irreversibly damaged (pyknotic) as well as the cellular structure of the retinal pigment epithelium (RPE). Distruction was greatest at the center of the lesion, tapering off toward the periphery because maximum temperature occured at the center of the irradiated area. Thus, a minimal burn lesion was always smaller than the irradiated area. In contrast, minimal blue light (441nm) lesions were nearly uniform across the irradiated area and did not appear until 48 hours after exposure. Histologically, damage appeared initially in the RPE at 48 hours postexposure. The RPE was inflammed and edematous, melanin pigment granules were agglutinated resulting in depigmentation, and macrophages filled with melanin granules appeared in the subretinal space.[3] The photoreceptors did not begin to show major damage until 5-6 days postexposure. By 20 to 30 days postexposure a minimal blue light lesion had healed leaving only hypopigmentation and macrophages in the subretinal space. Tests with rhesus monkeys trained to perform a visual task showed that 20/20 vision was lost 5-6 days postexposure but returned in 20-30 days.[4] After 90 days the macrophages had disappeared from the subretinal space; a slight granular and depigmented area remained in the RPE that bore a suggestive resembalance to age-related macular degeneration (AMD).

We extended our investigation of retinal sensitivity to radiation into the near ultraviolet (UV). Aphakic monkeys (lens removed surgically from one eye) were exposed to 405, 380, 350 and 325 nm radiation from our 2500 W xenon lamp system with quartz optics. We found that the rhesus retina was 6 times more sensitive to wavelengths 350 and 325 nm than to 440 nm blue light.[5] The photochemical effects of near UV radiation were similar but more exaggerated than those of blue light damage and included, in addition to injury to the RPE cells, extensive damage to the photoreceptors, especially the cones.

The basic mechanisms promoting or causing photochemical reactions in the retina are unknown but there is good reason to believe that oxygen free radicals and reactive molecules like superoxide, hydrogen peroxide, hydroxyl radical and singlet oxygen play an important role in producing toxic effects. To test this hypothesis we exposed the retinae of anesthetized macaque monkeys under high levels of arterial blood-oxygen tension (PO_2's ranging from 100-350 mm Hg) to short wavelength light (435-445 nm) and compared the threshold for retinal damage to that determined under normal conditions. The results were definitive.[6] Threshold radiant exposure in $J \cdot cm^{-2}$ decreased exponentially with increase in PO_2. We also showed that oxygenation reduced the threshold for near UV retinal damage by a factor of three or more. Histological analysis showed excessive damage to the RPE.[7] These experiments strengthened but did not prove the hypothesis that oxygen free radicals were involved in toxic reactions produced in the retina during light or near UV exposure. In another experiment, a monkey fed beta-carotene over a 2 year period was definitively protected from blue light retinal damage when exposed under high levels of arterial blood-oxygen tension. The protective action of beta-carotene under these conditions implied that singlet oxygen might be an important toxic factor since beta-carotene was known to be an efficient scavenger of singlet oxygen. However, it is also an effective scavenger of many other excited molecular species.

In a series of recent experiments we have attempted to detect the effects of superoxide dismutase (SOD) and catalase (CAT) on the retinal toxicity of blue light (440 nm).[8] These enzymes are specific for the dismutation of superoxide to hydrogen peroxide and oxygen and the catalysis of hydrogen peroxide to oxygen and water. They were injected intravenously (i.v.) into monkeys both before and after exposure of the retina to measured radiant exposures of blue light. The results were erratic and difficult to interpret and we concluded that this method of administration was fraught with difficulties because of the short half-life of these enzymes in the circulation and their inability to penetrate the blood-retinal barrier at the RPE.
Pulses of 40 microseconds duration at pulse repetition

frequencies (PRF) of 100, 200, 400 and 1600 Hz at the laser wavelengths 647 and 488 nm were investigated for minimal or threshold damage in the macaque retina. The threshold for 488 nm pulses was always lower than the threshold for 647 nm pulses and for 1000 s exposures at 1600 Hz, the 488 nm threshold was even lower than the cw threshold for 647 nm. For each PRF the difference in threshold between the two wavelengths increased with exposure time; the difference widened as the PRF increased. Technical difficulties with the acoustic modulator attachment to the argon-krypton laser have prevented us over the past two years from investigating pulse trains at PRF's of 10 and 100 KHz and 1, 10, and 20 MHz. These technical difficulties have been corrected.

