THE DEVELOPMENT AND TESTING OF AN ISOTROPIC LIGHT SOURCE

THE DEVELOPMENT AND TESTING OF AN ISOTROPIC LIGHT SOURCE OR DETECTOR AND ITS APPLICATION TO PHOTOCHEMOTHERAPY

By

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ABSTRACT

The prcduction of an isotropic source or detector by fixing a small resin sphere onto one end of an optical fibre is discussed. The potential application of these fibres to Photochemotherapy is reviewed.

Isotropic fibres are used as both sources and detectors in experiments designed to measure the amount of light loss in a 1% solution of Neutralipid (an intravenous nutrient supply). Determination of light loss in this solution is important in one application of Photochemotherapy where an estimate of the irradiation time is required.

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CHAPTER 1

INTRODUCTION

This paper describes a number of projects in the development of light delivery and detection systems for experimental and clinical Photochemotherapy (PCT). Photochemotherapy (also called photoradiation therapy, phototherapy and photodynamic therapy) is a relatively new procedure and has been shown to be effective in treating a wide range of solid, malignant tumors (Dougherty, 1982).

1.1 Photochemotherapy

During the PCT procedure, a photosensitizing drug e.g. hematoporphyrin derivative (HPD), is injected into the patient. This drug is initially taken up by all of the tissues of the body; however, 2-3 days later it has been retained primarily in the tumor cells alone. If light of the appropriate wavelength (i.e. the wavelength to which the drug is sensitive) is then delivered to the tumor cells, a toxic reaction occurs and those cells die (Dougherty, 1982). The exact mechanism of this reaction and subsequent cell death is as yet unknown.

As with any new procedure, many problems in PCT have not yet been resolved and the present interest in fully exploring the capabilities and limitations of PCT comes from

the prospective advantages over conventional techniques that this method offers. First, tumor response to PCT is frequently seen within 1-2 days following treatment (Dougherty, 1982). Second, unlike chemotherapy and large amounts of ionizing radiation, the exposure and damage to healthy tissues are rather slight (Dahlman et al., 1983). Third, unlike surgery, PCT is a non-invasive (or minimally invasive) way of eradicating tumors. However, the attractiveness of using photosensitizing drugs and light in cancer treatment calls for careful analyses of not only the chemical and biological properties of the drugs involved, but also of the nature of light interactions with tissue. This report will deal with the problems encountered in knowing how much light is delivered during treatment.

An ideal photosensitizing drug would have the property of being taken up and retained only by malignant tissues (Dougherty, 1982). No ideal substance has yet been found. That is, even several days after injection, small amounts of the drugs presently used are withheld by healthy tissues (Dougherty, 1981) and thus normal tissue effects are the major factors limiting the amount of light that can be used during therapy (Dougherty, 1981; Profio and Doiron, 1981). It is necessary then, to know exactly how much light to deliver in order to just eliminate the tumor and not damage other tissues. This requires a detailed under-

standing of how light interacts with tissue and the percentage of photons that are scattered and absorbed as a function of distance from their source. There is not, however, an abundance of data available in this area as measuring the level of photon flux at depth in biological tissue is extremely difficult (Preuss et al., 1983).

1.2 Difficulties in Measuring Photon Flux

i) Optical properties of mammalian tissues vary widely from tissue to tissue due to different refraction, reflection, absorption and scattering characteristics (Wilson et al., 1984; Bolin et al., 1984). These differences will influence the intensity of light reaching the area of interest. Further, because of the variation in tissue composition, measurements of the optical properties of one tissue type may not be useful when dealing with other types (Bolin et al., 1984).

ii) The presence of boundaries and interfaces between tissues, and inhomogeneities within a tissue will affect the distribution of light (Wilson et al., 1984; Bolin et al., 1984). Further, light will be affected differently, depending on its wavelength.

iii) If the detector used to measure the light is a particularly invasive device - then this introduces more boundary surfaces for the light to interact with. It also disturbs the tissue such that its optical properties may be

changed and biological damage may occur.

The difficulties mentioned here are compounded by the fact that there are many different tissues of interest and several photosensitizing drugs available which are sensitive to different regions of the visible spectrum. Further, because the optical properties of tissue can be changed with the presence of a large, invasive detector, *in vivo* and *in vitro* measurements taken with these devices may not be reliable indicators of true optical characteristics. Optical fibres are very thin, flexible conductors of light and therefore can be very useful as detectors in biological tissue. The rest of this report will focus on attempts to measure 630 nm (red) light at depth in an *in vitro* situation using optical fibres that have been fitted with "isotropic" tips.

1.3 Optical Fibres

Optical fibres have the ability to conduct light with very little transmission loss. They are made of translucent materials, most commonly glass or fused silica, and are 10-1000 microns in diameter (The Optical Industry & Systems Purchasing Directory, 1982). The glass or silica core is coated with a layer of material having a lower refractive index, usually plastic. By Snell's law then, total internal reflection within the fibre and therefore efficient light conduction, is possible.

One of the features of optical fibres that can be seen as either a drawback or an advantage is its very small numerical aperture (see Figure 1). Note that there is a maximum value of the angle of incidence for which the light beam or photon will be internally reflected. Rays incident on the fibre face at angles greater than the maximum acceptance angle (θ_{max}) will strike the interior wall at an angle too small to be completely reflected. They will only be partially reflected at each encounter with the core-cladding interface and will quickly leak out of the fibre (Hecht and Zajac, 1974).

In using an optical fibre as a light detector then, one is limited to measuring only that portion of the flux incident within the acceptance angle of the fibre aligned with the longitudinal axis of the fibre (Marynissen and Star, 1984; Siegmund, 1978) (see Figure 1). This means that a single reading from the fibre detector will <u>not</u> give a true estimate of flux unless there is no angular dependence to the radiance i.e. isotropic light distribution. However, given the occurrence of boundary surfaces (Bolin et al., 1984) (i.e. the heterogeneity) in tissue, assuming an isotropic flux may be an oversimplification which contributes unacceptably large errors to the measurements of light intensity. Ideally, the problem due to the angular dependence of the flux can be eliminated with the use of an isotropic detector (Marynissen and Star, 1984) - one that

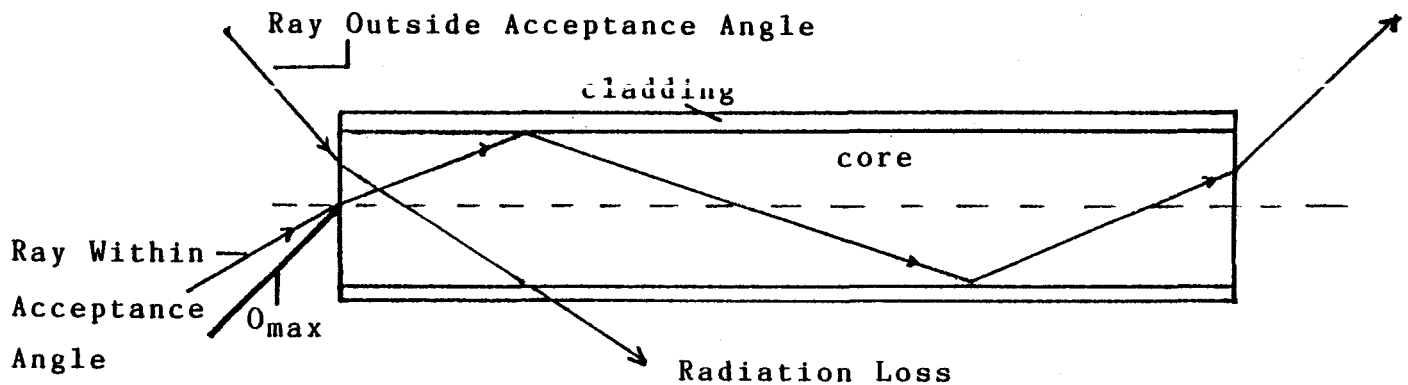


FIGURE 1: LIGHT TRANSMISSION THROUGH AN OPTICAL FIBER

detects any light photon it encounters and not just those travelling in a certain direction. This report will discuss the construction and testing of isotropic-tipped optical fibres and their subsequent use as light sources and/or detectors.

1.4 Experimental Application of Isotropic-Tipped Fibres

The isotropic fibres developed at this lab were involved in making measurements on a therapeutic device used in the (PCT) treatment of brain cancer. This therapeutic, light-delivering apparatus is used following the surgical removal of solid tumors in the brain.

Because of the diffuse nature of cancerous tumors, it is impossible to surgically remove the entire malignancy without taking with it some of the adjoining healthy tissue. Due to the nature of the tissues surrounding a brain tumor however, it is more essential to ensure total safety of the healthy tissue than to totally remove the cancer. Unfortunately, the residual tumor cells subsequently cause tumor regrowth and will ultimately kill the patient. With the brain applicator developed at this lab, it now appears possible to eradicate the tumor cells left behind with minimal damage to the healthy brain.

The spherical portion of the brain irradiator (see Figure 2), that portion which delivers light, is inserted into the cavity that tumor removal has produced. This

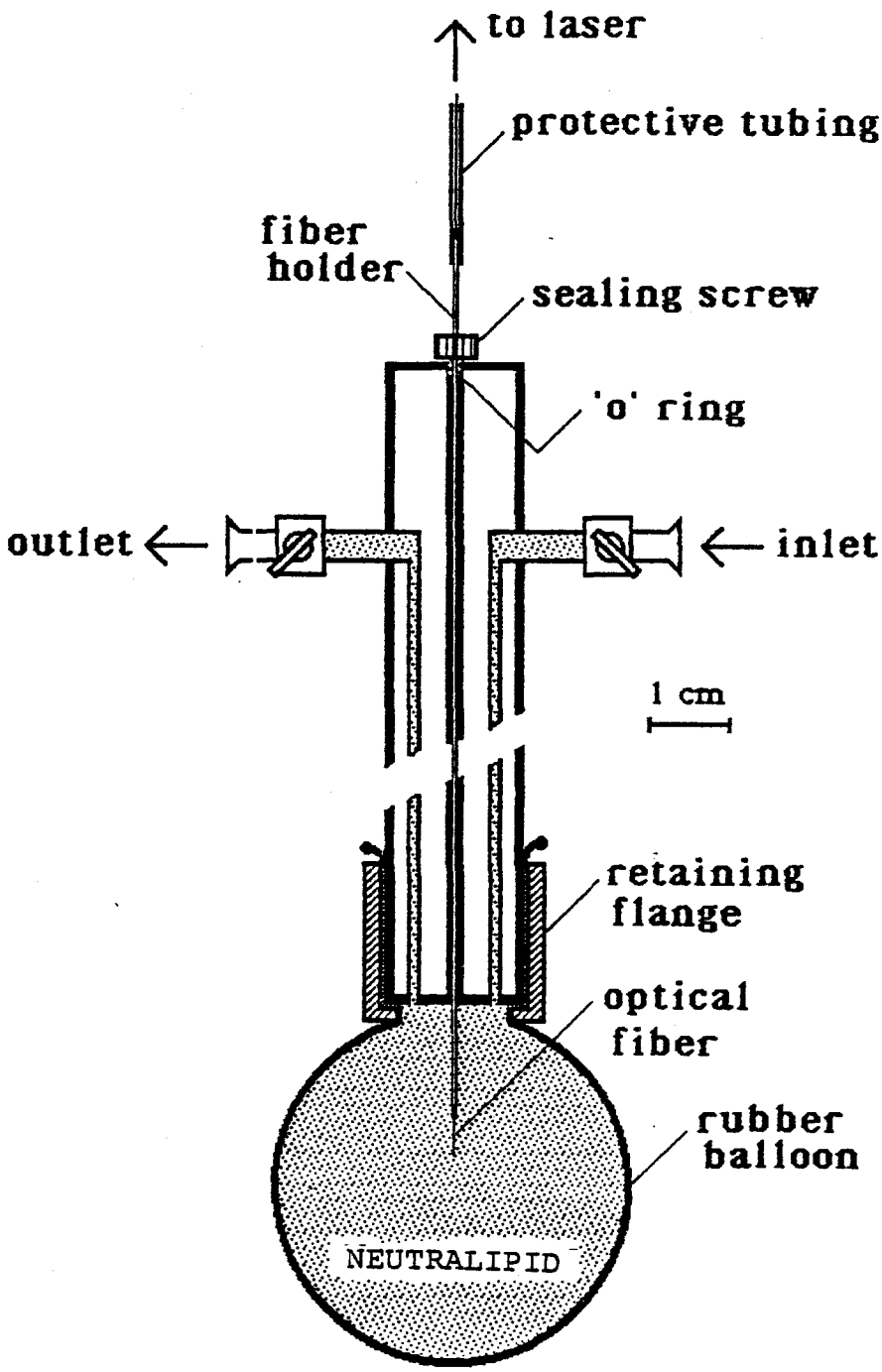


Figure 2: Brain Irradiator (Mark II)

balloon-like end is inflated to fit the size of the cavity. The inflation is carried out by filling the balloon with a lipid-glucose colloid, Neutralipid. (Neutralipid is a milky-white fat emulsion used as an intravenous nutrient supply). Into the centre of this fluid-filled balloon is inserted an optical fibre through which 630 nm light is passed. The Neutralipid acts as a scattering medium so that when the 630 nm photons emerging from the fibre finally reach the outer edge of the rubber balloon, their angular dependence has been lost and the flux from the balloon is isotropic. That is, the Neutralipid is used to ensure that all areas of the tumor bed are irradiated equally.

