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Arnold S. Brownell, et al

Joint AMRDC-AMC Laser Safety Team
Philadelphia, Pennsylvania

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ARNOLD S. BROWNELL, DR.
BRUCE E. STUCK, MR.*
JOINT AMRDC-AMC LASER SAFETY TEAM
FRANKFORD ARSENAL, PHILADELPHIA, PENNSYLVANIA

INTRODUCTION

The rapid development of new laser systems with greater military significance continues unabated. The current and projected field deployment of these systems has intensified the need not only to define the potential hazards to military personnel but also to investigate the mechanisms involved in laser induced radiation injuries. For example, many of the newer carbon dioxide (CO_2) lasers are potentially hazardous because of their high power output. Definitive data are urgently required to provide additional information essential to the establishment of safety standards which would be relevant to all laser systems, for use by both system developers and field personnel.

Research establishing laser damage thresholds have generally been empirical. Each present and future generation laser system has or will have unique and varied radiation parameters such as wavelength, intensity, repetition rate and beam geometry. Similarly, the various vulnerable tissues have their own distinct physical, chemical and biological properties. Expensive and time consuming laboratory experiments are required to estimate threshold damage levels for all possible laser systems. Consequently, there is a need for a more expeditious approach. Mathematical models that accurately predict the extent of laser induced damage and provide insight into the mechanisms of the interaction of laser radiation with biological systems will significantly improve cost effectiveness.

The purpose of this paper is threefold: First, to provide data necessary for military and civilian safety communities by

presenting experimentally determined threshold doses, from two independent studies, for the minimal detectable changes in cornea and skin following exposure to CO_2 laser radiation. Second, to test the validity of a mathematical model in predicting damage thresholds. Third, to determine the extent this model accounts for differences in the experimentally determined dose-response relationships for the two tissues studied.

EXPERIMENTAL METHODS

Details of the experimental procedures, and results, have been reported (1-5). A Coherent Radiation Model 41 continuous wave CO_2 laser was used for skin exposures of less than 0.1 sec in duration and for all corneal exposures. For these experiments the beam incident on the tissue was formed by illuminating a circular aperture with the laser beam. The radiant intensity distribution in the central portion of the resulting diffraction pattern closely approximated a Gaussian distribution. The relative intensity distribution was measured with a scanning thermal sensor. The total power was measured with a CRL Model 201 power meter whose calibration had been checked at the National Bureau of Standards. The values reported in the paper represent the peak irradiance (watts/cm^2), calculated on the basis of the measured total power of the beam and its relative intensity distribution. For skin exposures in excess of 0.1 sec, a CO_2 laser designed and constructed by Martin Marietta Corporation provided the radiant energy. The multimodal, collimated output beam consisted of a mosaic of many closely spaced regions with different intensities. The relative intensity distribution within the beam varied within 25%. The reported values represent the average irradiance in the beam.

Rabbits (Oryctolagus Cuniculus) and monkeys (Macaca Mulatta and Aotus Trivirgatus) were used in the cornea threshold studies. Previous results (3) by this laboratory have shown less than a 10% difference between the damage thresholds for these three animal species. Pentobarbital sodium and halothane gas were used to anesthetize the monkeys and rabbits respectively. The pupils were dilated to enhance the observer's visualization of corneal changes. The eye was gently irrigated with physiological saline before exposure and closed for approximately 1 minute to prevent drying of the corneal surface and to maintain a near "natural" tear film. The lid was retracted and immediately irradiated at normal incidence. Two to four exposure sites on each eye of fifteen to twenty animals were irradiated for each threshold determination. The criterion for a minimally detectable response was the appearance of a greyish-white circular opacity

on the outer surface of the cornea as seen with a Zeiss biomicroscope 30 minutes post exposure.

For skin experiments, white pigs, 20 to 40 pounds each, were the test animals. Pentobarbital sodium was used as an anesthetic for animals whose skin was exposed in excess of 0.1 sec. Those whose exposure times were less than 0.1 sec received halothane gas. Three to eight animals were used for each irradiance level. The skin test area was closely clipped, cleaned, and then divided into a grid pattern of 4 rows and 10 columns. To minimize variation in area-to-area sensitivity, the exposure times were randomly assigned to the grid pattern of each animal within each irradiance group. The visual appearance of each test site was observed at the time of exposure and within 24 hours post exposure. The criterion for a positive response for a minimal lesion was the presence of a mild erythema 24 hours post exposure.

