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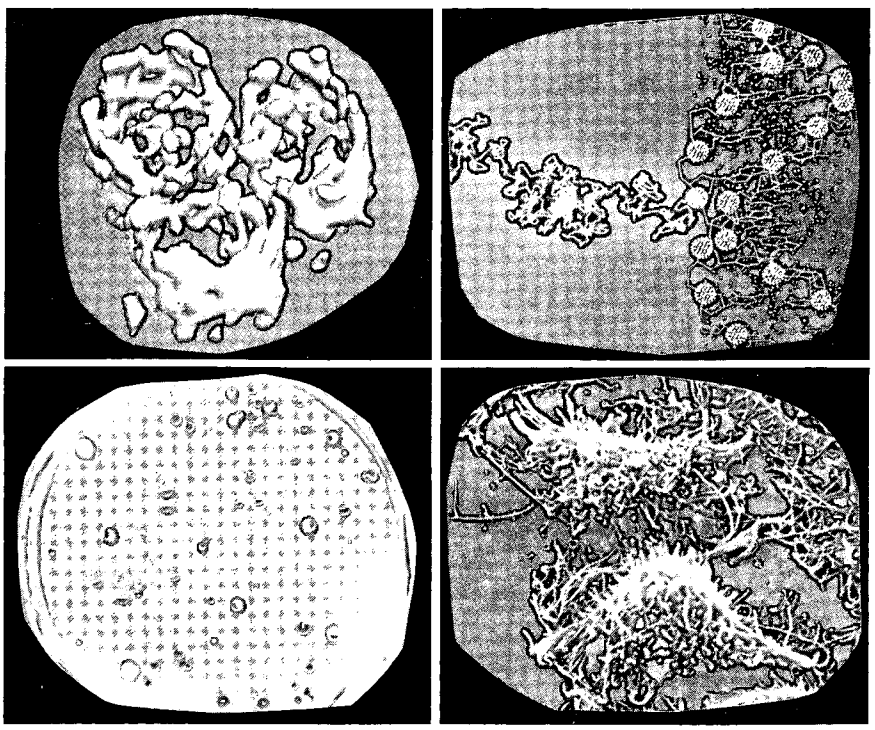

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Biological Beam Characterization

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<heading 0>Biological Beam Characterization

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<heading 1> Introduction

Physical characterization of ion beam fields is conventionally accomplished in the practice of radiotherapy to ensure uniform clinical effects. A demonstration of a uniform physical dose across a radiation field does not always guarantee however a uniform clinical outcome. It is acknowledged that there are tissue-specific differences in both acute and late tissue effects to low-LET radiations, as well as considerable variability in individual radiosensitivities presumably due to inherent genetic susceptibilities. (1)

The additional consideration of variations in radiosensitivity due to radiation quality can be at first somewhat staggering due to the large number of variables and the range of potential differences. The higher ionization densities of alternative radiation modalities, such as neutrons or heavy ion beams are known to be associated with greater biological effectiveness than what is measured for conventional photon therapy (2-4). The picture becomes further complicated as published experimental data at very high LET (greater than 2,000 keV/μm) indicate a reduction in the radiobiological differences between radioresistant and radiosensitive systems (5). Most alternative radiation modalities for cancer therapy (such as protons, alpha particles, pions, or carbon ions) involve intermediate LET values (eg., between 20 to 200 keV/μm) where the greatest variation in RBE is observed. This presents a practical problem to the clinician in choosing a specific appropriate dose regime at intermediate LET.

Neutron radiotherapy was initiated in 1938 and proton radiotherapy in 1956, yet even today there is controversy regarding the assignment of quality factor or RBE for neutrons and protons, especially as a function of dose or energy (6-9) For charged particles the range of changes in biological effectiveness can be even greater. After Stone's (10-12) early experience with neutron cancer radiotherapy resulted in severe adverse reactions in normal tissue, considerable attention has been given to reducing the total dose to normal tissues unavoidably in the treatment volume of alternative radiation modalities having a high-LET radiation dose component. The limiting radiosensitive normal tissue is identified in the treatment field, and a reduced dose fraction of the high-LET radiation is

selected based on what is thought to be equivalent or comparable to what is tolerated in conventional photon radiotherapy. Although physical detectors of altered radiation quality are available, their use for this purpose has been limited and biological characterization has historically served as the basis for the measure of the reduction in dose fraction needed. This chapter reviews aspects of this practical approach, and discusses the need that remains in the field to standardize the protocols for biological measurements. Although not intended to be all-inclusive, several examples of techniques currently in use to measure radiobiological parameters are reviewed. Preclinical radiobiology for charged particle radiotherapy is provided as illustrative of the methodologies that have been used to complete biological beam characterization.