Neutralipid is a highly scattering medium. It also has a finite, but very small absorption coefficient and therefore absorbs some of the light that comes from the optical fibre. Because the size of the balloon is varied to fit each individual tumor bed, then the amount of Neutralipid required to fill the balloon changes from patient to patient. What is needed then, is a measure of how much light is absorbed as a function of Neutralipid volume (or alternatively as a function of balloon radius) so that the total amount of light that reaches the tumor cells can be calculated. This paper describes the way in which an estimate of the effective absorption loss Neutralipid (how

much light leaves the sphere as a function of radius) and the true absorption coefficient (the probability of a photon being absorbed per unit path length) are determined.

CHAPTER 2

MATERIALS AND METHOD

2.1 Manufacture of Isotropic-Tipped Fibres

As discussed in section 1.3, the small numerical aperture of optical fibres limits their usefulness as light detectors. Accurate measurements of irradiance can only be made in a light field where there is no directional dependence. Thus there are strong reasons for attempting the manufacture of detectors with an isotropic response. In this laboratory, it was found that building a resin sphere on one end of the fibre resulted in a near-isotropic response.

The manufacture of the isotropic tip begins by stripping the cladding from one end of the fibre, merely by burning it off and wiping the ash residue. This was found to be less damaging to the fibre than cutting the cladding; cutting often resulted in scarring of the silica. This scarring would cause light loss and would also weaken the fibre so that breakage would occur more often.

After the cladding had been removed it was necessary to make the end of the fibre slightly bulbous by melting it with a Hydrogen-Oxygen blow torch. This was necessary so that the resin sphere would not slip off the glass core when it had dried. The rounded tip was then dipped into a

commercial epoxy mixture to which a quantity of glass microspheres (nominal diameter - one micron) had been added*. The microspheres acted as scatter centres that would allow light to enter the fibre regardless of the angle of incidence. After the epoxy had dried, the tip was dipped into a mixture of dilute polyvinylacetate (PVA) and microspheres†. Undiluted PVA tended to produce creasing on the ball as it dried. This was presumably because the outside layer shrank as it dried, putting pressure on the softer, inner portion.

The tip was dried, and then repeatedly dipped into PVA and dried, 10-15 times. Next, because dried PVA is soluble in water, the tip was dipped in a second mixture of epoxy-plus-microspheres. At this point the tip measured 3 - 3.5 mm in diameter so care had to be taken to ensure that gravity did not pull the viscous epoxy into an ellipsoidal shape while drying i.e. the tip had to be inverted several times during the five minute drying period to keep the spherical shape. Finally, to make the epoxy non-absorbent, it was sprayed with a thin layer of commercial artist's lacquer.

*The volume of epoxy to microspheres was approximately 4:1.
†The volume of PVA to microspheres to water was approximately 4:2:1.

A photograph of an isotropic-tipped fibre can be seen in Figure 3 and a schematic diagram in Figure 4. Although potentially very useful as either a light source or detector, the main drawback of this isotropic tip is its fragility. Because the protective plastic cladding of the fibre has been removed near the tip, it is very easy to break the exposed glass between the unstripped portion, and the resin sphere.

Variations on the above method of making the isotropic tips were attempted but usually resulted in reducing the isotropy of the fibre. For example, making the tips larger not only reduced transmission of light through the fibre (i.e. due to absorption in the PVA or resin), but also make it more difficult to keep the tip spherical while drying.

2.2 Measurements of Transmission of Isotropic Tip

The resin sphere on the end of the fibre is quite opaque. In order to measure how much light is absorbed in the resin or is reflected back into the fibre, a radiometer and a Helium-Neon laser were used. The He-Ne laser (Spectra-Physics Model 145) produces a 0.5 mm diameter beam of 632.8 nm (red) light and has a power output of approximately 2 mW.

The beam of the laser was directed into the flat end of the isotropic fibre (i.e. the unmelted end). This

Figure 3

Photograph of Resin-Tipped Fibre

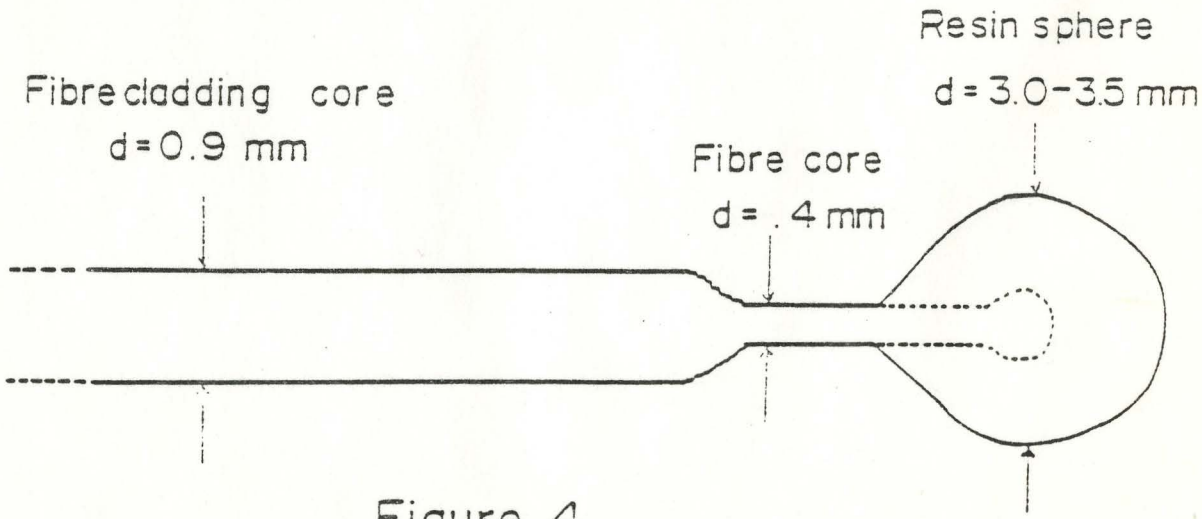


Figure 4

Schematic Diagram of "Isotropic" Resin-Tipped Optical Fibre

end of the fibre was held rigid in the beam by mounting it in a styrofoam block which was fixed to a microscope stand. The fibre could then be manipulated in a given plane such that it was centered in the beam, and maximum light output from the other, isotropic end was obtained (see Figure 5).

The radiometer/photometer (Optikon 88XL) is a photoconductive instrument used for measuring optical power, i.e. the total radiant energy per unit time. The radiometer had two interchangeable sensor heads. The first (#150) had a flat entrance window and only detected that radiation which was incident upon its face. To measure the <u>total</u> flux from a source radiating into directions other than toward the source (e.g. the case of the isotropic fibre), it is necessary to detect all of the light. This was accomplished by placing the source in an integrating sphere which was attached to the alternate (#350) sensor head. The integrating sphere used for the isotropic fibre transmission measurements was a 3 inch diameter sphere coated on the inside with barium sulphate. The barium sulphate coating reflects all light emanating from the source many times. Thus the amount of energy that enters the detector is a constant fraction of the total energy radiating from the source, regardless of the initial direction of the photons.

With the flat end of the fibre exposed to the He-Ne

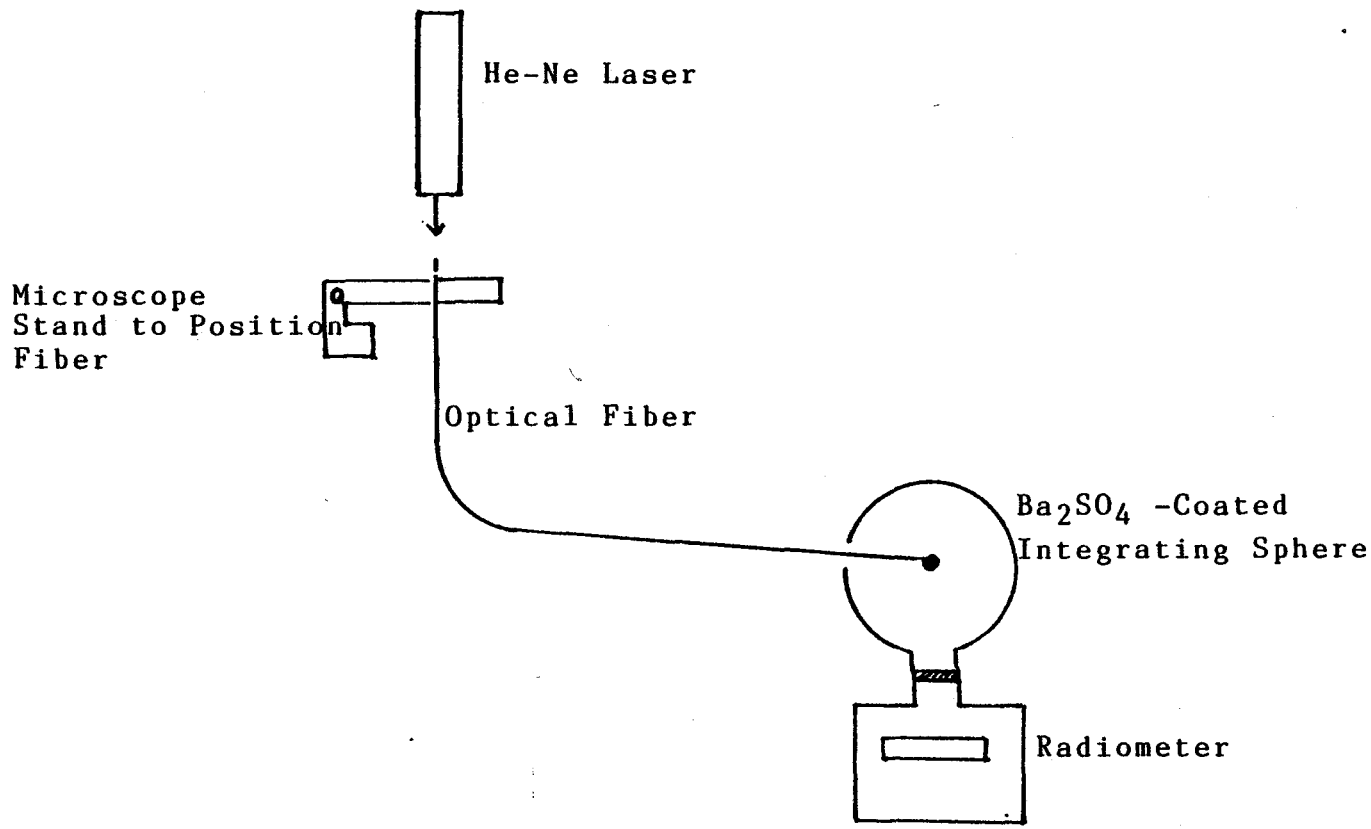


FIGURE 5: EXPERIMENTAL APPARATUS USED TO TEST % TRANSMISSION OF RESIN-TIPPED FIBERS

laser beam, the illuminated isotropic end was lowered into the integrating sphere. Comparing the power reading obtained with this set-up with that obtained by shining the laser beam through the ordinary fibre (i.e. with the isotropic tip removed) and into the integrating sphere gave an estimate of how much light is lost in the isotropic fibre tip.

2.3 Measurement of Isotropy of Tip

The isotropy of the tip was measured as follows. Keeping the flat-cut end rigid, the laser beam was directed into the fibre so that the spherical tip at the other end acted as a source as in Section 2.2. An apparatus was constructed which held the fibre at the same height as the radiometer, and at the same time allowed the fibre to be rotated through 360 degrees, keeping the isotropic tip at the same point in space (see Figure 6). With the fibre mounted in its holder, the optical power was recorded every 10 degrees.

2.4 Application of the Isotropic Fibres to Measurements of the Brain Applicator

It was originally proposed that the isotropic-tipped fibres would be used as light sources in the "brain applicator" i.e. the device used in the PCT treatment of brain tumors. The balloon-like portion of the brain