EXPERIMENTAL RESULTS

The probit method (6,7) was used in the analysis of the data. This statistical technique was developed to treat quantal response data and define dose-effect relationships. This analysis yields the median effective dose (ED_{50}), which is the irradiance for a given exposure time that has a 50% probability of producing the specified response. In this paper the ED_{50} value is defined as the damage threshold for a specified injury.

Figure 1 presents a log-log plot of the experimentally determined ED_{50} values for both CO_2 laser radiation induced minimal erythema and corneal opacities. The exposure durations range from 1 msec to 7.4 seconds while the irradiances vary from 1.2 to 800 watts/cm^2. The numerical values represented by the data points are used to generate two of the variables in the model described in the following section.

DAMAGE INTEGRAL MODEL

Theoretical Development

Most injuries resulting from exposure to laser radiation are considered to be thermal in nature. The degradation of the radiant laser energy to thermal energy leads to temperature rises in the exposed tissue. The basic principles involved in the analysis of thermal injuries in tissue were defined in a series of papers by Henriques and Moritz. Henriques (8) considered the development of thermal injuries to be time and temperature dependent, a rate process

common to many physical and biological systems. He suggested that by integrating the injury rate process over the thermal time period involved, the contributions from each time increment could be summed to yield a measure of the total damage incurred.

If the kinetics of any specific state of thermal injury can be regarded as a first order reaction at all temperatures under consideration, then the sum of the injury can be expressed as

$$\Omega = \int_{t_o}^{t} k\,dt \qquad (1)$$

where k is the specific reaction rate constant for a given thermal process and temperature, and Ω is the damage integral.

If the reaction is similar to that of many chemical and physical rate processes, the thermal inactivation rate constant should vary with temperatures as

$$k = Ae^{-B/T} \qquad (2)$$

when A and B are constants and T is the absolute temperature. For a reaction meeting the necessary thermodynamic criteria, this expression is equivalent to the integrated form of the Arrhenius equation, where B equals $\Delta E/R$, ΔE being the energy of activation and R the gas constant. In the present use of the model, A and B are considered empirical constants with no special implications.

Combining Equations 1 and 2 yields

$$\Omega = A\int_{t_o}^{t} e^{-B/[T(t)+T(0)+273]}dt \qquad (3)$$

where T(t) is the temperature rise at time t and T(0) is the initial tissue temperature in ^{o}C. This concept is equivalent to that proposed by Henriques (8) and subsequently expanded by Fugitt (9).

A mathematical equation that defines T(t) during the thermal episode for the various exposure and tissue conditions is required by Equation 3. The diathermanous, semi-infinite heat flow equation given by Carslaw and Jaegar (10) and extended by Davis (11) to apply to problems involving radiant heating of tissues is appropriate in

situations where the heat flow in the tissue space of concern can be considered to be unidirectional and perpendicular to the surface. This equation has the following form:

$$T(l,t)=\frac{2H}{\sqrt{\mu}}\left\{\sqrt{\frac{t}{\pi}}\,e^{-l^2/4\alpha t}-\frac{l}{\sqrt{4\alpha}}\,\mathrm{erfc}\left(\frac{l}{\sqrt{4\alpha t}}\right)\right.$$
$$\left.-\frac{e^{-\gamma l}}{\gamma\sqrt{4\alpha}}+\frac{e^{\gamma^2\alpha t}}{4\sqrt{\alpha}\gamma}\left[e^{\gamma l}\,\mathrm{erfc}\left(\gamma\sqrt{\alpha t}+\frac{l}{\sqrt{4\alpha t}}\right)+e^{-\gamma l}\,\mathrm{erfc}\left(\gamma\sqrt{\alpha t}-\frac{l}{\sqrt{4\alpha t}}\right)\right]\right\}. \qquad (4)$$

Although the diathermanous heat flow equation assumes a radiation beam infinitely wide with no variation in its intensity distribution, the beam widths were sufficiently large for all skin exposures to justify the use of this equation in these calculations.