<heading 1>What to measure and why

Biological characterizations for clinical radiotherapy have primarily been accomplished with cell systems in vitro and with animals in vivo. (13,14)

For reasons of practical necessity, representative biological systems have been selected for the measurement of biological effectiveness.Due to the ease of techniques and availability, emphasis has been given to the measurement of cell killing and repair using cells that grow easily in tissue culture, and using tissues having highly proliferative cell renewal systems amenable to quantitative assays. However general concern exists in the field that appropriate biological assays are not available for all of the critical tissues and endpoints that perhaps should be screened for a thorough understanding of clinical responsiveness to a particular radiation. The shortcomings of the present approach still need to be evaluated.

Essential to any of these studies is the need for deliberate coordinated physics measurements (including a dose calibration, assessment of radiation field composition and uniformity, other microdosimetry.) under the exact conditions of the biological exposure, and for parallel studies of the biological response to a standard low-LET reference radiation (see 15-17 and additional discussion below).

<heading 2> In vitro systems

Cell systems in vitro can generally be divided into two categories: primary and established cultures. Primary cultures are those that are newly derived from normal or tumor tissues and have not undergone many passages in culture, during which changes in the cells or selection of specific cell types

could have occurred. The primary normal cells, and even some tumor cells are usually difficult to grow on tissue culture plastic, as evidenced by low plating efficiencies for colony-forming assays. Low plating efficiencies mean that large numbers of cells are required to statistically measure the colony-forming assay endpoint. Established cultures are cell lines that have been in culture for a significant number of passages to convincingly allow a characterization of the system. Plating efficiencies are usually higher than for primary cells, probably because there is a selection for cell sub-populations that grow well under the artificial conditions in tissue culture. The question that remains is, "Are the selected cells that survive representative of the original population of cells from which the culture was derived?". The answer is highly dependent on the criterion selected for the comparison.

Radiobiological characterization of accelerator-based alternative radiation modalities frequently requires one to compare experiments completed over the course of several years. Since the living cell can be a very sensitive LET-detector of alternative ionization densities, it can be used to determine changes in radiation quality. For technical ease, established cultures of mammalian cells, including those of human and rodent origin have been used to examine cell killing, repair, chromosomal rearrangements, mutagenesis and transformation, and the reduction of the radiobiological oxgen effect, long thought to be a significant factor in overcoming tumor resistance (18). The merits of this approach are that a very large matrix of data has been generated with a large assortment of established cell systems. The remaining problem is that except where individual investigators have conducted exhaustive comparisons of various radiation modalities with the same system, (14,19) there are in most cases, very few opportunities to make identical RBE comparisons. In many cases the low-LET reference for the RBE determination has been either ^{60}cobalt, 100 kVp-250 kVp x-rays, or ^{137}cesium, which confounds any strict RBE comparison since physical differences among these sparsely ionizing radiations can themselves produce up to 20% differences in the biological responses.

<heading 2> In vivo systems

An early observation made in vitro was that single, acute dose responses of cell systems were not revealing all of the necessary information required for adequate treatment planning in the clinic. Dose-fractionation and delayed

plating studies revealed that repair of radiation damage moderated the end effects considerably. (20,21) Repair studies conducted in vitro are limited in scope due to technical considerations. Experiments with animals are more amenable to the dose-fractionation regimes used in the clinic. Rodent tumors are a good indicator of superficial human tumors in terms of actual physical size and geometry. Extrapolations must be made to predict the effects of larger, deeper tumors found in man.