Daily exposures of the two trained monkeys to near UV radiation (330-420 nm) were terminated in February 1985. One animal with 3 mm pupillary diameter received 1171 daily exposures of 1000 s duration to 5 $mW \cdot cm^{-2}$ as measured at the cornea. The other animal with dilated pupils (>8 mm) received 584 daily exposures under identical conditions. No evidence of cataract in the exposed eye of either animal has been detected up to the present time (Aug. 1988).

The research objectives of the current contract DAMD17-87-C-7186 follow naturally from the background outlined above. A primary objective is to continue our investigation of the basic mechanisms leading to photochemical damage in the mammalian retina. We attempt to overcome the problem of penetrating the blood-retinal barrier at the RPE by injecting superoxide dismutase (Cu-Zn-SOD) and/or catalase (CAT) into the vitreous humor of the macaque monkey so that the effects of these enzymes, separately and in combination, on pre and post exposure to 435-445 nm blue light can be determined. Either a therapeutic or deleterious effect would demonstrate that the oxygen radicals and hydrogen peroxide are involved in photochemical light toxicity. A better understanding of these mechanisms might lead to therapeutic measures.

Closely allied to these experiments is a study as to whether there is an oxygen effect at the longer wavelengths in the visible and near infrared spectrum. A positive effect would suggest that photochemical reactions as well as thermal effects are important and that singlet oxygen may be involved.

It is also important to find out whether short pulses (< 1 s) of 441, 488 and 514.5 nm wavelengths can produce photochemical effects at radiant exposures that are below the threshold for thermal damage. This might help to explain why short laser pulses produce visual defects at exposure levels well below the thermal threshold. The production of free radicals and excited molecules by short pulses of blue light should lead to photochemical injury.

The pulse train retinal data at 488 and 647 nm wavelengths should be extended to pulse repetition frequencies (PRF's) beyond 1600 Hz The acoustic modulator in combination with the Ar-Kr laser can be used to investigate PRF's of 10 and 100 KHz and 1, 10 and 20 MHz.

The long-term exposures of two monkeys to the near ultraviolet spectrum (330-420 nm) produced negative results up to the mid-term of this contract, August 31, 1988. We do not plan to continue this program.

4. BODY:

Essentially there are 5 separate but interrelated experiments in the protocol of this research contract. They are:

(a) Threshold retinal data in 6 macaque monkeys for exposure times less than 1 s to wavelengths 514.5, 488 and 441 nm.
(b) Investigate the effects of SOD and CAT injected into the vitreous, separately and in combination, on pre and post exposure of the macaque retina to measured radiant exposures of 435-445 nm light.
(c) Determine whether there is an oxygen effect for retinal damage in the macaque monkey for exposures to the longer wavelengths in the visible and near infrared spectrum (540, 640 and 840 nm).
(d) Complete threshold data in the macaque monkey retina for exposures to 40 microsecond pulse trains with pulse repetition frequencies (PRF's) of 10 and 100 KHz and 1, 10 and 20 MHz.
(e) Complete and terminate long-term study on cataractogenesis from daily exposure to near UV radiation (330-420 nm) on 2 rhesus monkeys.

(a). During the first year of this contract (September 1, 1987 - August 31, 1988, experiment (a) has been completed for wavelengths 514.5 and 488 nm and partially completed for wavelength 441 nm. During the latter months of 1987 trouble was experienced with the power supply to the Ar-Kr laser; after considerable delay spent in "trouble shooting", the problem was corrected and an optical system with a spatial filter was designed to produce image diameters of 500 micrometers at the $1/e^2$ points in the monkey retina. This corresponded to the image sizes in our earlier work for exposure times greater than 1 s[1]. The expanded laser beam was scanned with a photodetector and the Gaussian parameters measured. The original protocol as defined called for threshold data in 6 eyes from 3 monkeys. However, we had 6 monocular aphakic monkeys remaining in our vivarium from a former experiment; examination of the phakic eyes in these animals showed that the retinae were normal. Accordingly it was decided to use these 6 eyes in 6 different monkeys, a more advantageous statistical design than 6 eyes in 3 monkeys and also helpful in conserving our limited supply of animals. The criterion for minimal photic damage was the appearance of a visible lesion in the fundus camera at 24 hours postexposure for thermal lesions and 48 hours postexposure for photochemical lesions. The interpolation technique was used to define a minimal lesion. The entire laser beam having the proper divergence for a 500 micrometer spot size on the retina entered the dilated pupil (> 8 mm) of the anesthetized animal by means of a beam splitter, so that the fundus camera could be aligned coaxially with the laser beam to view and photograph the retina. Exposure times of 0.5, 0.125 and 0.016 seconds were electronically controlled. Maximum retinal irradiance, E_m in $W \cdot cm^{-2}$, for a Gaussian distribution was calculated by the