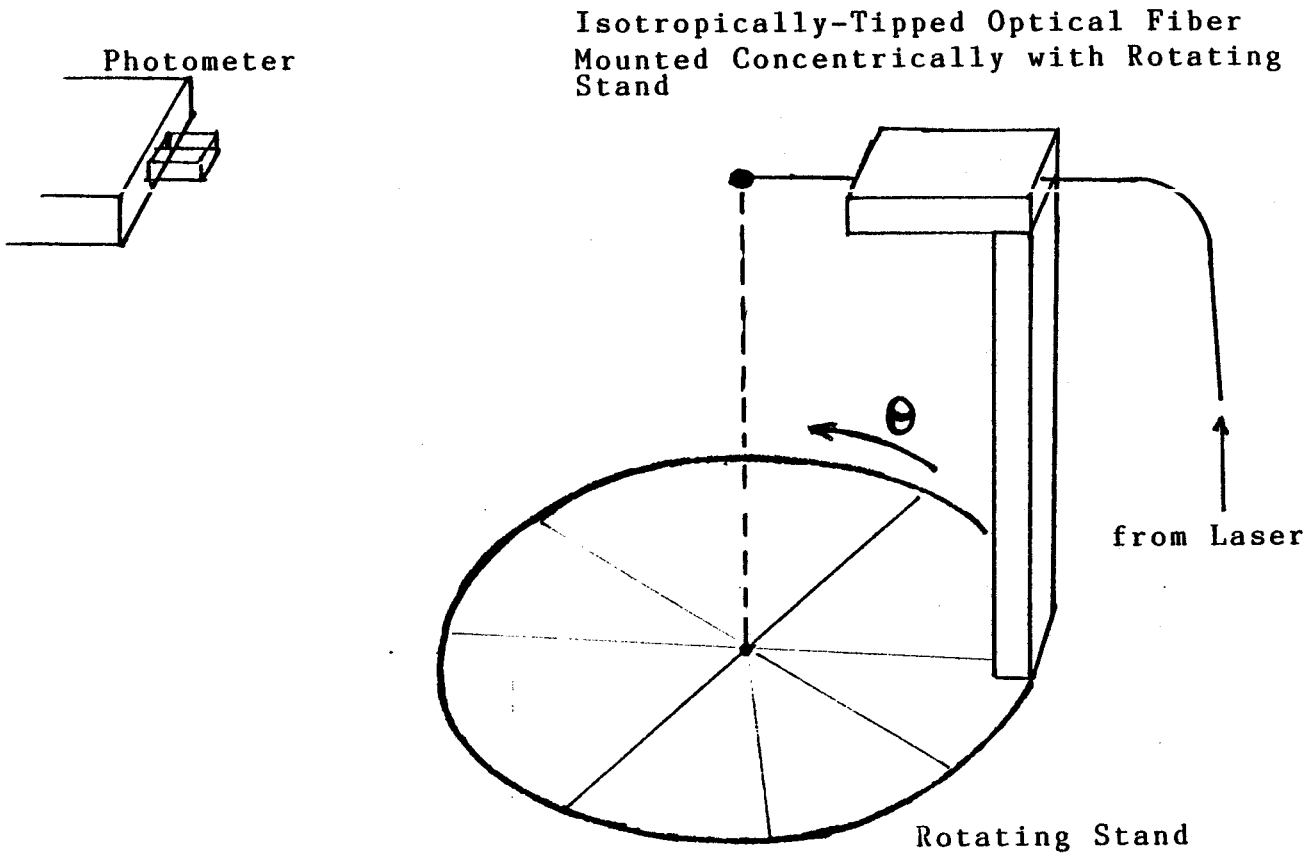


FIGURE 6: APPARATUS FOR MEASURING IRRADIANCE AS A FUNCTION OF THE ANGLE θ: ISOTROPY TEST

applicator, which is inserted into and irradiates the tumor cavity, would be filled with distilled water. At the centre of this balloon, an isotropic-tipped fibre would irradiate the balloon, and thus the tumor bed, isotropically. However the design was changed to favour flat-cut fibres over isotropic fibres for several reasons. 1) The resin tips are somewhat too fragile for use in a surgical situation. 2) As noted, the resin spheres only transmit a portion of the light that is delivered to the other end of the fibre. A flat-cut fibre delivers more light per unit time and surgery can be terminated sooner. 3) While the laser used for testing the isotropic tips has a power output of only 2 mW, the therapeutic lasers are much more powerful (up to 1500 mW) and there was some concern for heat damage to the resin/PVA.

It was found that with a flat-cut fibre, isotropic light output from the balloon could be obtained by using a light scattering liquid consisting of a 1.0% solution of Neutralipid*. Neutralipid can be sterilized and is non-toxic. If the radius of the balloon exceeds 2 cm, enough scattering will take place to ensure isotropic irradiance of the tumor bed (see Figure 7). The total attenuation

*The 1% solution referred to here is 1% of the bottled, 10% solution obtained from the pharmacy.

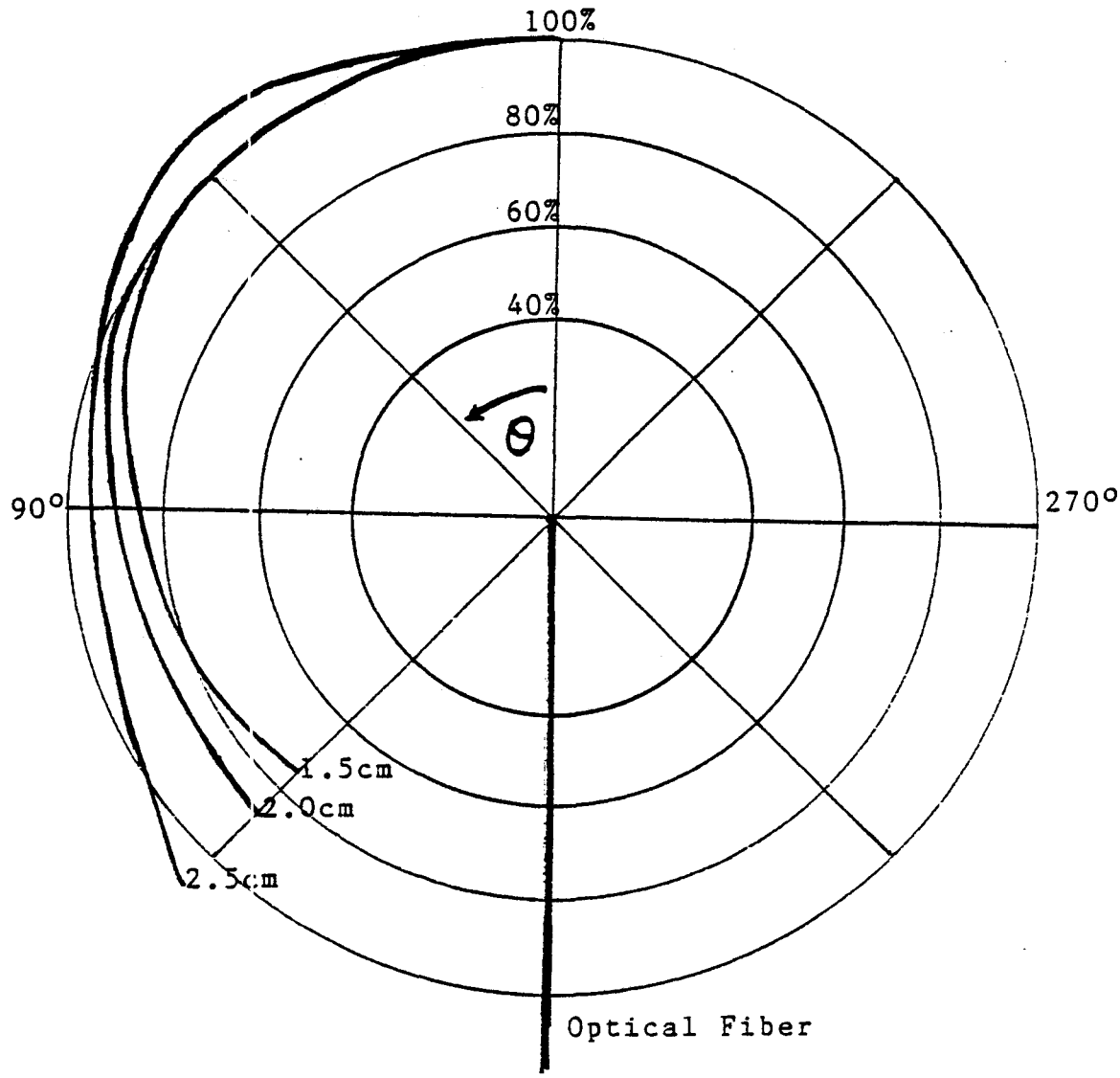


FIGURE 7: POLAR DIAGRAM FOR THE RELATIVE IRRADIANCE AT THE SURFACE OF SPHERES OF RADIUS 1.5-2.5 cm FILLED WITH 1% NEUTRALIPID AS SCATTERING MEDIUM. Only one half of the symmetrical angular distribution is shown. The irradiance is normalized to the value in the forward direction ($\theta=0^{o}$)

coefficient of Neutralipid was measured. This involved aiming the laser beam through a quartz cuvette filled with solutions of differing concentrations of Neutralipid. A 1.83 cm diameter iris was placed 12.7 cm from the cuvette (see Figure 8). A 0.5 cm iris was positioned 100 cm from the first, and light passing through both was collected by an isotropic fibre coupled to a photon counter (discussed below). The value of the attenuation coefficient obtained from a plot of $-\ln (I/I_o)$ vs. concentration of Neutralipid where I_o is the photon count at 0.0% Neutralipid was 0.44 ± .09 mm%.

Although isotropic fibres will not be used clinically in the treatment of brain tumors, they were used in the laboratory to determine how much light is absorbed by the Neutralipid in the brain applicator as a function of radius. In these experiments the isotropic fibres were used both as sources and as detectors.

Hollow glass spheres of different diameters (2.5 - 7.1 cm radii) were used to simulate inflation of the applicator balloon to various sizes. The balloon itself was not used as it was difficult to reproduce required sizes, and the unsupported rubber balloon did not remain spherical at larger diameters due to the weight of the fluid.

The flat-cut end of the source fibre was held secure in the microscope stand and coupled with the laser

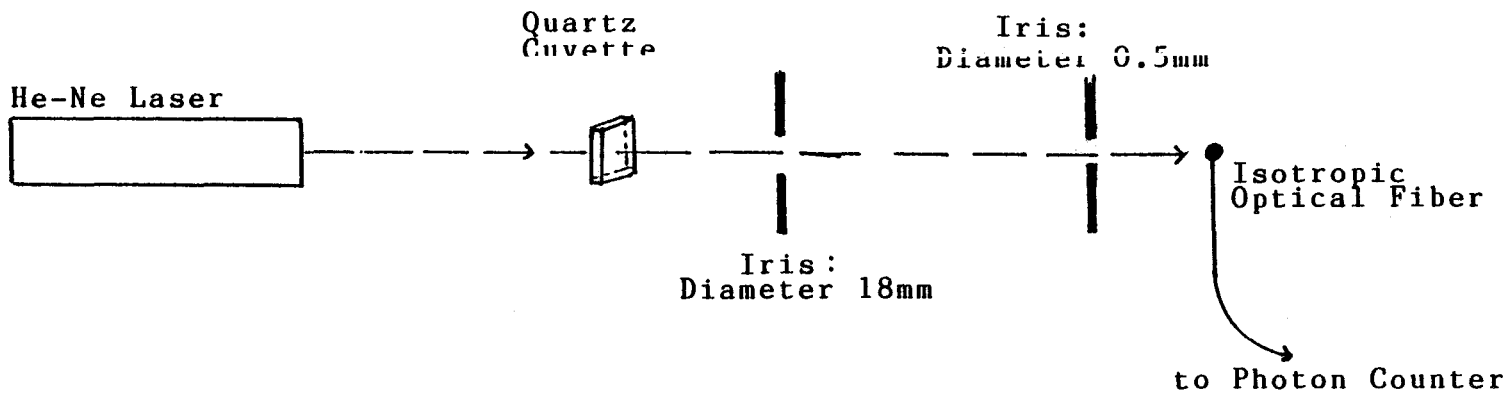


FIGURE 8: APPARATUS FOR MEASURING TRANSMISSION OF LIGHT THROUGH NEUTRALIPID TO OBTAIN VALUE OF μ_t

output. The other (isotropic) end was held in a 17.5 cm long stainless steel biopsy needle. Only the resin sphere remained exposed. The biopsy needle ensured that the fibre did not move after being placed in a fibre holder (the plastic-clad fibre is very flexible). It also covered that portion of the fibre near the resin sphere that had been stripped of its cladding. In this way the biopsy needle helped to protect the weak, exposed portion of the fibre from breakage.

The light source (the isotropic tip) was suspended by the fibre holder (see Figure 9). With a retort stand and clamp, the glass spheres could be positioned such that the source was always situated in the centre of each sphere. The detector, a second isotropic fibre, was placed at the same height as the source, and far enough away for the illuminated sphere to approximate a point source. This distance was determined by measuring the number of photons emanating from the largest source sphere as the detector fibre moved further and further away. When the photon count (corrected for the square of the source-detector separation) no longer varied as a function of distance, then the source approximated a point.

The detector fibre was coupled to a photon counter. This apparatus consisted of a fibre holder which could contain up to 21 separate fibres, a narrow slit to admit the light of one fibre, and a stepping motor to align the slit