Where radial heat flow must be taken into consideration, Heimbach's combined model (12) is more applicable, as follows:

$$T(l,t)=e^{-\gamma l}\sum_i\frac{\delta_i I_0\left(r_i\frac{r}{a}\right)}{\gamma^2-\left(\frac{r_i}{a}\right)^2}\left\{e^{\alpha\gamma^2 t}\,e^{-\alpha\left(\frac{r_i}{a}\right)^2 t}-1\right\}+\sum_i\frac{\gamma\delta_i I_0\left(r_i\frac{r}{a}\right)}{\gamma^2-\left(\frac{r_i}{a}\right)^2}\left\{\frac{1}{2\left(\frac{r_i}{a}\right)}\left[e^{-r_i l/a}\,\mathrm{erfc}\left(\frac{l}{\sqrt{4\alpha t}}-\sqrt{\alpha\left(\frac{r_i}{a}\right)^2 t}\right)\right.\right.$$
$$\left.-e^{r_i l/a}\,\mathrm{erfc}\left(\frac{l}{\sqrt{4\alpha t}}+\sqrt{\alpha\left(\frac{r_i}{a}\right)^2 t}\right)\right]-\frac{1}{2\gamma}\,e^{\alpha\gamma^2 t}\,e^{-\alpha\left(\frac{r_i}{a}\right)^2 t}\left[e^{-\gamma l}\,\mathrm{erfc}\left(\frac{l}{\sqrt{4\alpha t}}-\sqrt{\alpha\gamma^2 t}\right)-e^{\gamma l}\,\mathrm{erfc}\left(\frac{l}{\sqrt{4\alpha t}}+\sqrt{\alpha\gamma^2 t}\right)\right]\left.\right\} \qquad (5)$$

This equation considers a radiation beam finite in cross section with an intensity distribution exhibiting cylindrical symmetry. It was used to fit the corneal data where the small beams require the more complex equation.

Equations 4 and 5 define the temperature rise only during the exposure interval. During the post exposure period the complete expression is the identical equation minus the same equation where t is replaced by $t-\eta$ (η = exposure time). The complete development of these equations is given by Heimbach (12).

The following assumptions are applied to the application of both heat flow equations: the tissue is a semi-infinite isotropic receiver, initially at a uniform temperature throughout; its thermal properties are constant and do not vary with temperature; its surface is perfectly insulated and there are no radiation losses; the radiation input is a square wave and normal to the surface and the tissue absorbs the radiation at an exponential rate.

Thus Equations 4 and 5 are used to calculate T(t) in Equation 3 to obtain the damage integral Ω. To determine the constants A and B (Equation 3) their numerical values were adjusted until the calculated dose yielding an $\Omega = 1$ corresponded closely to each experimentally determined ED_{50} value for the minimal responses given in Figure 1.

Figure 2 shows representative histological sections of normal pig skin and monkey cornea. Although morphologically the two tissues are complex, they can be structurally described as simple three layer systems.

In the skin the three layers are: (1) The outer layer, the stratum corneum, is composed of compacted keratinized scales. The average thickness of this nonviable layer is approximately 15 microns. (2) The more deeply stained layer is the viable portion of the epidermis. Its thickness is quite variable, but in general ranges from 50 to 75 microns. (3) The underlying dermis, composed primarily of a matrix of collagen and elastic fibers, ranges up to several hundred microns in depth. Capillary loops of the skin blood supply and many nerve endings terminate within the upper portion of this layer.

Similarly the corneal layers are: (1) In vivo a 7-9 micron thick tear film covers the cornea (13). Obviously this tear film is not evident in Figure 2. (2) The epithelium averages 40 microns in thickness and, as in the skin, is capable of regeneration. (3) The stroma comprises about 90% of the entire cornea and is approximately 400 microns thick. It consists of collagenous lamellae.

The damage integral model, as presented, assumes that the thermal episode occurs in an isotropic medium. It is evident that neither tissue is homogeneous in a morphological sense. However, with the exception of the cornified upper layer of the skin, the various layers of the tissue are of an aqueous nature with a water content of approximately 80%. So, in a physical sense, as a first approximation they can be considered homogeneous and satisfy the requirements of the model.

Table I defines the variables used in the temperature calculations. The last 2 columns give the numerical value of those variables held constant to determine the damage integrals.