formula $E_o = P_c T \cdot (2\pi\sigma^2)^{-1}$ where P_c is power at the cornea in W, T is transmittance through the ocular media and is calculated from the laser beam profile $E = E_o\, e^{-r^2/2\sigma^2}$ where r is the radius in cm. Power levels at the cornea were measured with a calibrated Scientech calorimeter. Results are given in Table 1 and plotted log-log in Figure I, where the radiant exposure in $J \cdot cm^{-2}$ is plotted along the ordinate vs the exposure time in seconds along the abscissa. Discussion of these results is best postponed until data for wavelength 441 nm is available. However, it can be seen that exposures less than 1 s fit well with our previous data for these two wavelengths 514.5 and 488 nm. The approximately straight lines for exposures less than 10 s are interpreted as meaning that thermal injury is the predominate mode of damage. This is confirmed by our observations that the minimal lesions at 24 hrs. postexposure are much smaller than 500 micrometers and that these lesions do not appear larger at 48 hr postexposure. In our experience, minimal photochemical lesions correspond in size with the area irradiated whereas minimal thermal lesions are always smaller than the irradiated area. Although photochemmical events are undoubtedly present during irradiation they are completely overshadowed by the structural damage resulting from thermal injury.

Table I

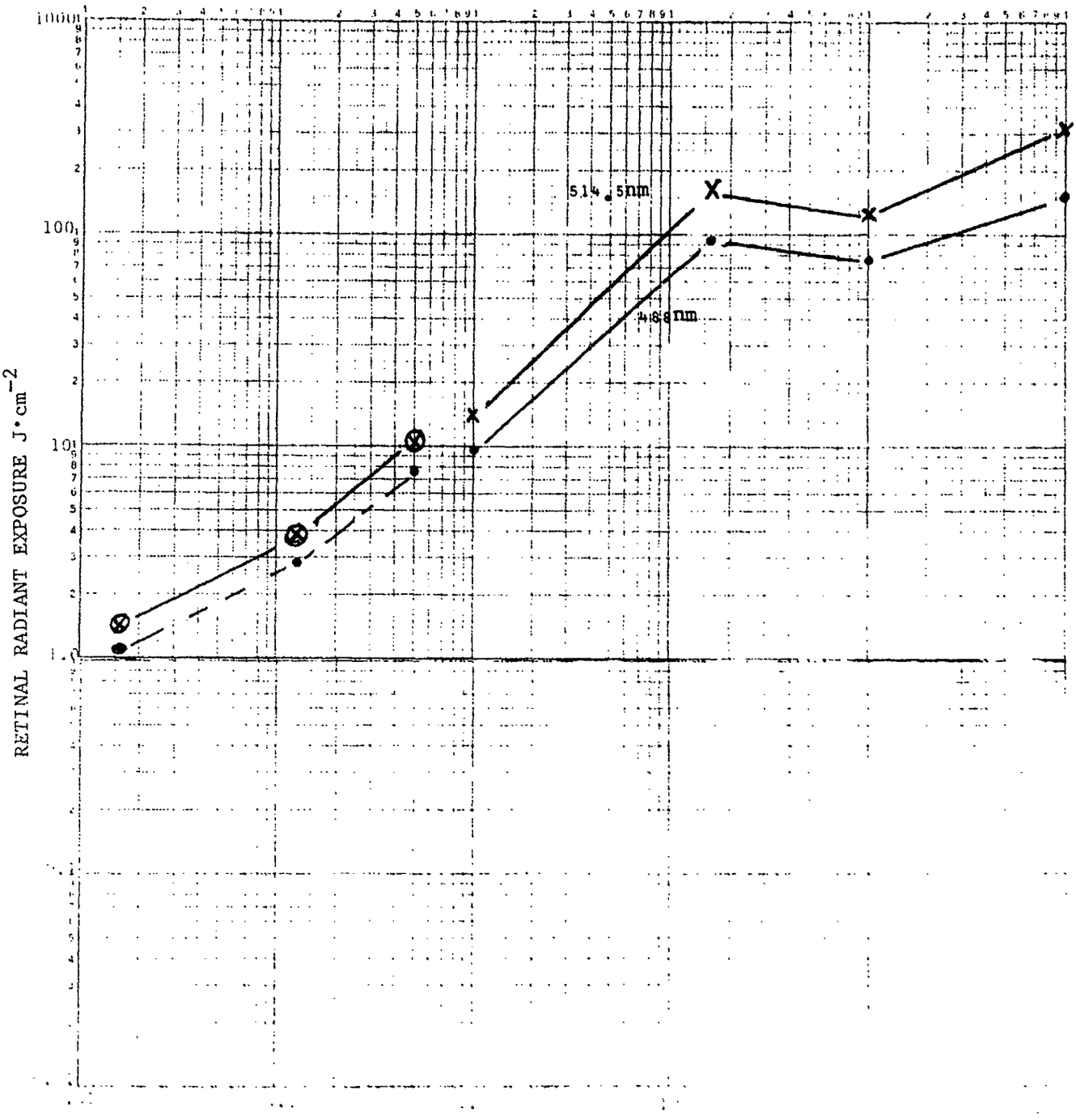
488 nm Radiation

0.5 Second Exposure			0.125 Second Exposure			0.016 Second Exposure		
P_c W	E_o W·cm^{-2}	H_o J·cm^{-2}	P_c W	E_o W·cm^{-2}	H_o J·cm^{-2}	P_c W	E_o W·cm^{-2}	H_o J·cm^{-2}
.017			.028			.084		
.018			.030			.082		
.021			.027			.088		
.016	15.68	7.84	.026	22.93	2.877	.081	69.7	1.11
.0205			.0255			.0796		
.0146			.0273			.083		
.01867			.0273			.0824		

514.5 nm Radiation

P_c W	E_o W·cm^{-2}	H_o J·cm^{-2}	P_c W	E_o W·cm^{-2}	H_o J·cm^{-2}	P_c W	E_o W·cm^{-2}	H_o J·cm^{-2}
.023			.033			.091		
.025			.033			.104		
.021			.036			.102		