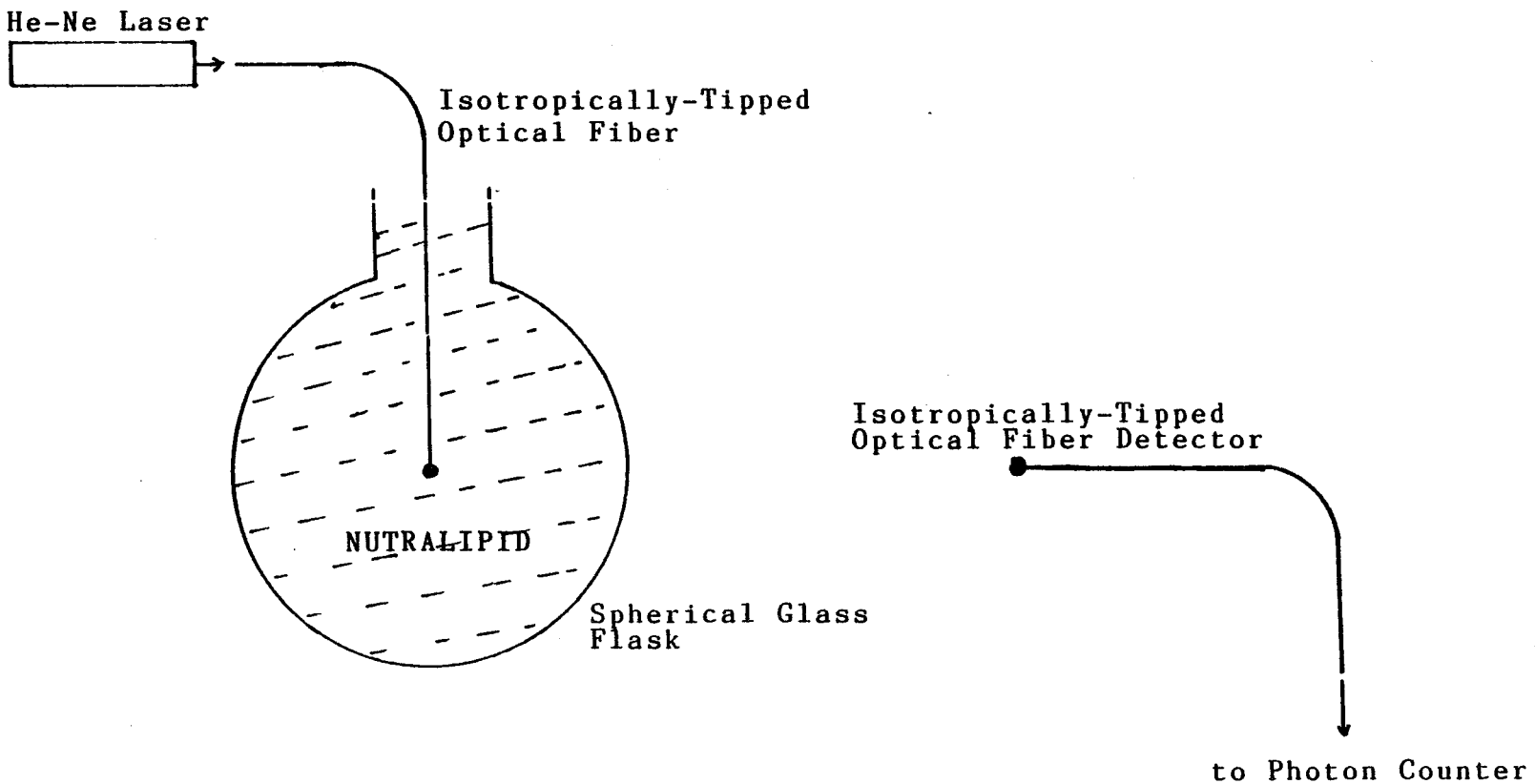


FIGURE 9: APPARATUS FOR MEASURING ABSORPTION LOSSES PER UNIT SPHERE RADIUS IN NEUTRALIPID

with the required fibre. It was possible to operate this system under computer control. The light that passed through the slit entered a diffraction grating monochromator. Light from the monochromator was then sent to a photomultiplier and discriminator. The scalar and timer were set so that photons could be counted for a predetermined length of time. This could also be manipulated by appropriate software.

The experimental set-up thus consisted of an isotropic tipped fibre illuminating a glass sphere with light from a He-Ne laser, and a second isotropic fibre detecting this light and sending it ultimately to a photomultiplier tube. There were eight glass spheres used for the experiment and eight sets of two measurements each were taken. The first measurement in each set involved filling the sphere with water and recording the number of photons counted over a given period of time. The water was then removed using a hypodermic syringe and rubber tubing. The water was removed in this way, rather than unclamping the sphere and emptying the water, so that the isotropic tip would remain in the same position with respect to the sphere for both measurements. For the second measurement, the sphere was filled with a premixed solution of 1% Neutralipid and 99% water, and the photon count was taken for the same period of time.

Taking the natural logarithm of the ratio of the photon count with Neutralipid to that with water, and plotting this value against sphere radius should produce an estimate of the effective absorption loss per unit radius for the 1% Neutralipid solution. However, the initial results of this experiment were not only inexplicable they were also non-reproducible. For example, a smaller sphere would often appear to absorb more light than a larger sphere and that particular sphere which was most absorbing in one trial would not be the most absorbing in the next.

A. It was then suggested that the changes in the amount of light absorbed in Neutralipid may be too small to be seen above the variations in background light. This background would consist mainly of the light emanating from the sphere in directions other than directly into the detector; light which would scatter off parts of the experimental apparatus and only indirectly reach the detector. The amount of this background light would vary, depending on the size of the sphere and the nature of the fluid it contained. To measure the background, a piece of flat black paper was used to cover that portion of the sphere seen by the detecting fibre. The detector would then see only that light which was scattered by objects near the source. A background measurement was taken for

all conditions i.e. for each sphere, with and without absorbing medium.

B. Measuring and subtracting the background in each case, however, did not produce understandable or reproducible results. It was then thought that the source fibre may have been moved during removal of the water by the rubber tube and syringe. This would alter the position of the source with respect to the detector and would mean that the water and Neutralipid measurements could not be easily compared, i.e. geometric factors would have to be considered before taking a simple ratio. However, moving the source fibre 3 mm in any direction in a 3.0 cm (radius) sphere containing Neutralipid, or 5 mm in a 4.1 cm sphere (both of which are unreasonably large movements), resulted in deviations in the photon count which were less than 4% of the count in the centre of the sphere. This deviation is too small to explain the erratic results of the experiment.

C. The possibility was then considered that background other than light scattered off the apparatus may constitute a large portion of the measured readings. If this were so, the small changes in readings expected to occur between spheres would be marked. To eliminate most of this background, a large (28 x 32 x 52 $inch^3$) plywood box was constructed. The inside was painted flat black. One side

was attached to the box by hinges and could swing open to allow manipulation of the experimental apparatus which was set up inside. The set-up was the same as already described except for the presence of a wall which separated the source and detector (see Figure 10). This wall contained a 'window' through which the detector could see the source. The window could be fitted with cardboard inserts (also painted flat black). Each of these inserts contained its own window which corresponded to a particular sphere size. The window allowed the detector to see only the sphere, and eliminated as much of the scatter radiation as possible. To measure background, a black cardboard shield was placed between the light source (the sphere) and the window. Unfortunately, performing this experiment with the aid of the black box did not yield the expected results. It now became clear that the absorption losses in Neutralipid are very small. The new set-up using the black box, however, eliminated most of the background and therefore even small absorption should be measureable. It was necessary to find another source of error. The possibility that the laser-to-source alignment may be shifting was considered (e.g. variation in laser input due to small movements of the laboratory bench or even to movements of the laser beam with respect to the laser housing).

D. To correct for small changes that may occur in the

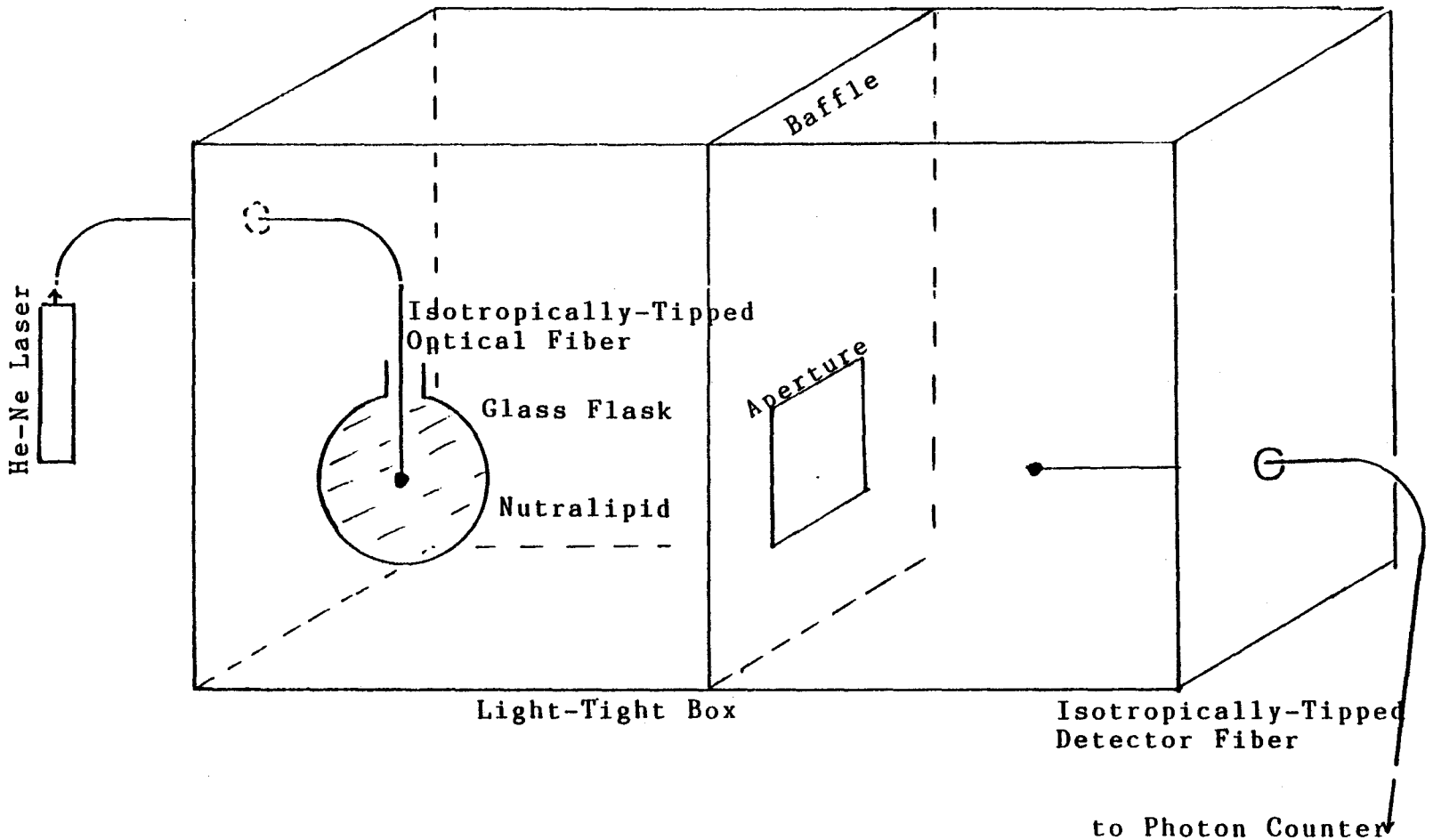


FIGURE 10: APPARATUS FOR MEASURING ABSORPTION LOSSES PER UNIT RADIUS IN NEUTRALIPID USING A LIGHT-TIGHT BOX

spatial orientation of the laser input to the source between measurements on the same sphere, the beam was split before entering the source fibre. To accomplish this a microscope slide was placed at 45 degrees with respect to the beam, sending 8% of the light into the 3 inch integrating sphere which was connected to the radiometer (Optikon 88XL). The integrating sphere has an input aperture of one inch so that small movements of the beam or the bench would not alter the radiometer reading as all of the light would still enter the sphere (see Figure 11). The remaining 92% of the laser light passed through the glass slide and shone directly into the flat-cut end of the source fibre. Detection of light from the sphere was still carried out in the black box by an isotropic fibre coupled with the photon counter (photomultiplier). It was possible to monitor both inputs and divide one reading by the other to determine if and by how much the laser output varied during the water and Neutralipid measurements.

E. The results of running the experiment with this set-up showed that there was very little correlation between the radiometer readings and those of the photon counter. Further investigation (monitoring the laser alone for long periods of time) indicated that some component of the photon counter (e.g. the photomultiplier tube) was not functioning properly. At this point an alternate measuring device, an

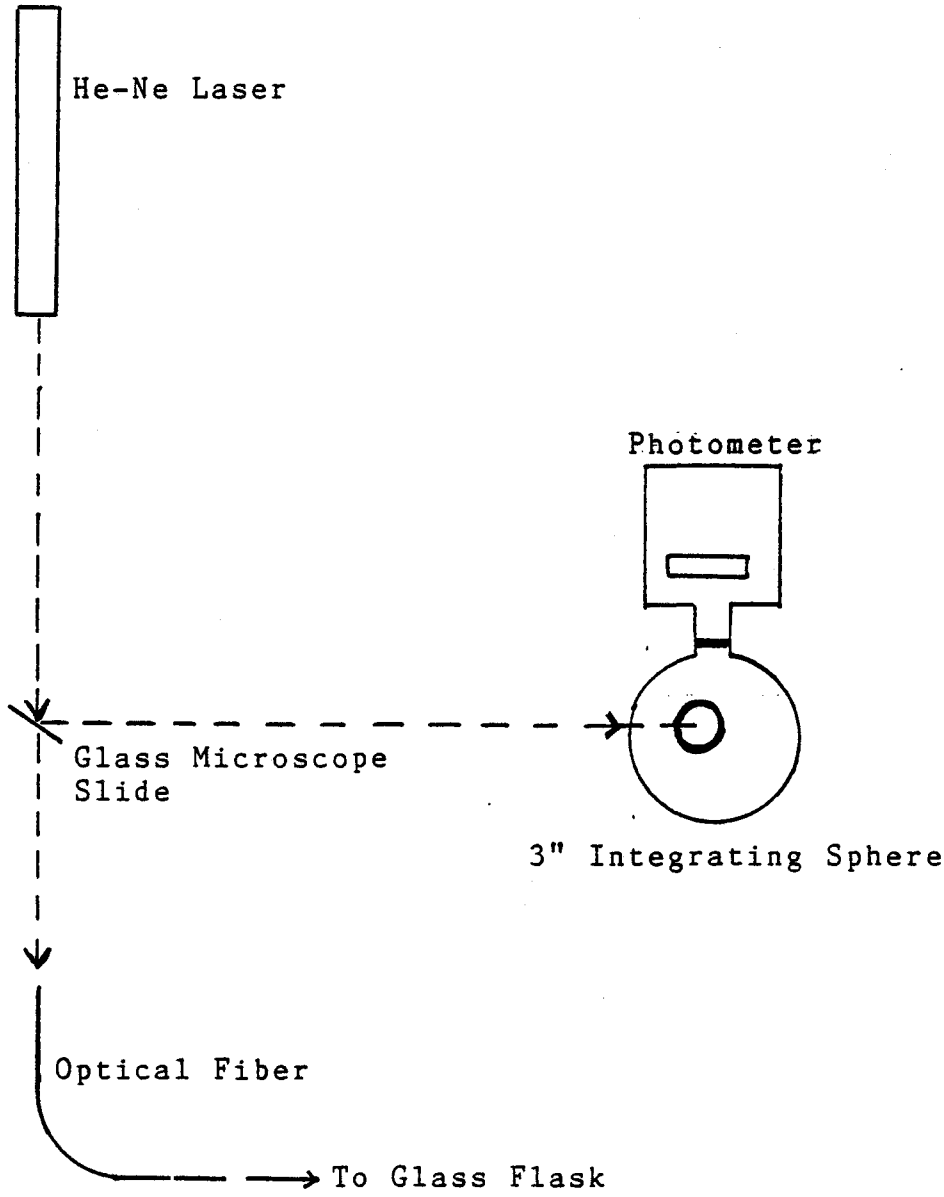


FIGURE 11: APPARATUS TO SIMULTANEOUSLY MONITOR LASER OUTPUT AND OUTPUT FROM OPTICAL FIBER IN GLASS SPHERICAL FLASK

ORIEL 7070 photomultiplier tube and electrometer were used. This instrument detects the light with a fibre bundle which is directly connected to the PM tube. (A fibre bundle is a collection of fibres which are clad as a unit). The detector face on the ORIEL 7070, which consists of the flat ends of all fibres contributing to the bundle, is 7.1 mm^2.