<heading 1> RBE mapping techniques

Once the decision is made about which cell is appropriate for representative biological characterization, one must next decide what geometry should be used to complete the radiation exposures. Cells grown in tissue culture that attach well and make individual colonies are highly amenable for the biological characterization of accelerator-based radiations. This is primarily due to the fact that accelerators designed for physics usually have fixed horizontal beam lines that necessitate a vertical exposure geometry. If the question being asked is "what is the average biological effect over a range of beam depth?", then exposures can be made with cell suspensions. However, if one is interested in the mapping of RBE as a function of depth over a few millimeters range, for example to cover in detail the drop off of dose in the distal portion of the Bragg peak, then cells must be held in a rigid conformation during the exposure. This can be accomplished for example by using cells attached to vessels in monolayer or held in a gelatin matrix. Illustrations of each of these approaches is described below.

<heading 2> In vitro

<heading 3> Cell suspensions

Chapman et al (22) designed a cylindrical glass chamber which allowed cells to be in a stirred-suspension of less than about 2 cm width. This chamber might be placed at various depths within an extended Bragg curve. This chamber is depicted in Fig. 1A. A glass sampling port allowed the removal of control, unirradiated cells prior to the start of an experiment, and subsequent sampling after a sequence of graded doses. The irradiated cell samples were immediately diluted into a test tube containing warmed medium for rapid serial dilution to the appropriate cell number required for the level of cell killing anticipated. A magnetic stir-bar driven by a motor under the chamber assured a uniform cell concentration throughout the experiment. The sampling time was short enough (less than 2 minutes) that

the dose fractionation was inconsequential to the survival measurement. There are several merits to this approach: 1) the technique is easy and rapid, 2) the uniformity of cell treatment, handling and origin in the suspension technique is well-controlled, allowing for good reproducibility in the survival measurement, and 3) there is a significant saving of beam time since the survival measurements are from accumulated doses. Limitations include: 1) the depth of radiation field to be studied is defined by the width of the vessel over which the survival effect is averaged, 2) the requirement for the cells to easily be held in single-cell suspension without clumping or adverse plating effects, and 3) restrictions on the use of the technique for the study of fractionation effects.

<heading 3> Cell monolayers

The traditional radiation exposure protocol for many cultured cells has been to grown the cells in monolayer attached to tissue culture plastic petri dishes or flasks. For colony-forming assays, cells are trypsinized, counted and the cells are serially diluted to the appropriate concentration for the anticipated survival. There are several variations on the monolayer protocol that have been devised to accommodate small beam diameters for eye tumor treatments for example, or to map variations in cell killing radially. Figure 1B illustrates a linear array of tissue culture flasks filled with either medium or water. Flasks with medium have cells grown on one of the inner surfaces. Flasks can be exposed in such arrays where each plane of cells is approximately separated by 1.8 cm, the width of one flask. Alternatively, in a variation first proposed by John Lyman, pairs or arrays of flasks can be exposed with only nominal thicknesses of additional absorber upstream to shift the full depth of range covered. This approach allows a measure of biological effects at closer spacings (see Figure 2). An illustration is given (Fig. 3) of the kind of cell survival effects that were measured with this technique for a high energy helium ion beam configured for eye tumor treatments.

If the diameter of the beam is limited to an area within the width of the flasks either due to accelerator constraints, or due to the configurations imposed for a specific treatment geometry under study, cells can be plated only within a small circular region on the flask. Figure 4 demonstrates this concept. Depending on the cell line used, the cells firmly attach to the flask within one or two hours, after which the flask can be filled with additional

medium. If the radiation field covers the complete surface area of the flask, the flasks can be exposed to a horizontal beam and then processed for colony formation in the traditional fashion, or allowed to grow in situ to permit an assessment of the radial uniformity of cell killing (see Figs. 5 and 6). For a fixed dose, cells surviving within the irradiated field can be scored in radial sectors and plotted as a function of beam diameter to assess flatness of the biologically effective dose.

<heading 3> Cells in gel

Skarsgard et al (23) devised a clever gel technique for biological characterization involving suspending single cells in a stiff gel matrix. After irradiation, the gel is extruded and sliced at intervals of 2 mm or more. Each 2 mm slice contains about 10^5 cells which are resuspended by melting the gel/medium in a tube containing warm medium (see Fig. 7) for the biological assay desired. Spatial reconstruction of the biological effect can then be mapped, allowing a detailed and accurate description of the radiobiological properties of the radiations studied which were pion beams. Raju et al (24) have adopted this approach for the study of a number of different radiation types.