.0226	20.4	10.2	.0345	30.1	3.75	.101	88.3	1.41
.023			.035			.1038		
.0245			.0333			.100		
.02318			.0341			.1003		

Threshold retinal data for 6 eyes from 6 monkeys for wavelengths 488 nm and 514.5 nm at exposure times of 0.5, 0.125 and 0.016 s. P_c is the power entering cornea in W, E_o is retinal irradiance in W·cm^{-2} and H_o is retinal radiant exposure in J·cm^{-2}. E_o is calculated from the formula $E_o = P_c T (2\pi\sigma^2)^{-1}$ where T is transmittance through ocular media (0.83 for 488 nm; 0.87 for 514.5 nm) and image size on the retina is 500 μm to the $1/e^2$ points of the Gaussian distribution where $E = E_o \exp(-r^2/2\sigma^2)$.


514.5 nm 0.87
514.5nm
488nm
RETINAL RADIANT EXPOSURE J·cm⁻²
EXPOSURE TIME IN SECONDS

(b Experiments with superoxide dismutase (Cu-Zn SOD) and catalase (CAT) injected into the vitreous of the rhesus monkey. The plan proposed uses 3 monkeys, one for SOD injection, one for CAT and one for SOD+CAT. Each animal under anesthesia receives 6 blue light (435-445 nm) radiant exposures of 33 $J \cdot cm^{-2}$, 100 s exposure duration, 500 micrometer spot size spaced evenly across the superior paramacula area in both eyes, during a 5 day period, Monday to Friday; one radiant exposure in each eye on Monday, Tuesday, Thursday and Friday with two exposures to each eye on Wednesday, spaced about two hrs. apart with intravitreal injection midway in time between the two exposures. One eye receives an injection of the enzyme, the other (control) eye is injected with a similar quantity of phosphate buffer. Light exposures are performed with the 2500 W xenon lamp equipped with quartz optics, using our well established technique for producing accurate radiant exposures to the retina. This protocol was adopted to make it possible to compare the effects of SOD, CAT and SOD+CAT at 24 and 48 hrs. preinjection, immediately before and after injection and at 24 and 48 hrs. postinjection. At a later date the entire procedure was scheduled to be repeated using the inferior paramacular area in each eye.