F. The results of performing the experiment with the ORIEL 7070 were plotted. The data points tended to fall on a straight line with a slope of $.021 \begin{smallmatrix} + .067 \\ - .021 \end{smallmatrix}$/cm. The results, however, were still somewhat scattered about the 0.021/cm line. To check whether this slope is reasonable, the experiment was repeated with a solution of Neutralipid doped with India Ink, a very strong light absorber. This experiment was carried out three times, each time the concentration of ink was reduced by a factor of two. It was hoped that extrapolating the curve of slope (the effective losses in the ink-plus-Neutralipid solution) vs. concentration of ink back to 0.0% would produce an intercept of 0.021/cm as already obtained.

A slope of .021/cm represents an estimate of the <u>effective</u> absorption loss, i.e. how much light is absorbed in the Neutralipid per unit distance through the fluid. The <u>real</u> absorption coefficient refers to the probability of photon absorption per unit path length in the medium. To obtain this number from the effective absorption per

unit radius, the average path length of the photon through the medium must be known. That is, how many interactions does the photon undergo before escaping the sphere (see Figure 12). This can be estimated by a Monte Carlo simulation of the travel of photons through a Neutralipid-like medium.

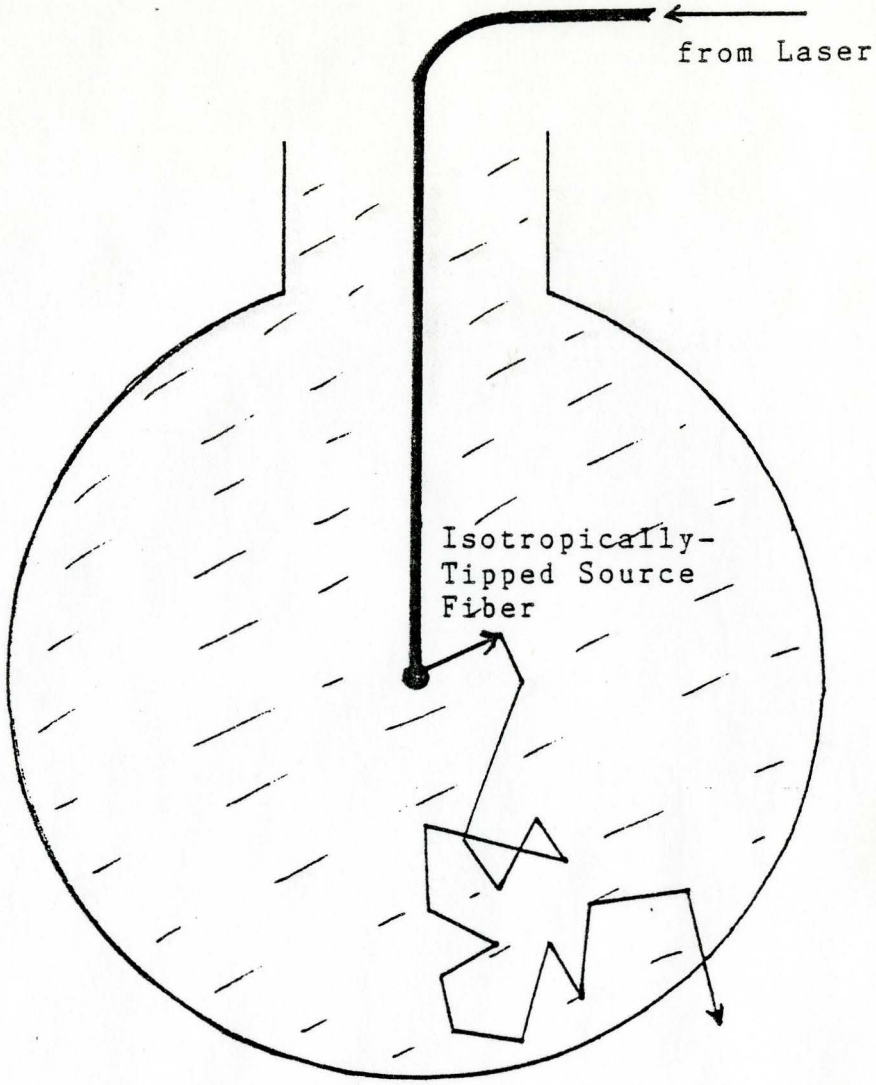


FIGURE 12: TYPICAL RANDOM MULTIPLE-SCATTERING PATH TAKEN BY A PHOTON IN A SCATTERING MEDIUM (NEUTRALIPID) BEFORE LEAVING THE SPHERICAL VOLUME

CHAPTER 3

RESULTS

3.1 Transmission

Although rather opaque in appearance, the isotropic fibres transmit approximately 89% of the laser light that enters the flat-cut end. Because the beam diameter exceeds that of the fibre core, however, this number represents only 27.6 ± 1.2% of the unfocussed laser output.

3.2 Isotropy

Because of the difficulties in quantifying the procedure for manufacturing the tips (e.g. size of the melted portion of the core, amount of resin adhering to the sphere, etc.) it was necessary to test the isotropy of each fibre individually. This was carried out as discussed in Section 2.3.

Figure 13 illustrates, on a polar diagram, the results of an isotropy test on a typical fibre. Note that monitoring the isotropy with the apparatus displayed in Figure 6 (see Section 2) does not permit measuring the full 360 degrees about the tip. This is due to the obstruction of the radiometer's view of the tip by the fibre holder when the apparatus is rotated to monitor the flux over the 20 degrees on either side of the fibre.

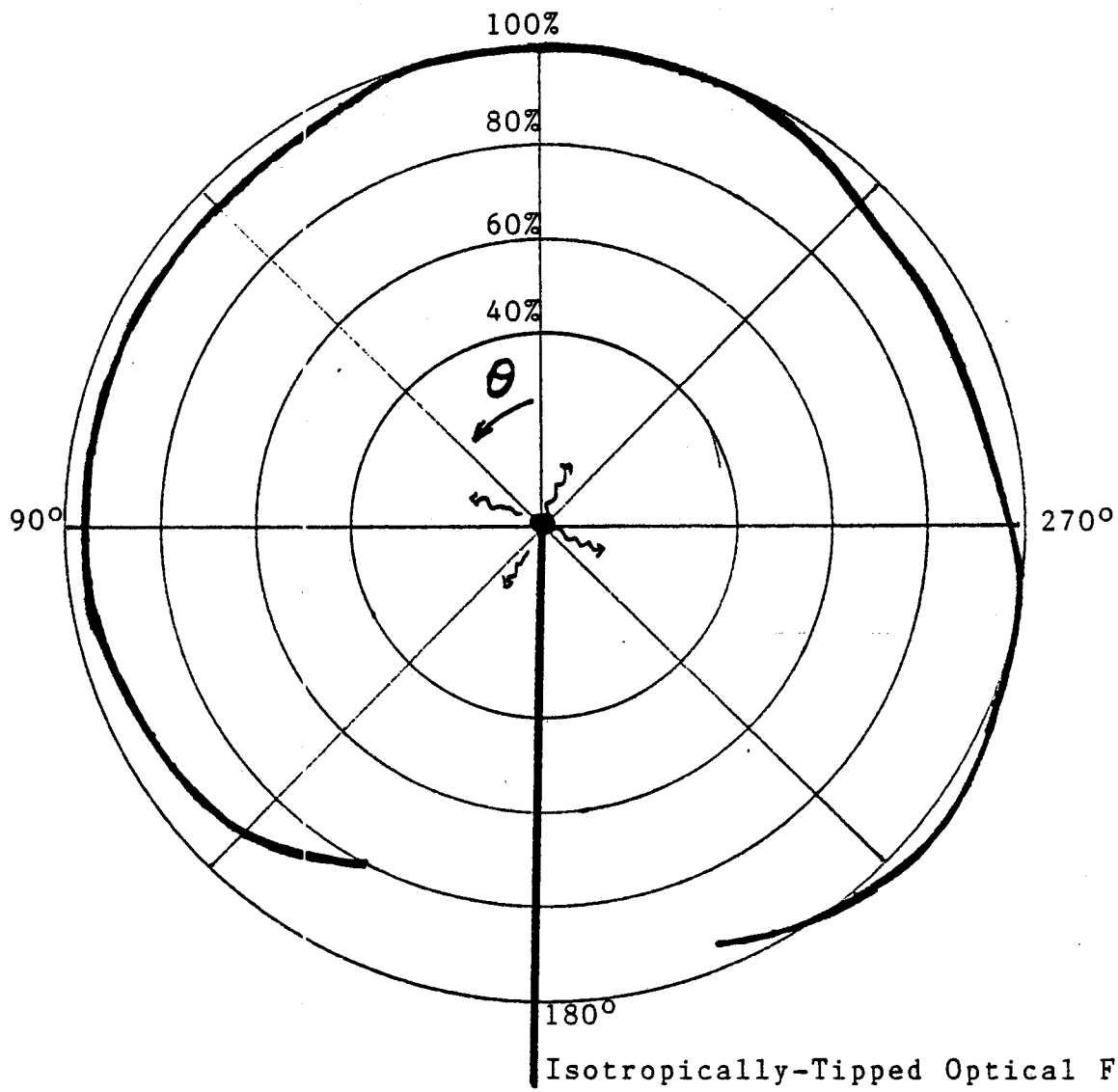


FIGURE 13: POLAR DIAGRAM FOR THE RELATIVE IRRADIANCE AT THE SURFACE OF THE RESIN-TIPPED FIBER (diameter 3-3.5mm) The irradiance is normalized to the value in the forward direction ($\theta=0^{o}$). Angles in the backward direction were not measured due to obstruction by the fiber holder.

It was possible to produce fibres that were isotropic to within ± 5%. That is, the best fibres showed only a ± 5% deviation in the flux measured at any point on the forward 180 degrees (see Figure 13) from that measured at 0 degrees. Wherever possible, these fibres were used as isotropic detectors or sources in subsequent experiments. Fibres found to deviate more than ± 20% from 100% isotropy were broken between the resin sphere and the unclad fibre and could be made into a new tip.

3.3. Measurements on Attenuation Properties of Neutralipids

3.3.1 Total Attenuation Coefficient:

Figure 14 displays a graph of $-\ln (I/I_o)$ vs concentration of Neutralipid; I is the number of photons detected by the photon counter for a given concentration of Neutralipid in the quartz cuvette, and I_o is the photon count at 0.0% (i.e. distilled water). Taking the slope of the straight portion of this graph (i.e. the values corresponding to Neutralipid concentrations of less that or equal to 2.0%) yields an attenuation coefficient of 0.44 ± 0.09/mm%. This number represents the sum of the scattering and absorption coefficients. Because Neutralipid is very scattering (recall Figure 7), the absorption coefficient is assumed to be very small.