The gel technique has been further refined by Skarsgard et al (25) with the use of a cell sorter to deliver a known number of cells into the test tubes for plating for survival. Cells were identified on the basis of light scattering in the cell sorter, without the use of a cell stain. This additional step increased the accuracy and precision of the gel technique. Merits of this modified technique include: 1) excellent reproducibility and RBE-mapping precision, 2) resoluton for dose range covered, especially at low doses, 3) ease of exposure technique, and 4) reduced beam time requirements. The only limitations involve the moderate degree of preparation and handling required for sample processing.

<heading 2> In vivo

Since single, acute cellular responses in vitro do not provide complete information on tissue responses and their repair, most new radiation modalities have been screened with a few specific in vivo endpoints. The primary goals are to investigate dose-fractionation effects after a significant number of fractions as is used in the clinic, and to assess late sequelae, neither of which can be modeled well by cells in vitro. Although there is literature on late tissue effects from neutron exposures, there are very few

published studies of late effects from ion beam therapy. Our description of in vivo endpoints here will be limited to three biological assays involving rodents. One of the major limitations of the in vivo techniques is the degree of resolution of measurement of RBE which changes across the depth of the pristine Bragg ionization curve. This fact prevents the study of the sharp, unmoderated Bragg curve, but allows one to map RBE values over defined widths of Bragg curves that have been extended to cover the width of a tumor. The physical dimensions of the animal used in particle studies defines the width of the Bragg ionization curve that can be studied since RBE averaging is implicit over that tissue thickness.

<heading 3> Intestinal crypt cells

The Withers intestinal crypt assay was an important contributor to our understanding of neutron effects (26,27) It is highly amenable to the exploration of dose-fractionation effects. This led to its selection in the preclinical feasibility testing of heavy charged particles. The work of Goldstein et al (28) revealed the relative value of predicting peak-to-plateau RBE ratios to provide information on the relative damage to tumor and intervening normal tissues. Additional particle-induced effects on jejunal tissue have been reported by Alpen et al (29) and Fu et al (30). As a biological endpoint, the crypt assay is also a technique that can be recommended as a standard protocol for inter-laboratory comparisons, since it has few uncontrolled variables and good replication of the technique can be achieved. There is recent interest in using the intestinal crypt assay to standardize some aspects of the proton therapy programs that are increasing in number world-wide.

<heading 3> Skin reactions

Traditionally skin erythema reactions have been the most immediate and visible part of a course of radiotherapy. Skin reactions have been used to investigate the time-dose relationships of radiation effects. The biological reaction is directly proportional to the total dose delivered. The time of appearance of the erythema reaction is inversely proportional to the time course of the irradiation. With the acquisition of sufficient information necessary for radiotherapy treatments using conventional radiations and neutrons, and with the advent of animal rights advocates who questioned the necessity of further studies, this work has received much less emphasis in the laboratory. None the less, when the novel high-LET ion beams became

available, skin reaction studies were scored in rodent models because it was one of the baseline biological measurements understood and trusted by radiotherapists. Acute skin reactions to 160 MeV protons were scored by Raju and Carpenter (31) and skin effects from a 20 fraction course of 160 MeV protons were scored by Tepper et al (32). Both groups reported nearly the same RBE values (referenced to ^{60}cobalt) of 1.13 to 1.2 respectively.
Leith et al (33) estimated an RBE at 2 Gy per fraction (relative to x-rays) of 2.1 for proximal peak 400 MeV/u carbon ions, using a reciprocal dose versus dose per fraction approach, Although skin reaction studies have large confidence limits, he found that for comparable amounts of injury, the ability of hamster skin to repair 400 MeV carbon ion irradiation to be only 0.67 of that found after x-rays. Recently there have been retrospective attempts to score acute skin reactions from patients who had scorable skin reactions from their charged particle therapy (34). These data clearly indicate an RBE relationship that scales with LET value. Smaller doses per fraction per field of increasingly higher atomic number ion beams yield the same maximum acute skin reaction.

<heading 3> Spinal cord effects

Due to the serious medical complications that can result from nervous tissue toxicities to radiation, spinal cord effects have long been a normal tissue of interest to screen for complications such as paralysis. The charged particle radiotherapy community supported the investigation of this late effect that takes more than one year to develop in rodents at clinically relevant doses to avoid duplicating the serious complications that resulted in early applications of neutron therapy. Several important conclusions were drawn from the single and fractionated dose studies of Leith et al (35) who compared the effects of xrays, helium, carbon and neon ions on the thoracolumbar region of the rat spinal cord. Unlike other normal tissue endpoints such as skin and intestinal crypts, the spinal cord radiosensitivity has a significantly different x-ray response, and the particle studies suggested a caution in situations in which spinal cord might be exposed to even moderate fractions of high-LET particles.