TABLE I

		Cornea	Skin
μ	Thermal Inertia ($cal^2\ cm^{-4}\ deg^{-2}\ cm^{-1}$)	1.5×10^{-3}	1.18×10^{-3}
α	Thermal Diffusivity ($cm^2\ sec^{-1}$)	1.5×10^{-3}	0.86×10^{-3}
γ	Absorption Coefficient (cm^{-1})	814	814
T(0)	Initial Tissue Temperature ($^{\circ}C$)	32	35
r	Distance from Beam Center (cm)	0	0
z	Tissue Depth (cm)	.0010	.0025 .0100
H	Irradiance ($cal\ sec^{-1}\ cm^{-2}$)		
t	Time After the Onset of the Exposure (sec)		

The complex variable δ_i is defined in the following equation:

$$\delta_i = \frac{\sqrt{\alpha\mu}\, A_i}{\gamma H}$$

where A_i are the expansion coefficients obtained by expanding the intensity distribution of the radiation beam into a Fourier-Bessel series of zeroth order. The roots of the zeroth order Bessel function are represented as r_i and 'a' is the radial extent of the expansion. For the corneal calculations the intensity distribution is considered Gaussian with a 1/e radius of 0.14 cm.

In the case of the skin, the two thermal constants, μ and α, were experimentally determined by a radiant heating method (11) for porcine skin. Measurements of the absorption of 10.6 micron radiation by epidermal tissue (14) was not significantly different from that of water; therefore, the latter absorption coefficient (15) was used. T_o was chosen as a close approximation to a measured mean temperature of 35.2°C for 3 sites on each of 12 experimental animals.

Since the cornea including the tear film is essentially aqueous in nature, the thermal constants and the absorption coefficient of water were chosen (16,15). For the initial corneal temperature the experimentally measured value of 32°C was used (17).

For the cornea, the minimal response is direct and immediate. The resulting opacities were 200 microns in diameter. The fact that the coagulum disappears within 24 hours substantiates the suggestion that only the anterior portion of the epithelial layer is involved. Consequently, a depth of 10 microns, which includes the tear film, was selected to calculate the damage thresholds for this tissue.

On the other hand, the erythemic reaction is a secondary response. Epithelial injury produces a substance which diffuses to the underlying capillary bed and thus stimulates an increase in blood volume in that region. The result is an increase in redness relative to the surrounding tissues, as seen through the translucent epidermis. The minimum histological changes in tissue samples showing an erythemic response were detected within a 10 micron depth in the viable layer of the epidermis. The depth of 25 microns chosen to calculate damage thresholds for the erythemic reaction includes the 15 micron cornified layer of the epidermis.

Results and Discussion

The curves in Figure 1 represent the values generated by the damage integral model for the minimal responses. The inactivation coefficients (from Equation 3) were obtained by fitting the curves to the experimentally derived data points given in the figure. They are:

	Skin	Cornea
ln A	146.5	141.6
B	49,000	48,400

The nearly equivalent numerical values for B suggest that the two responses have essentially the same inactivation energy requirements.

The two curves in Figure 1 have some similarity in shape. At the lower exposure times both show an increase in slope with decreasing exposure time. However for pulse durations in excess of 0.1 sec, while the slope for the erythemic curve is constant, that for the corneal opacity data shows a significant change.

The same curve fitting the corneal opacity data for the time interval from 0.1 to 40 sec is given in Figure 3. The calculations were repeated, using the same input parameters with the diathermanous heat flow equation which generated the second dashed line (- - - -). The resultant curve also shows a constant slope for the longer exposure times. For times less than 0.1 sec the calculated damage threshold values are essentially identical using either heat flow equation. Therefore the difference in the two curves can only be attributed to the radial heat flow in the tissue.

This difference reemphasizes the need to carefully consider beam geometry in deriving safety standards from experimental data. The model predicts even at depths less than 10 microns the beam size can significantly affect the amplitude and duration of the thermal episode. This phenomenon markedly increases with increasing depth.

As a further test of the predictive value of the model, damage thresholds for white burns in skin were calculated and compared with experimentally derived values. White burns in the skin are similar to the corneal opacities. They are an immediate coagulation of the superficial layers of the skin. However, the opacification must be rather extensive in order to produce enough contrast to detect this level of damage. Hysell, et al (18), indicated that white skin burns had histopathological effects extending into the dermis, some of which showed coagulated collagen bundles in the superficial dermis. For calculations involving these burns, a depth of at least 100 microns appears appropriate.