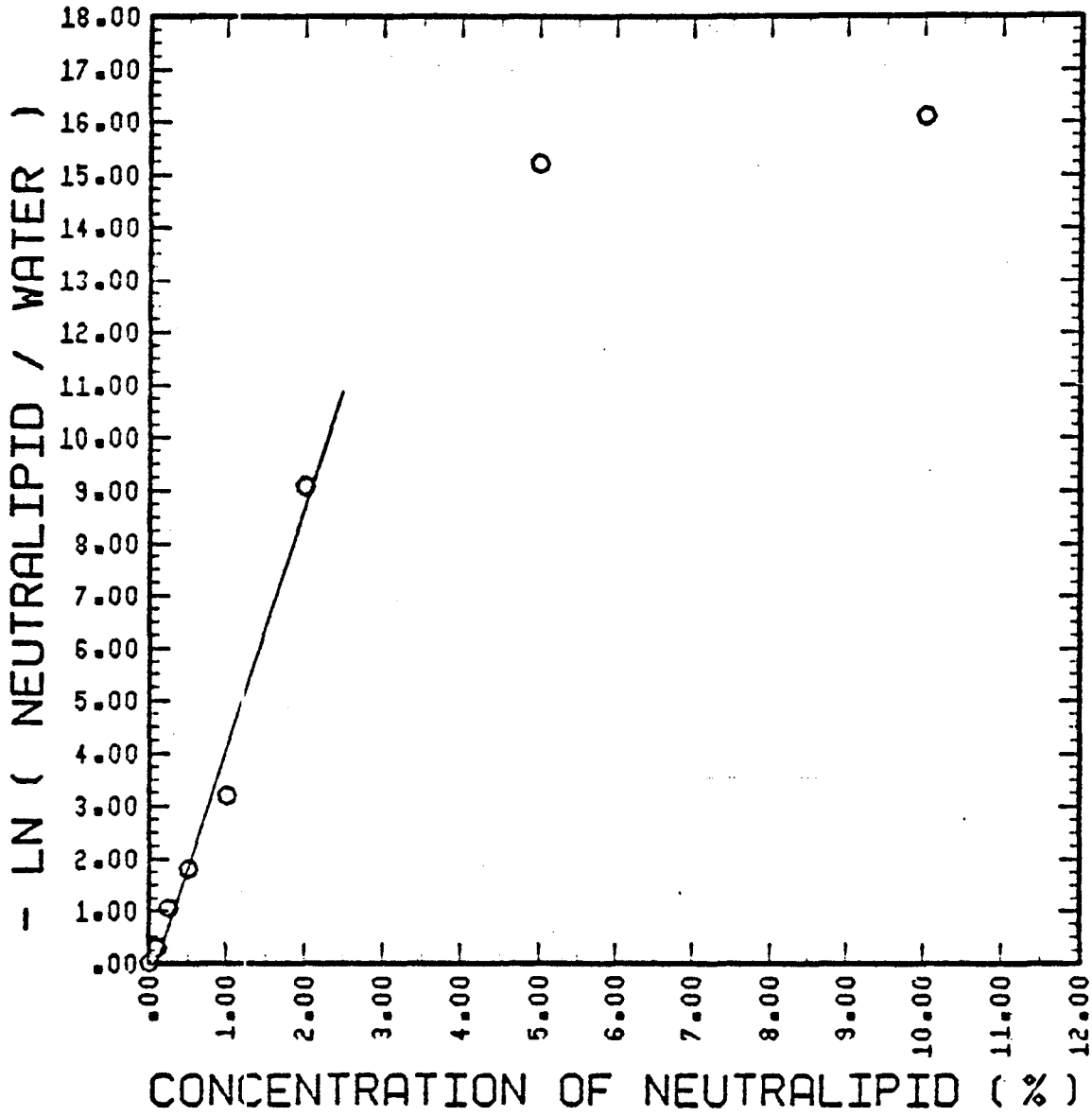


FIGURE 14

MEASUREMENT OF TOTAL ATTENUATION COEFFICIENT OF NEUTRALIPID (OBTAINED FROM SLOPE OF DATA POINTS FOR 2 % AND BELOW)

3.3.2 Absorption Losses:

The heading letters A through F refer to results of performing the experimental manipulations listed similarly in the Materials and Methods.

A. Removal of Background Consisting of Light Scattered from the Experimental Apparatus: The graph shown on Figure 15 illustrates the results of several early runs of the experiment. The data for trial 1 were taken before the decision was made to measure background by covering the face of the sphere (seen by the detector) with black paper. Trials 2, 3 and 4 are later runs and show the results obtained when the background, measured in this way, was removed. Note that the earliest runs were carried out using only five glass spheres. The remaining three spheres were acquired somewhat later.

B. Accounting for Variations in the Source-Detector Distance: As already mentioned, it did not seem possible that the inconsistencies in the experimental results were due to minor changes in the position of the source fibre with respect to the detector. Even large movements resulted in only small changes in the photon count.

C. Further Removal of Background: The use of the "light-tight" box reduced background light levels to approximately 2.5 photons detected per second, or about 0.8% of the average experimental reading. Figure 16 shows

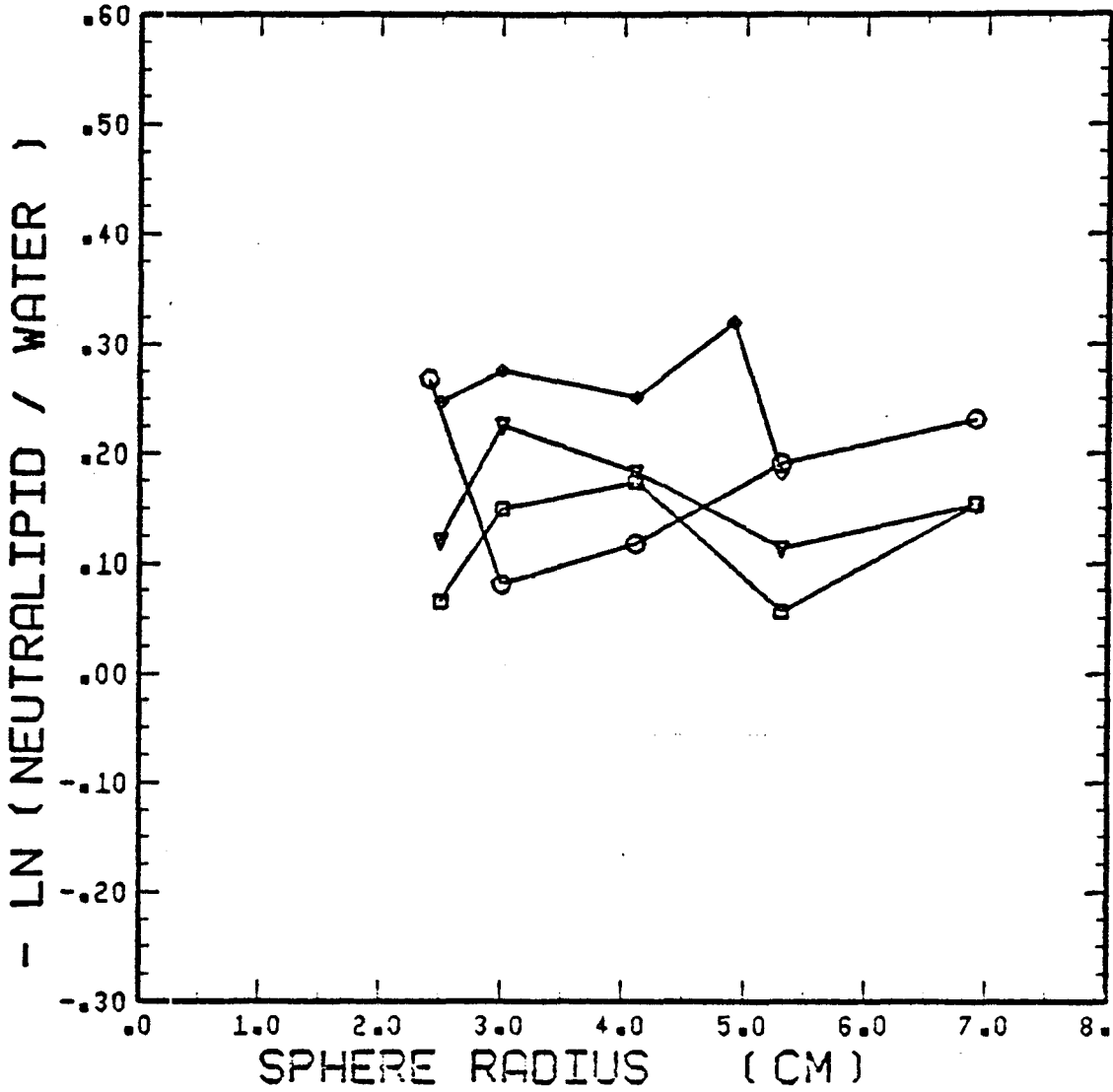


FIGURE 15
EARLY ATTEMPTS AT MEASURING THE EFFECTIVE ABSORPTION LOSSES IN 1 % NEUTRALIPID AS A FUNCTION OF SPHERE RADIUS

⊙ = Trial One

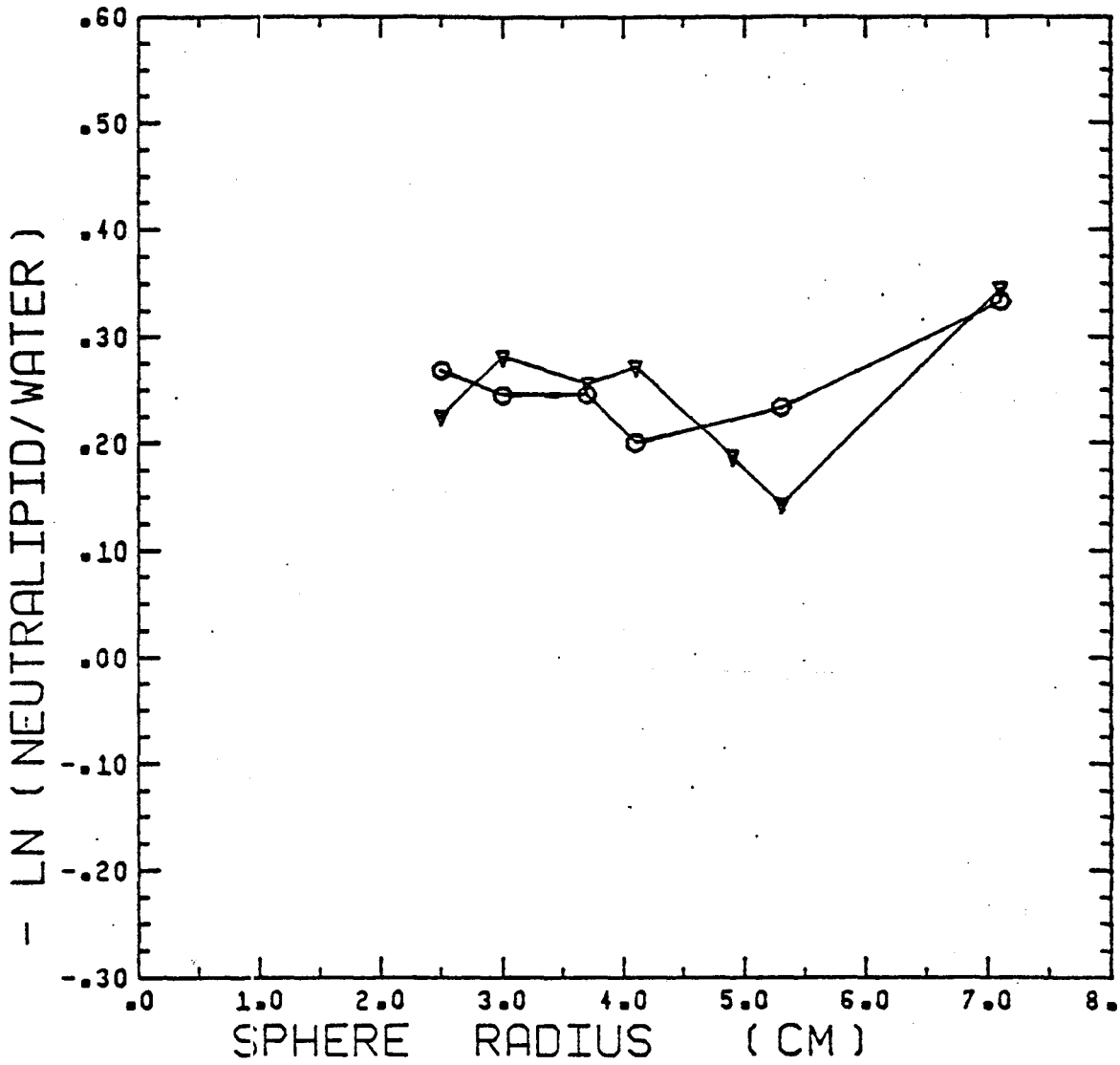


FIGURE **16**

TWO ATTEMPTS AT MEASURING THE EFFECTIVE ABSORPTION LOSSES IN 1 % NEUTRALIPID AS A FUNCTION OF SPHERE RADIUS USING THE LIGHT-TIGHT BOX

the results of two runs using an isotropic fibre and the photon counter as detector.

D. Accounting for Movement in the Laser-to-Source Alignment: The beam splitting arrangement (see Figure 11) was implemented to detect and correct for small shifts that may have been occurring in the laser-to-source alignment. The experimental results again show no pattern consistent with expectation or with results from other trial runs. Further, the results indicated that the photon counter set-up, and not the laser, was functioning improperly. At this point, the photon counter and isotropic fibre were replaced by an ORIEL 7070 photomultiplier and fibre bundle.

E. Use of an Alternate Detector System: The results of using an alternate photomultiplier in the next two trials are shown on Figure 17. The data tended to fall on a straight line with slope of $0.021\ ^{+0.067}_{-0.021}$/cm.