<heading 1> Summary of Pertinent Issues

Frustration with the variables introduced in the photon Gray-equivalent concept have led several clinical programs investigating new high-LET radiation modalities to report only physical dose. However, Gray-equivalent

dose must still be considered in treatment planning to avoid normal tissue toxicities. This issue will become even more important as alternative ion beam delivery systems are implemented to optimize tumor treatments.

<heading 2> Model systems

In the opinion of the author, the choice of model systems should not based on trying to be all inclusive in determining RBE. Instead, the selection should be based on having a representative radiosensitive and a radioresistant responding system. This provides the clinician with an appreciation of the range of responsiveness that may be anticipated. Depending on the treatment site, particular normal tissue toxicities should be investigated for individual organs. It would be exceedingly helpful to the international effort to compare clinical protocols and results if radiobiologists could agree with the clinicians about which representative measurements should be made. Many primary cell lines are very radiosensitive with very small shoulders on the survival curve, even after exposure to low-LET radiations. This means that there will be very little variation in RBE in primary cells, in comparison to cell lines with large shoulders on the survival (as is the case for many tumor and established cell lines) where the high-LET response collapses the shoulder.

<heading 2> Statistical significance

None of the radiobiology of ion beams is worth doing unless adequate controls and sample numbers allow a statistical assessment of the significance of the results. The error analysis of a relative measurement between two independent modalities (one low-LET study and one high-LET study) is at best a challenge. The typical photon daily dose fraction is 2 Gy, and equivalent high-LET dose fractions are usually smaller. Biological endpoints therefore must be able to examine the biological response selected with sufficient accuracy to distinguish what may be similar responses as biological endpoints come together at low doses. Some may argue that measurement of high dose responses are adequate, since theoretical modeling would allow extrapolation to the low dose region. However this statement assumes certainty in selection of an appropriate theoretical model to use for the extrapolation. The "stretch" to low dose response is well known to be variable with supra-linear, linear and quadratic fits all represented among the various low-LET radiation responses

measured. Very few low-dose responses are available for high-LET radiations.

<heading 2> Reference radiation

The strictest definition of RBE requires one to compare the high-LET biological response to ^{60}cobalt. Since cobalt sources are not available as commonly as was true when the RBE definition was made, the high voltage x-ray machine has gained acceptance in the field as a substitution low-LET reference. When comparing results obtained by different investigators, it is critical to correct for differences due to the choice of the low-LET reference radiation. Obviously in the need to establish a common standard, a low-LET reference that is available to the largest number of groups is desirable. The author would argue that it may even be important to propose a low-LET particle as a reference.

<heading 2> Application to the clinic

Once there is a solid basis for defining equivalent doses, a decision must be made regarding how the measurement should be included into the treatment planning effort. Three-dimensional analysis of isodose contours accomplished by examining all pertinent two-dimensional axial tomographs for each treatment port begin with the physical dose, but must include a consideration of criticial tissues that may each may have unique values in each field. The 1987 NCI report on evaluation of treatment planning for particle beam radiotherapy (36) concluded that there was no satisfactory way of handling the potential variation of biological effectiveness in a particle beam, and they were not able to come to any conclusion about the additional need to compensate for internal inhomogeneities jor for the shape of the target or the external patient surface. One of the primary reasons for the lack of a conclusion by this report for this problem, was the lack of sufficient particle data on individual normal tissue toxicities. These data are still required for the fullest optimization of ion beam radiotherapy, no matter what mode of beam delivery is chosen.

<heading 2> Need for standardization

The main conclusion of this paper is that there is a strong need in the field of ion beam therapy to standardize the biological beam characterization and to complete parallel, coordinated physics calibration and dosimetry under the exact geometry of the biological measurements. Several candidate approaches are reviewed and recommendations are made to steer the

selection of the standards. Such effort will advance the international effort to optimize ion beam radiotherapy.

