REVIEW: Investigations of Laser Damage to Ocular Tissue
by A. Vassiliadis et al
TR AFAL-TR-67-170, March, 1967

S. Fine et al

On page 1 the statement is made that the retina is the most valuable part of the eye for radiation in the visible and near infrared. Although this is true for parts of the visible spectrum it may not be true for those regions in the near infrared - e.g., at 10μ.

On page 1, there are references in addition to those of 1 to 5 which have been published - e.g., the electron microscope studies by Fine and Geeraets. The studies on threshold injury to the skin, presented at NEREM are of significance with regard to threshold studies per se, and should have been included in conjunction with reference 6 on the top of page 2.

On page 2, the statement is made that these measurements were obtained at minimal attainable spot sizes. The minimal spot size attainable may actually be less than that used.

On the bottom of page 2, a statement is made that irradiation of a few square millimeters of cornea is the most dangerous. This is not necessarily true. The importance of depending on a blink reflex requires further thought. - is it dependent on a sensation of warmth, and if so, will this occur too late, since there is heat flow. Also is sensation of warmth above the threshold for injury.

On page 8 the output of the EGG radiometer is compared with a thermopile placed in the same position as the eye. The total energy per pulse used is of the order of a few millijoules for the long pulse laser and of the order of 10 microjoules for the Q-switched laser.

For a single short comparison, the sensitivity and accuracy of the primary standard (the undescribed thermopile) must be high at these energy levels. Since reputable standards groups have not reported on low level laser calorimetric devices at these energy levels, it would be interesting to have some information regarding use of their thermopile for pulsed operation. If they have used high energies - e.g., several joules - for this comparative calibration, then the problem of linear extrapolation should be discussed. If they have used multiple shots at low energy for calibration, their averaging technique allowing for calorimetric heat losses and laser fluctuations should be discussed. The calibration accuracy for Q-switched pulses is not discussed. Is this the same as for the long pulse case?

On the bottom of page 4 and the top of page 6 and 7, a polarizer - analyzer system is used. The polarizer may not be "black" at 6943A. If the analyzer is rotated, the fraction of the beam will not vary as expected, and indeed may be significantly different - e.g., consider a polarizer - analyzer system, crossed at 90°, in which some of the light has gone through the "non black" polarizer.

On bottom of page 7 and top of 8, a theodolite system is used for spot size measurements. A Gaussian image shape is assumed and the focal length of the eye is assumed. However, the edges of the beam are cut off by an iris. The initial ruby laser beam itself may not be Gaussian. Therefore the assumption of a Gaussian beam shape has no evident basis.

The accuracy of the theodolite measurements per se are not discussed. Since there is a statement that these spot sizes are minimal, and errors in diameter are squared in computing energy density, accuracy in measurement of spot size is of obviously great importance. If the report had considered the studies to be preliminary, then this problem might be considered less significant. However the possibility of standards being set, based on this data, warrants closer attention to the problems outlined.

On page 9, the majority of lesions had spot sizes ranging between 40μ and 60μ. I presume that these are not minimal spot sizes. If they assume that these are minimal spot sizes, then the data conflicts with human data by Westheimer. (An error of $60\mu/10\mu$ in spot size would result in an error of 36 in threshold energy density if the threshold energy density were the same for all spot sizes. The above argument of course neglects the variation in energy density for threshold lesion production with spot size (Ham et al).

On page 11, a threshold lesion is defined as one that develops a clinically visible lesion within one hour after laser irradiation. Does this mean that no lesions were seen at greater times than 1 hour post irradiation.

With regard to figures 6 and 7 on pages 15 and 16.

1. There is more than one injury per eye. Independence of these injuries must be proven.
2. How many animals were done?
3. Although there may be some validity for their value of 1.1mj.

for their 50% probability for long pulse irradiation of the paramacular region, based on the number of experiments done (all other errors being neglected), it is difficult to be certain that their value of 0.5 mj for macular lesions is valid because of the few data points presented (all other errors such as spot size, energy measurement, operation of the polarizer system being neglected). The ratio of 2.2 therefore requires some thought. For this ratio to be presented in the abstract, which is all that will be read by some, it would have been desirable for tests of statistical significance to be shown.

4. Figure 6 and figure 8 are very interesting. Presumably, they are based on the same experiments. Therefore, one would expect that a lesion in 6 would appear as a lesion in 8 and that no damage in 6 would appear as no damage in 8. This does not seem to be the case, by just counting x's. Probably this was a slight oversight on the part of the technician in charge of counting.

5. Going back to page 9, it is stated that the majority of the eyes had measured spot sizes with the theodolite between 40μ and 60μ. If in the graphs, values outside this range are used, then the relationship of the 50% points in the graphs to minimal spot size retinal lesions requires clarification.