F. Neutralipid Doped with India Ink: Because of the large uncertainty in the value for the effective absorption coefficient of Neutralipid obtained above, the experiment was repeated three times with solution of 1% Neutralipid doped with India Ink. The plotted results are shown in Figure 18. (The results of part (E), 0.0% India Ink are also included). Plotting the slope of each of these lines as a function of concentration of ink (Figure 19) produces

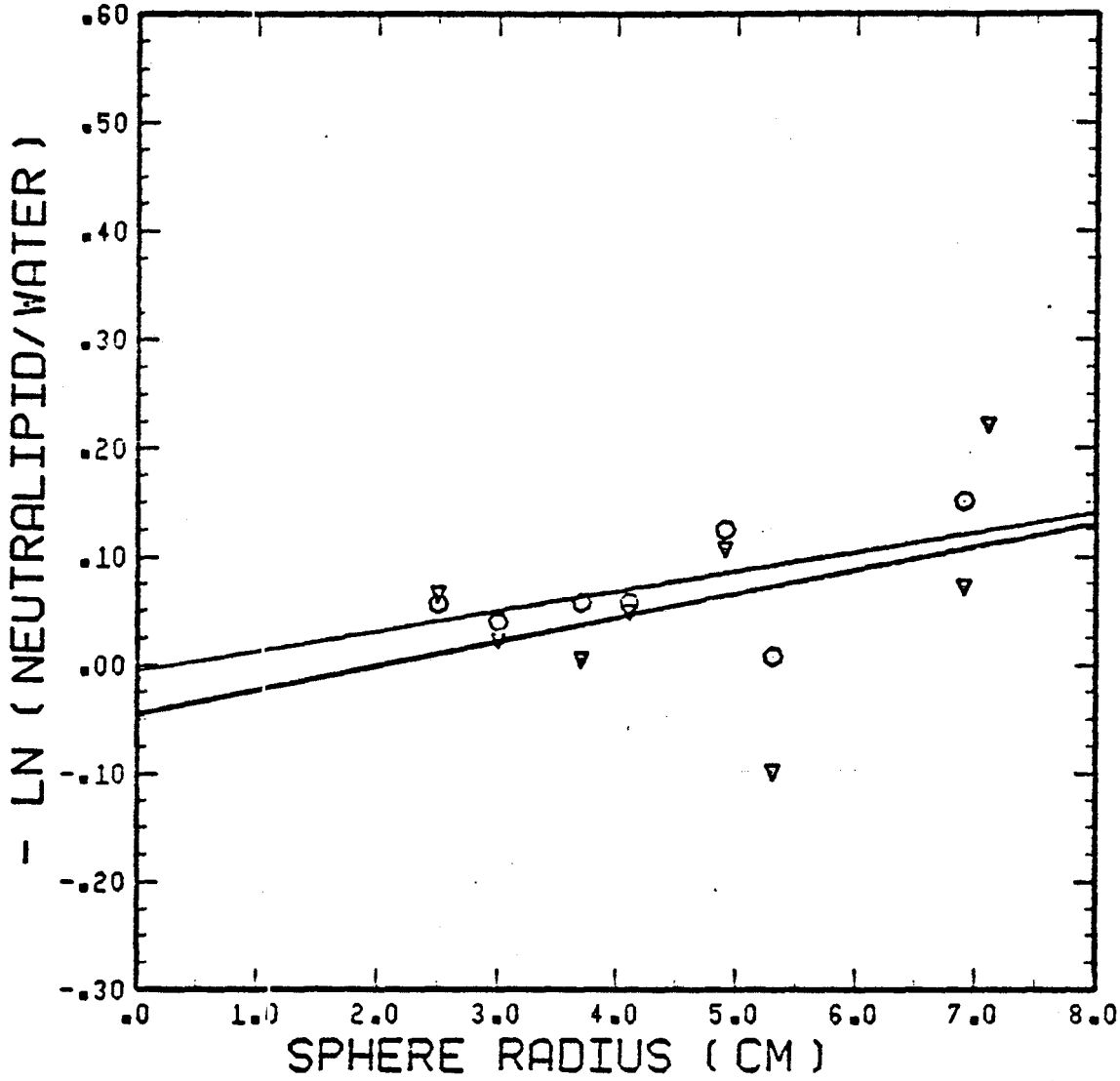
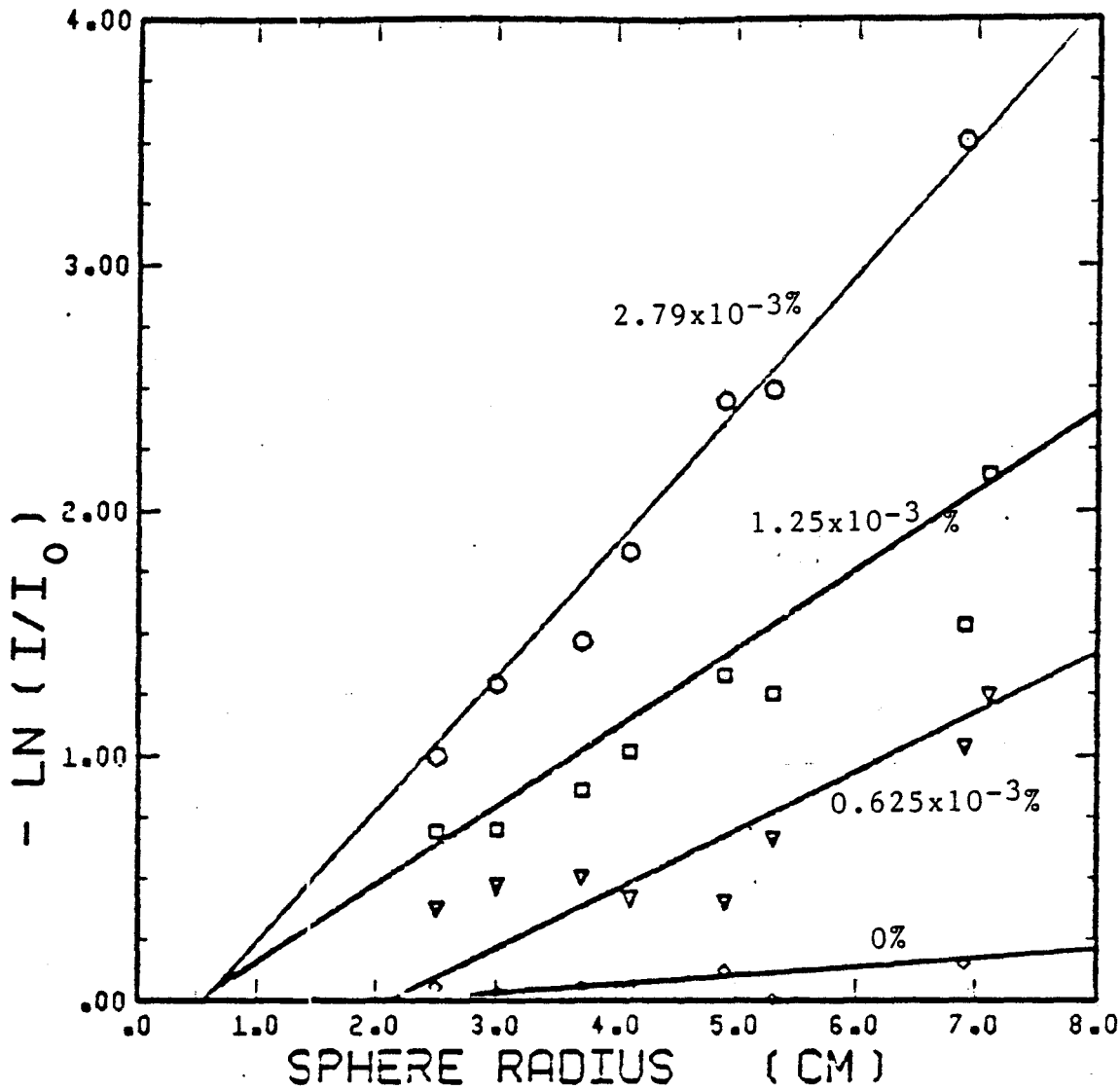


FIGURE 17
TWO ATTEMPTS AT MEASURING THE EFFECTIVE ABSORPTION LOSSES OF NEUTRALIPID AS A FUNCTION OF RADIUS WITH ORIEL 7070



EFFECTIVE ABSORPTION LOSSES OF NEUTRALIPID-PLUS-INK AS A FUNCTION OF SPHERE RADIUS FOR DIFFERENT CONCENTRATIONS OF INK

FIGURE 18

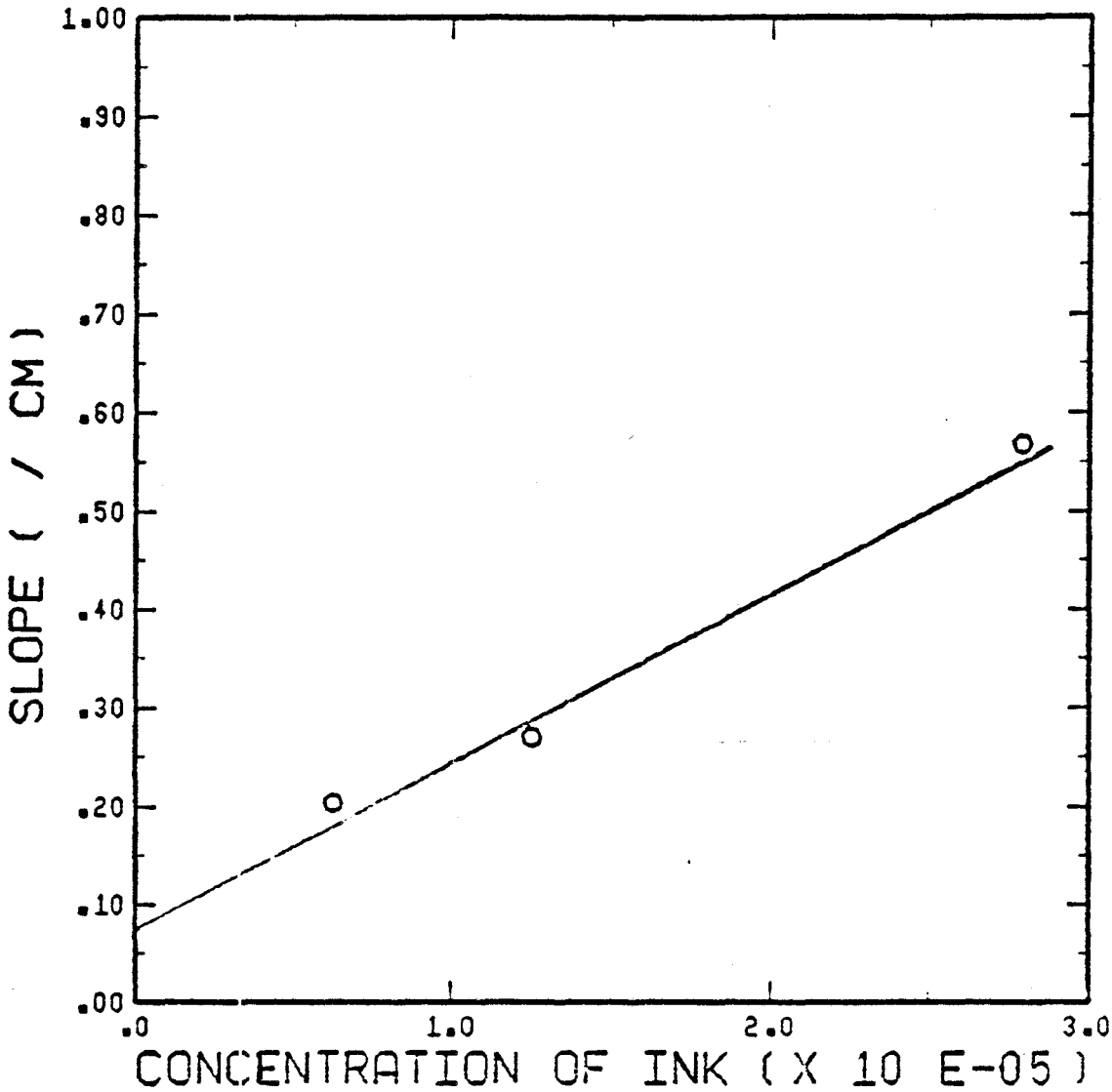


FIGURE 19

SLOPE OF (-LN (INK/WATER) VS SPHERE RADIUS) VS CONCENTRATION OF INK/CONCENTRATION OF WATER
Y-INTERCEPT: .078 +/- .029 /CM

a line with intercept of 0.078 ± .029/cm which agrees, within experimental error, with the results obtained in part (E).

CHAPTER 4

DISCUSSION

4.1 Isotropic Fibres

Transmission losses through the resin tip of an isotropic fibre are due primarily to absorption of light in the epoxy and PVA. That light which is absorbed in the tip is, in large part, dissipated as heat. Transmission losses could also be due to (Fresnel) reflection of the light back out of the tip (if the tip were used as a detector) or to light being reflected back into the fibre (if used as a source). Fresnel reflection refers to that quantity of light which is reflected when it interacts with the interface between different dielectric media (Siegmund, 1978). The combined Fresnel reflection for both ends of an ordinary glass fibre core (i.e. flat ends) is about 12% (Marynissen and Star, 1984).

If the reflected light is incident on the fibre face at angles less than the acceptance angle (θ_{max}), such that it strikes the interior walls at angles greater than the critical angle, then this light will travel through the fibre (recall Figure 1, Section 1). If the incident angle exceeds θ_{max}, however, then the light hits the walls at an angle less than the critical angle and it will only be partially reflected at each encounter with the core-cladding

interface. This light will very quickly leak out of the fibre. It was not possible to measure the extent of this leakage with the apparatus used for determining the percentage of light loss in an isotropic fibre. This is because transmission was measured with a large portion of the resin-tipped end well inserted into the integrating sphere. Any light leaking out of the fibre within 3 cm (several hundred scatter lengths (The Optical Industry and Systems Purchasing Directory, 1982)) of the resin tip will be detected by the integrating sphere and considered as coming from the source.

As indicated by the polar diagram in Figure 13, the resin spherical tips, although almost 100% isotropic over the front 180 degrees, transmit less light from the back half of the tip than from the front. Marynissen and Star (1984) have encountered the same phenomenon with their version of a resin-tipped isotropic fibre. The reason for the abundance of light over the front face is presumably due to the forward scattering of the red light as it interacts with the glass microspheres.