<heading 1> Figure captions

Fig. 1 Vessels for the irradiation of cells in vitro on a horizontal accelerator beam line. Upper panel) glass cylindrical chamber for cells in suspension, Lower panel) an array of tissue culture flasks with cells grown in monolayer.

Fig. 2 Illustration of how the irradiation of several pairs of tissue culture flasks behind variable amounts of polyethylene tissue equivalent absorber allows a measure of cell survival over ion beam ranges with about 4 mm resolution.

Fig. 3 Illustration of human T-1 fibroblast cell survival data obtained with the techniques described in the text over extended 230 MeV/u helium ion Bragg peaks of 1.5, 2.0 or 2.6 cm width used in the radiotherapy of uveal melanoma.

Fig. 4 Sketch of tissue culture flask with central region indicating area where human fibroblasts are plated in preparation for cell survival measurements of the effects of narrow diameter beams.

Fig. 5 Twelve 25 cm^2 tissue culture flasks that contained a uniform density of single human T-1 cells in monolayer when irradiated with the collimated 225 MeV/u helium ion beam. The flasks were irradiated in pairs (as illustrated in Fig. 3) with variable amounts of absorber to cover the depth of the beam range. After irradiation, the media was replaced and the cultures were allowed to grow to clonal density. A highly collimated control region of cell killing can be seen on the right. Flasks on the left were beyond the range of the beam and show no killing.

Fig. 6 Three sets of four 750 cm^2 tissue culture flasks that contained a uniform density of single human T-1 cells in monolayer when irradiated with 580 MeV/u neon ions delivered in a rastered mode. Left panel) unirradiated control set; Middle panel) 1.5 Gy; Right panel) 3.6 Gy.

Fig. 7 The gel slicing procedure. The get/medium is extruded and sliced at intervals of 2 mm or more. Each 2 mm slice contains 10^5 cells, which are resuspended by melting the gel/medium in a 5 ml tube of warm medium. (Photo courtesy of Lloyd Skarsgard).