Using the inactivation coefficients obtained for the corneal data, a depth of 100 microns, and all other parameters used for the skin, the solid curve in Figure 3 was computed using the diathermanous heat flow equation. The solid data points represent the experimentally determined ED_{50} values for 'white' burns in porcine skin. The data points reasonably correspond to the theoretically derived curve except for exposures of 1 sec and less where the experimental results deviate significantly from those predicted. At these exposure times, the calculated temperature rise at the surface of the aqueous portion of the epidermis exceeds 100°C. Thus a portion of the absorbed radiant energy must be expended into the latent heat of vaporization. Consequently, more incident energy would be required to sufficiently

elevate the temperature at a 100 micron depth. This possibility is supported by experimental results using shorter exposure times in which steam blebs appeared during the exposure episode at doses lower than required to produce detectable white burns. The present model requires further expansion in order to account for these responses.

Rigorous testing of this model, which has been expanded to include cases of tissue damage from repetitively pulsed laser beams, as well as a two layer model is continuing.

From the foregoing discussion it can be generally concluded that: (1) The damage integral model can be used to predict the minimal response of the skin and cornea to CO_2 laser radiation. (2) The model describing the dose-response relationship for the coagulative process in the cornea gives a reasonable prediction for a similar response mechanism, white burn, in porcine skin within the limits assumed by the model. (3) Confirmation of the inactivation coefficients for the corneal and skin response mechanisms will permit the model to be used in predicting damage thresholds for different laser systems. (4) The success of this model over such a wide range of exposure durations and irradiances justifies its further testing and possible expansion in order to realize a significant reduction in the time and money required to provide data relevant to the evaluation of laser radiation hazards.

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In conducting the research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care" as promulgated by the Committee on the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Sciences - National Research Council.

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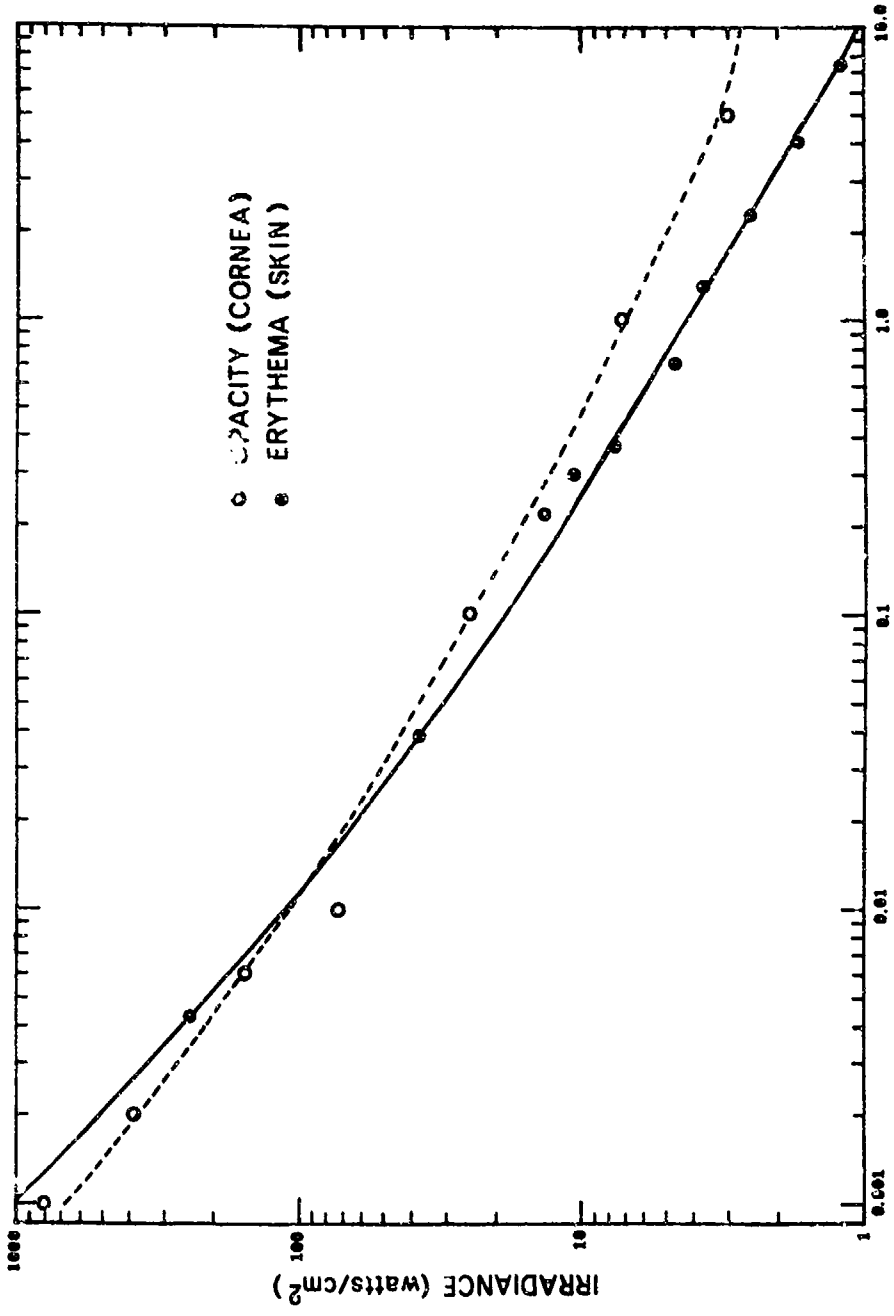