The size of the glass microspheres (1 micron) is roughly the same as the wavelength of the laser light (632.8 nm). In the case of the light and scatter centers having approximately the same dimensions, scattering varies inversely with the wavelength and is not isotropic but

somewhat forward directed (Wilson et al., 1984). The vast number of microspheres in the resin tip tend to distribute the light evenly in all directions. There remains, however, a slight peak over the front face of the tip. Presumably this peak could be eliminated with the use of more microspheres per resin tip to further scatter the forward-directed light. However, increasing the concentration of microspheres in the epoxy reduced its viscosity such that a spherically shaped tip was very difficult to produce. It is probable that the isotropy of the entire resin end can be improved in future models.

4.2 Uses of Isotropic Fibres

Optical fibres are very valuable in clinical as well as experimental photochemotherapy. As a means of irradiating cancerous tissue, the major advantage of these fibres is that they are small enough to be inserted into the tumor and thereby allow direct delivery of light. This is important for two reasons. First, as already mentioned, healthy tissues also retain some of the photosensitizing drug. Exposing a particular area of skin to enough light for adequate penetration of the underlying tumor creates a great deal of damage to the normal tissue above (Profio and Doiron, 1981). Second, overlying tissue types have very different spectral characteristics than those of tumors and

therefore it is difficult to estimate exactly how much light will reach the tumor cells. Optical fibres are also advantageous as light sources in that their flexibility can provide light to areas reached only with difficulty with static light sources (Dougherty et al., 1982).

With flat end source fibres there seems to be a problem of overkill (excessive phototoxic reaction) in the immediate vicinity of the fibre (Dougherty et al., 1982), and underkill some distance away. There may also be undesirable thermal effects in the area of tissue closest to the fibre end due to the extremely high light intensity at this point (i.e. up to 3000 mW/cm^2).

As detectors, isotropic fibres are useful in any light field where there is an angular dependence to the radiance. For measurements of light flux in biological tissue, a detector that is both isotropic and non-perturbing is required (Dougherty, 1981). A resin-tipped fibre has a response which is approximately isotropic, and is small enough to cause negligible biological damage. These fibres can be positioned to monitor the light flux density at a given point in a tumor. In this way the clinician can determine how much light to deliver in order to kill the cancer cells while causing minimal damage to healthy tissue. Fragility problems can be partially overcome by inserting the isotropic end of the fibre into a

biopsy needle so that the unclad portion between the spherical tip and the clad fibre is protected.

4.3 Attenuation Coefficient

The apparatus shown in Figure 8 was used to experimentally obtain an estimate of the total attenuation coefficient of (1%) Neutralipid. The first iris, placed close to the quartz cuvette, ensured that most of the light that was scattered by the experimental apparatus and the Neutralipid itself, was unable to enter the detector. The second iris was placed 100 cm from the first and very close to the detecting fibre. The diameter of this iris was similar to that of the laser beam (.5 mm). Thus, only that portion of the beam that was not attenuated by the Neutralipid could interact with the detector.

Figure 14 shows a graph of -ln (Neutralipid/water) as a function of Neutralipid concentration. At concentrations greater than 5%, the photon count is only slightly greater than background. Linear regression to the natural logarithm on the straight portion of the graph (i.e. data points corresponding to 2% Neutralipid and below) produces a slope of 4.4 ± 0.9/cm %. (The path of the light through the quartz cuvette is 1 cm so the units of slope become $(\text{cm } \%)^{-1}$.).

Light is attenuated in any medium by two processes, absorption and scattering. The extent of attenuation is

determined by the equation: $I = I_o e^{-(\mu a + \mu s)x}$ where μ_a and μ_s equal the total attenuation coefficient, and refer to the absorption and scattering coefficients respectively.

Figure 20 is a polar diagram illustrating, in a 2.5 cm sphere, the degree to which 632.8 nm light is scattered with increasing concentrations of Neutralipid. The distribution of light very quickly approaches isotropy. This would indicate that the coefficient of scattering is quite large (Bolin et al., 1984). The absorption coefficient will be conversely, very small. This is verified by the fact that later experiments with Neutralipid found the effective absorption of light per unit radius to be $.021\ ^{+.067}_{-.021}$/cm. The absorption coefficient will be smaller than this number; smaller by a factor equal to the ratio of the total path length of the photon through the medium, to the radius of the sphere.

Minimal absorption is necessary for the clinical application of the brain irradiator so that most of the laser output will be utilized and the flux required for total irradiation of the tumor bed can be delivered in a shorter period of time.

4.4 Discussion of Experimental Manipulations

The experimental apparatus shown in Figures 9 and 10 illustrate one way to measure the extent of light loss per unit radius in a Neutralipid-filled sphere. The slope found

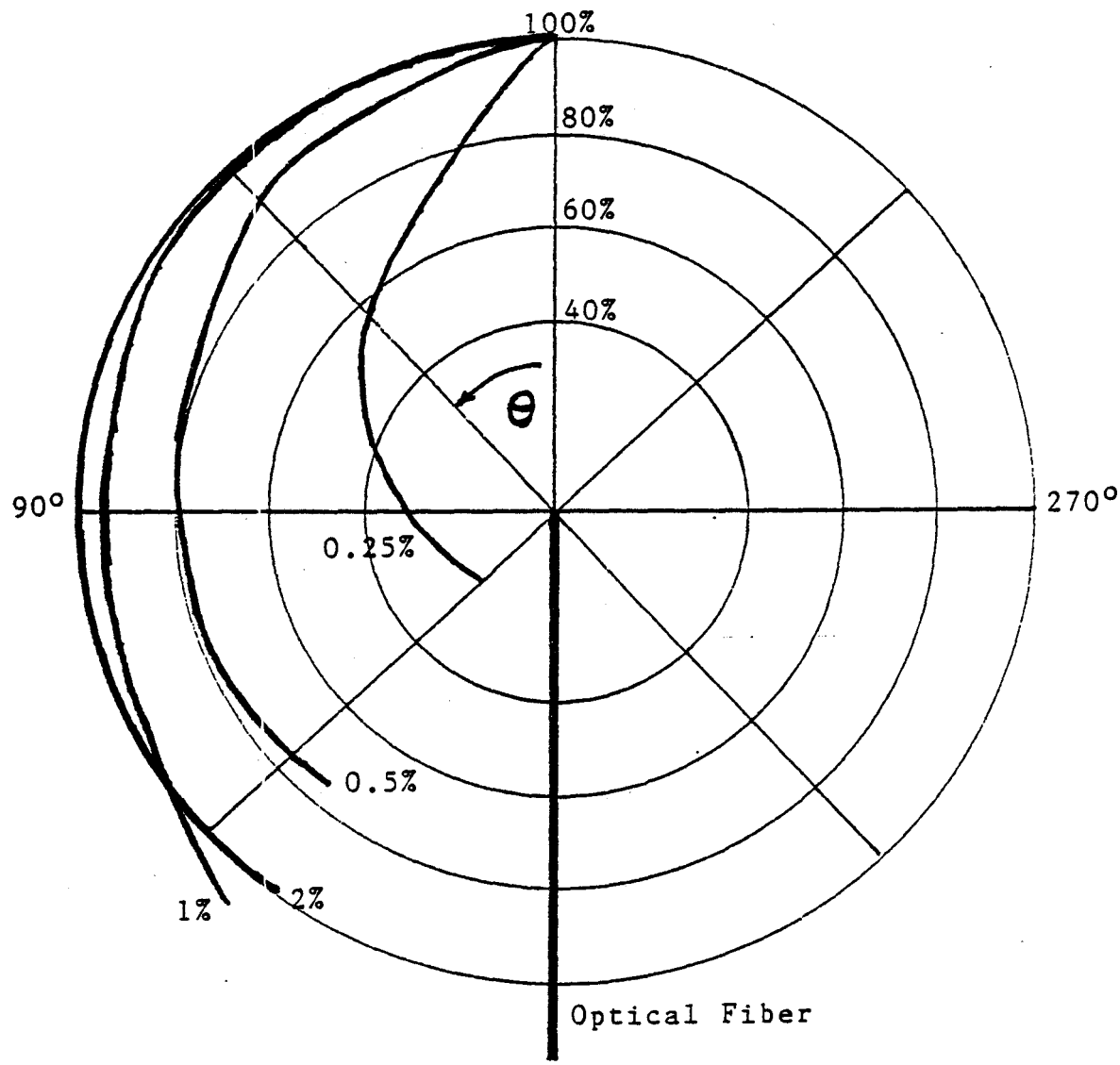


FIGURE 20: POLAR DIAGRAM FOR THE RELATIVE IRRADIANCE AT THE SURFACE OF A SPHERE OF RADIUS 2.5 cm FOR VARYING CONCENTRATIONS OF NEUTRALIPID (10%) IN WATER.
Only one half of the symmetrical angular distribution is shown. The irradiance is normalized to the value in the forward direction ($\theta=0^{o}$)

by plotting the negative ln of the ratio of Neutralipid to water as a function of sphere radius represents, not the attenuation coefficient (μ_a) of Neutralipid, but merely the proportion of light that is delivered to the sphere but is not detected.

The proportion of light loss ($_{.021}{}^{+.067}_{-.021}$/cm) will be larger than μ_a because it represents the total loss of light summed up over all of the interactions that the photon undergoes with the medium, whereas μ_a is an indication of how much light is lost per interaction.

The degree of absorption loss as a function of radius was determined by a second method. This procedure involved adding known amounts of absorber to the Neutralipid, determining the resultant effective absorption in each solution (by plotting - ln (solution/water) vs sphere radius as before), and then graphing this number as a function of concentration of ink. Extrapolating this curve back to 0% ink gives an estimate of the absorption losses due to Neutralipid alone. This method is similar to that used by Profio et al.(1985)to determine the diffusion coefficient of light in biological tissue. Basing their protocol on the "poisoned moderator" technique in neutron diffusion analysis, Profio et al., (1985) added known amounts of blood (an absorber) to homogenized beef brain.

The y-intercept on the plot of absorption losses in

ink-plus-Neutralipid vs concentration of ink (Figure 19) was found, by linear regression to the natural log, to be .078 ± .029/cm. This number agrees with the values previously obtained, within experimental error, and is an estimate of how much red light is absorbed per unit distance through the medium. Knowing this number allows the clinician to determine how long to leave the brain applicator in the tumor bed in order to deliver the required amount of radiation. The true absorption coefficient, however, refers to the probability of the photon being absorbed per unit path length. To obtain this value from the experimental determination of light loss/cm, a Monte Carlo simulation was carried out to determine how many scatters a photon will undergo from the time it leaves the source until the time it leaves the medium, or alternatively, the photon's total path length through the Neutralipid.

In a Monte Carlo simulation, a series of life histories of source photons is generated by the computer. Random numbers, appropriately weighted by the probability laws that describe the behaviour of real photons, are used to determine the outcome of chance events (e.g. absorption vs scattering, scattering angle, etc.) (Profio, 1979). The path through the medium is followed until that particular photon no longer contributes useful information (e.g. it

may be absorbed by, or leave the medium). It is then terminated and a new particle is started from the source (Wood, 1982).

The main advantage of using Monte Carlo calculations (over other transport theory methods) is the fact that the mathematical structure of the computer program contains a large amount of physical realism. Thus, intuition can be quite important in developing, debugging and interpreting the program. One of the drawbacks of the computer simulation, however, is the large statistical error that is involved. Monte Carlo calculations represent an attempt to arrive at some estimate of the average behaviour of all the photons, by sampling the behaviour of a few. Thus, the result of the calculations is merely an estimate of the true answer. Associated with this estimate is some confidence interval which is made smaller as the number of initial source photons is increased (Wood, 1982).

The Monte Carlo program used to estimate the absorption coefficient of Neutralipid generated source photons which emerge isotropically from a point in the centre of a sphere (Wilson and Adam, 1983). The spheres could have various radii and contained a medium with a scattering coefficient of 4.4/cm. The absorption coefficient was set at 0. This is because the experimentally determined value of absorption loss per unit radius

$(.021 \pm .067/cm)$, which is larger than the value of μ_a, was found to be negligible with respect to the total attenuation coefficient ($4.4 \pm .09/cm$). Thus, μ_s is essentially equal to μ_t.

The Monte Carlo program estimated that the average path length of a photon generated in the centre of a 3.0 cm (radius) sphere filled with a Neutralipid-like medium is 21.9 ± 0.7 cm. Or, each photon undergoes an average of 98.1 ± 3.1 scatters. The attenuation coefficient of 1% Neutralipid in water, then, is calculated by dividing the absorption loss per unit radius by the ratio of total path length to sphere radius:

$$\mu_a = .021 \pm .067 \text{ cm}^{-1}/(21.9 \pm 0.7 \text{ cm}/3.0 \text{ cm})$$

$$= 2.88 \pm 9.28 \times 10^{-3} \text{ cm}^{-1}.$$

$$= 2.88 \begin{matrix} + 9.28 \\ - 2.88 \end{matrix} \times 10\text{-}3 \text{ cm-}1.$$

CHAPTER 5

CONCLUSIONS

5. It was found that optical fibres could be made into isotropic sources or detectors through the fixing of a resin sphere onto one end. Fibre tips that were isotropic to within ± 5% over the front face of the tip were possible. These fibres are potentially useful in delivering or detecting light in Photochemotherapy, and other areas, where a small, flexible device is required.

The extent of light loss per unit radius due to absorption in a 1% solution of Neutralipid was found to be $.021 \begin{smallmatrix} + .067 \\ - .021 \end{smallmatrix}$/cm. The absorption coefficient was determined with the aid of a Monte Carlo simulation, to be $2.88 \begin{smallmatrix} + 9.28 \\ - 2.88 \end{smallmatrix} \times 10^{-3}$ cm^{-1}. The effective absorption loss per cm , however, is clinically the more useful parameter. This number allows the clinician to estimate the length of irradiation time needed in order to deliver the required flux to the tumor bed.

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