Our first experiment began on Monday July 25, 1988 with radiant exposures of 33 $J \cdot cm^{-2}$ to both eyes of a large rhesus monkey. This procedure was repeated on Tuesday. The monday exposure was not visible in the fundus camera on Tuesday, July 26; Wednesday the Monday exposure (48 hrs. postexposure) was visible but not the one delivered on Tuesday (24 hr.postexposure). Two radiant exposures were delivered on Wednesday, approximately 2 hrs. apart and Dr. Kennon Guerry injected a 0.1 ml solution of SOD in phosphate buffer into the vitreous of the right eye and 0.1 ml phosphate buffer without SOD into the vitreous of the left eye 1 hr between these two exposures. Cu-Zn SOD (Bovine erythrocytes) was obtained from Sigma Laboratories; 55 mg of lyophilized powder was dissolved in 1.5 ml of phosphate buffer at pH 7.3. A 30 gauge needle was used to inject 0.1 ml of this solution containing 3.67 mg of SOD into the vitreous. According to Sigma the activity was 2655 units per mg as determined by the McCord-Fridovitch test. The ocular media was clear after the injection and no difficulty was experienced in exposing the retina to 33 $J \cdot cm^{-2}$ 1 hr after the injection. After a suitable period following anesthesia the animal was returned to its cage. When examined in its cage on Thursday morning July 28th the right eye (SOD injected) was completely opaque. Over the next 12 days there was some improvement and on August 9th the animal was anesthetized and examined with the fundus camera. Though the cornea was much less opaque than before it was not possible to see the retina. The lens was opaque and it was not possible to dilate the pupil. The other (control) eye was normal. We surmized that we had injected too concentrated a solution of SOD into the vitreous. To test this hypothesis, a solution of 0.1 ml

of phosphate buffer containing 5 X 10^{-5} gms of SOD was injected into the vitreous of both eyes of a monocular aphakic monkey. Another similar monkey received a further diluted amount of 5 X 10^{-6} gms of SOD. Examination of the eyes of these two animals over a period of several days disclosed no anomalies in either the aphakic or normal eyes.

Accordingly, we decided to try another animal using an injection of 0.1 ml containing 5 X 10^{-5} gms of SOD. Radiant exposures of 33 $J \cdot cm^{-2}$ were given on Monday, Tuesday and about one hour before the SOD and/or phosphate buffer was injected on Wednesday. A second exposure to both eyes followed one hour after the injections. The ocular media was clear; no anomalies were noted. On Thursday both eyes appeared normal and received exposures of 33 $J \cdot cm^{-2}$. The previous exposures given on Monday, Tuesday and Wednesday appeared considerably enhanced, i.e. the lesions remained the same size but were very prominent - much above threshold in the eye that had been injected with SOD. This seemed to indicate that SOD exacerbated the damage. When the animal was anesthetized on Friday and examined with the fundus camera we were disappointed to find that the SOD eye was too opaque for viewing the retina. In particular, the lens was opaque but the cornea was relatively clear. Apparently, the weaker concentration of SOD took longer but still produced damage. Since SOD in concentrations of 5 X 10^{-5} and 5 X 10^{-6} gms did not prove toxic to the aphakic or the normal eyes in two test animals we have concluded that the toxicity must be associated in some way with irradiation by blue light, since this is the only major difference in these test experiments. In all events, the injection of SOD into the vitreous does not appear to be a feasible technique for studying photochemical events in the retina. In view of these negative findings we do not intend to pursue any further the effects of SOD on a retinal lesion produced by blue light. During the next quarter we plan to continue the effects of catalase on the photochemical blue light lesion.

c Oxygen effect at 540, 640 and 840 nm.
The untimely death of Dr. J.E. Millen has postponed the begining of this program. Dr. Millen was anesthesiologist with the Pulmonary Division, Medical College of Virginia and Veterans Administration Hospital. It has been necessary to enlist further aid from our Pulmonary Division. Nevertheless preliminary arrangements are now in progress and these experiments will begin during the next quarter. Three rhesus monkeys are ready, oxygen/nitrogen ratios (80/20, 60/40) are on hand and some preliminary thresholds at 840 nm have been obtained. The protocol as planned is as follows:

Monkey No.	Eye	Oxygen/Nitrogen Ratio		
		100%	80/20	60/40
1	O.S.	X		
1	O.D.		X	
2	O.S.	X		
2	O.D.			X
3	O.S.		X	
3	O.D.			X

This design gives thresholds at all wavelengths in two different animals for each oxygen/nitrogen ratio.

d Threshold data for 40 microsecond pulse trains at PRF's of 10 and 100 KHz and 1, 10 and 20 MHZ
This program could not begin until experiment a, the threshold data for wavelengths 514.5, 488 and 441 nm at exposure times less than 1 s is complete because the acoustic modulator has to be incorporated into the Ar-Kr laser. Experiment a will be completed during the next quarter and d will be started during the second quarter of the second contract year.

e Long term study on cataractogenesis from daily exposures to near UV radiation (330-420 nm) on 2 rhesus monkeys.