Figure 1. Experimentally derived ED_{50} values for CO_2 laser radiation induced minimal erythema in skin and corneal opacities.

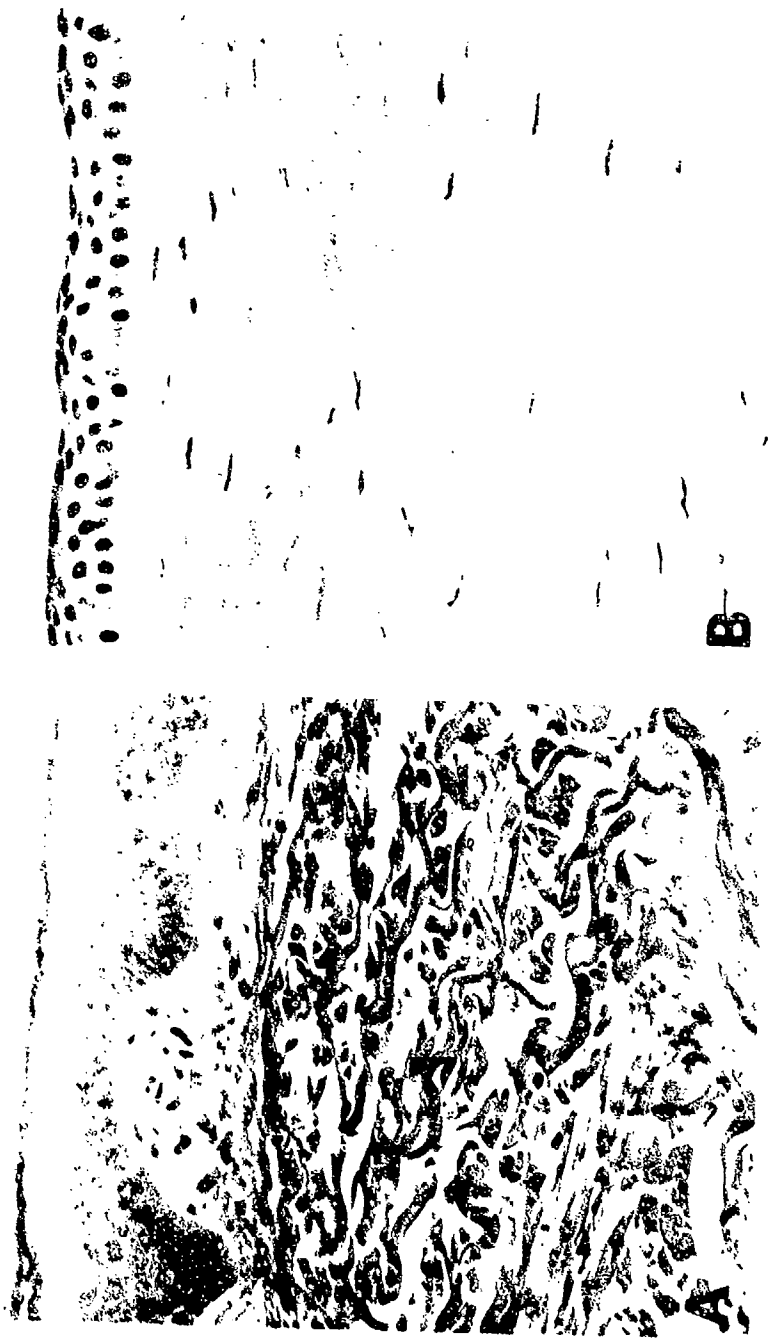

Figure 2. Histological sections of normal porcine skin (A) and monkey cornea (B) stained with hematoxylin and eosin. Separation of skin corneum is artifactual.