Mode Locked Ruby Laser

All spikes are not the same size. This might, to some extent, affect the interpretation of the results obtained. There also seems to be some problem, according to the authors, in obtaining consistent mode locking. The accuracy of the data on mode locked lasers therefore requires careful consideration. Apparently only 5 monkeys were used in obtaining paramacular and macular data. As shown in figure 16, a considerable number of total shots were taken in these regions, and therefore a considerable number of shots per animal. The independence of each shot in producing or not producing threshold lesion is therefore in question.

The reason for a higher total energy for threshold lesions ($\sim$4 joules/cm^2) on mode locked irradiation in contrast to that for Q-switched irradiation (0.8 joules/cm^2) may be due to thermal heat flow between the pulses from the microscopic target site on mode locked irradiation.

Q-switched Ruby Laser Data - page 27

The data for threshold injury to the rabbit retina on Q-switched irradiation - 0.1 joules/cm^2 - is essentially in agreement with Ham et al (neglecting effect of spot size).

On the rhesus monkey, on spot sizes of 25μ to 50μ, the 50% probability for damage was 0.8 joules/cm^2. There are two factors here - a) spot sizes of 25μ may be difficult to measure and b) the threshold for injury in joules/cm^2 (if it can be compared with rabbit data) did increase as the spot size became smaller, in agreement with the studies by Ham et al.

E. Discussion of Results and Related Mathematical Models
page 29 on......

Although the authors state that absorption of the energy by the pigment granules results in rapid heating to very high temperatures with little chance for thermal relaxation to surrounding tissue, no calculations are presented to substantiate this fact. Data concerning this fact was presented at the International Quantum Electronics Conference in Phoenix by the reviewers, and was attended by authors of this report. Whether vaporization of the melanin granules occurred might have been at least gauged by histology.

In discussing their threshold value for the long pulse data, statements are made concerning temperature increments for protein denaturation. It is the time - temperature history which is important in denaturation, and not the temperature per se - unless steady state conditions are assumed.

In Vos' model, melanin granules are not discussed. The authors appear to superimpose the two concepts of homogeneous energy absorption and melanin granule absorption, without credit being given to the origin of the melanin granule model. If an individual melanin granule is considered as the site of interaction, then redistribution of the granules under conditions of bright light illumination, will be of no significance insofar as threshold injury is concerned.

F. Retinal Pathology of Threshold Laser Damage in Rhesus Monkey - page 33 on...

The lesions studied were not threshold lesions. They are stated to be "about four times over threshold", whatever that means. It may mean at energy densities of about four times the 50% level - which in itself has been estimated. Also, the data is on Q-switched lesions. Where is the data on normal lesions?

G. Experiment on Human Subject

I presume "a very advanced malignant melanoma of the choroid" implies that the lesion was large, and does not refer to metastases of the tumor. I am uncertain that allowing one day between irradiation and enucleation can be considered as justifiable, in view of the authors own statements concerning possible pressures produced on Q-switched irradiation, and the data on viability of tumor cells following irradiation which has been reported by the reviewers. Since "the macular area was obscured because the tumor partially blocked the view through the fundus camera", the actual spread of the tumor and the possibility of direct irradiation of it with consequent tumor spread on Q-switched irradiation requires consideration. It is further stated that the tumor may have blocked part of the laser beam, thus substantiating the above.

Corneal Damage Using a CO_2 Laser - page 45 on....

B. Design of Experiment

There is no justification for the statement "it is assumed that normal sensitivity to pain certainly will preclude accidental exposures longer than 1/2 second and possibly exposures as short as

1/4 or 1/5 second". By the time the reaction to pain occurs - whether long or short, the damage may have been done!

On page 46, the authors state that "an appreciable fraction of the total area of the cornea would be involved in an accidental exposure" and then turn around and say that exposures of several square millimeters of cornea are appropriate. This is a contradiction, unless it is substantiated by a) heat flow equations to show this and b) some valid argument which shows that irradiation of a small portion of the cornea permits extrapolation to total corneal irradiation.

C. Calibration of Equipment

I hope the recalibration of the TRG ballistic thermopile was good at 10.6μ.

On page 48, there is a discussion concerning the invalidity of nonhomogeneous beams for studies. This depends on <u>how</u> nonhomogeneous, and to what extent heat flow smooths out the time - temperature history of the effect of inhomogeneities.

Insofar as the use of Kalvar film is concerned, the thermal spread on 10.6μ irradiation must be taken into account to determine actual spot size.

Threshold Damage in Rabbit Corneas

In the threshold studies on rabbit corneas, more than one exposure was carried out on each cornea. There is no histology. There is no evidence of epithelial facets on continued examination.

There is no reference to previous CO_2 threshold studies - albeit on the skin, - which was reported in the same issue of NEREM as in the article referenced as # 6. The data in the NEREM report gave energy levels of the same order of magnitude as that obtained by the authors.