These experiments began in 1980. They were designed to study the long-term effects on the lens of daily exposures to near UV radiation similar to that from the sun at sea level. The 2500 W xenon lamp with quartz optics was equipped with suitable filters and mirrors to produce a spectral bandwidth, 330-420 nm, corresponding very roughly to near UV radiation from sunlight. The lens absorbs a large proportion of the 330-420 nm spectrum; less than 1% reaches the primate retina. Two experiments with rhesus monkeys trained to sit in a chair and press a lever for food when a large Landolt C changed orientation on a screen were designed. The irradiated eye received 5 $mW \cdot cm^{-2}$ at the cornea for 1000 s on a daily basis, 5 days per week. The daily radiant exposure at the surface of the lens was calculated to be 3.6 $J \cdot cm^{-2}$. The unirradiated eye served as control. The first monkey with a normal pupillary diameter (3 mm) did not show any lens anomalies as examined with biomicroscopy (slit lamp) after 600 daily exposures. It was hypothesized that perhaps the iris protects the vulnerable equatorial region of the lens from near UV photons. To test this hypothesis a second rhesus monkey with pupils dilated to greater than 8 mm by topical application of atropine was exposed to the same spectrum, schedule, etc. beginning on August 12, 1982. Both animals were kept on this schedule until February 15,1985 at which time the monkey with 3 mm pupils had received 1171 daily exposures of 1000 s anf the second monkey with pupils dilated to greater than 8 mm had receivd 584 exposures. Examination by biomicroscope was continued at 3 month intervals until August 1988. Dr. Guerry was unable to detect any lens anomalies in either monkey. The monkeys used in this study were not sacrificed for in vitro lens studies. Since both eyes in both animals were normal it was decided to use them for our retinal research. We conclude that the spectrum used in these long-term chronic exposures (330-420 nm) is not cataractogenic for the rhesus monkey. However, it should be pointed out that most of the energy in this spectrum is above 350 nm and only 30% is between 330-350 nm. Fitts et al* have published threshold levels of exposure for cataract in the rabbit which show maximum sensitivity at 300 nm; at 325 nm the radiant exposure required to produce a threshold cataract in the rabbit was more than 300 times greater than at 300 nm. Thus, for wavelengths above 330 nm the mammalian lens may not be very sensitive to radiation cataract. Also, the period of latency is much longer in the monkey than in rabbits. Our animals were about two years old when exposures started in 1980; now at age 10, they are about halfway through their lifespan.

5.Conclusions:
Exposures less than 1 s to wavelengths 514.5 and 488 nm agree remarkably well with our previous laser data. Thermal injury is the predominate mode of damage as confirmed by our observations that the lesions appeared in 24 hours and were smaller than the irradiated area on the retina.

Superoxide dismutase (Cu-Zn SOD) injected into the vitreous of the rhesus monkey is toxic when irradiated with blue light. No further experiments with SOD are planned. We shall investigate the effects of catalase injected into the monkey vitreous in an attempt to define the role of hydrogen peroxide, H_2O_2, in photochemical damage.

Oxygen effects at 540, 640 and 840 nm will be studied during the first quarter of the second contract year.

Threshold data for 40 microsecond pulse trains at PRF's of 10 and 100 KHz annd 1,10 and 20 MHz. This program is delayed until threshold data for wavelengths 514.5, 488 and 441 nm at exposure times less than 1 s is complete. This is because the acoustic modulator must be incorporated into the Ar-Kr laser. This program will be started during the 2nd quarter of the second contract year.

No cataracts have been detected in the two rhesus monkeys exposed on adaily basis to a near UV spectrum 330-420 nm. This may be due to the long latency for cataract in the monkey or because wavelengths greater than 330 nm are not cataractogenic.

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7. ABBREVIATIONS AND SYMBOLS IN THIS WORK

AMD : age-related macular degeneration
mm : millimeter
nm : nanometer
s : second
ms : millisecond
PRF : pulse repetition frequency
RPE : retinal pigment epithelium
Hz : Hertz
Ar : argon
Kr : krypton
PO_2 : Oxygen Tension in mm
CAT : catalase
SOD : superoxide dismutase
W : Watt
UV : ultraviolet
J : Joule
cm^{-2} : centimeter squared
µ : micron
ml : milliliter