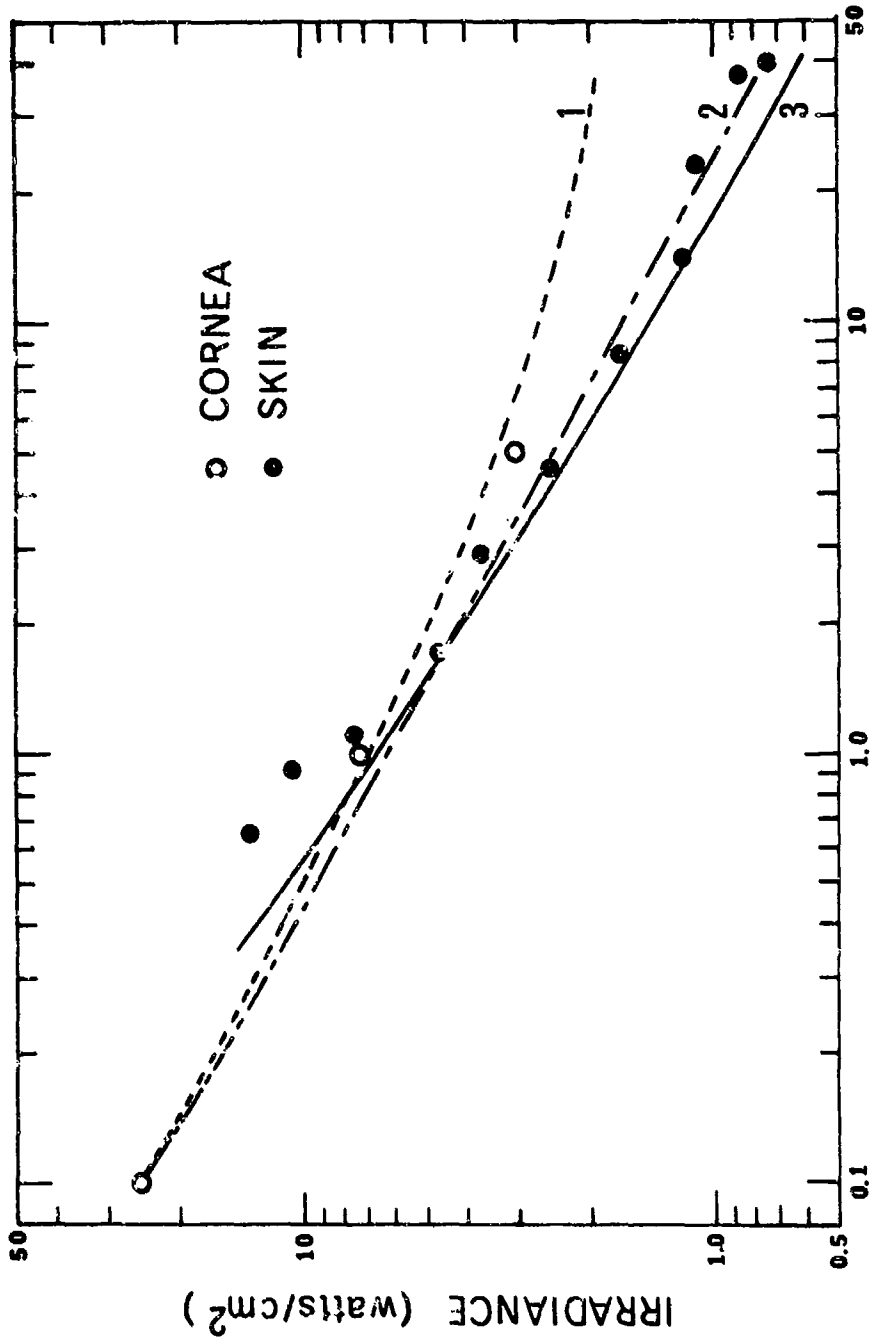

Figure 3. Comparison of coagulative effects using the damage integral model. Combined model for corneal opacities (1); diathermanous model for corneal opacities (2); and white skin burns (3).