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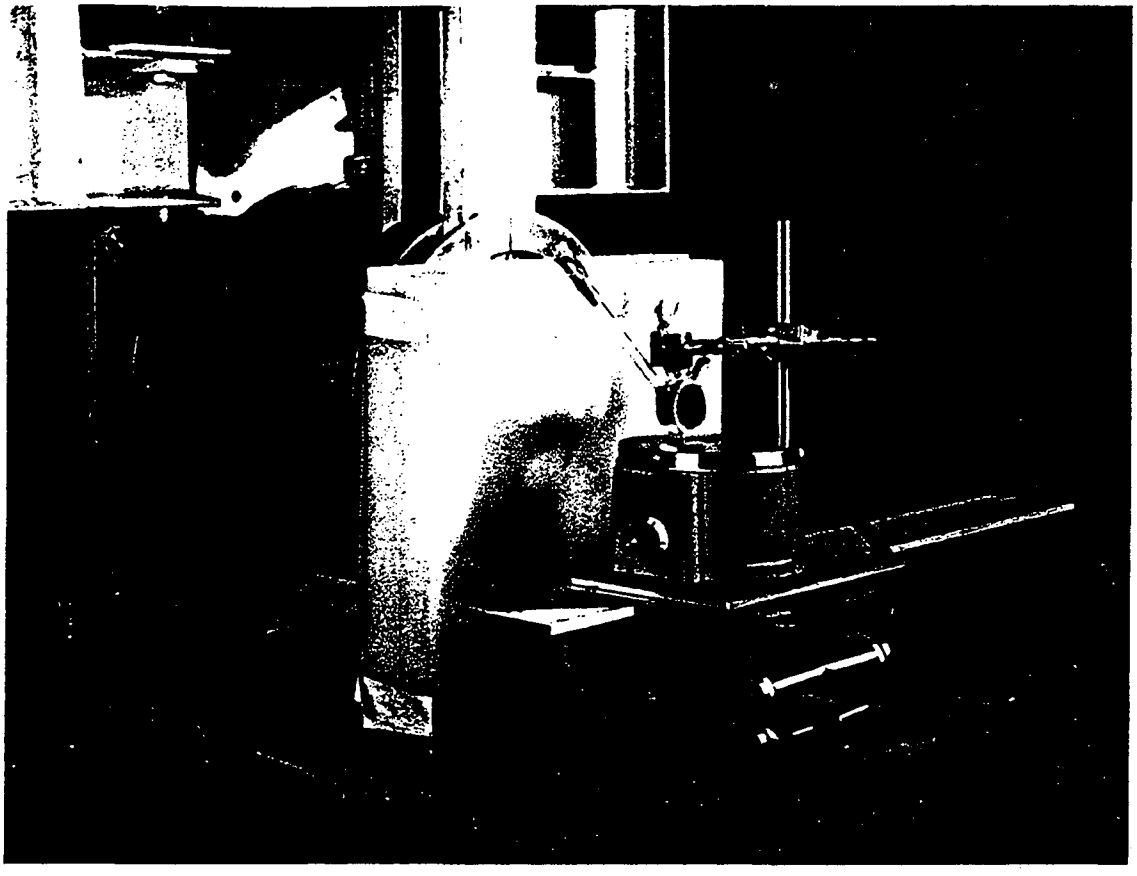
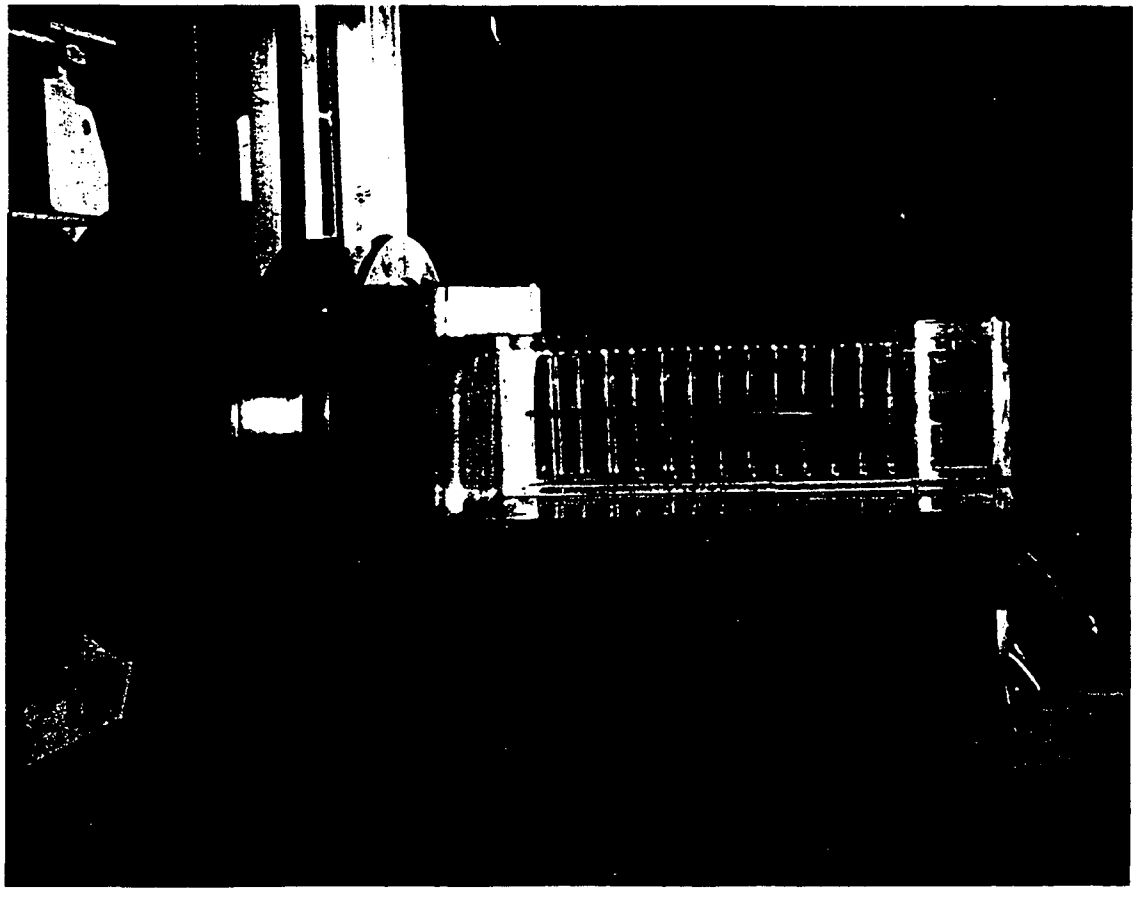
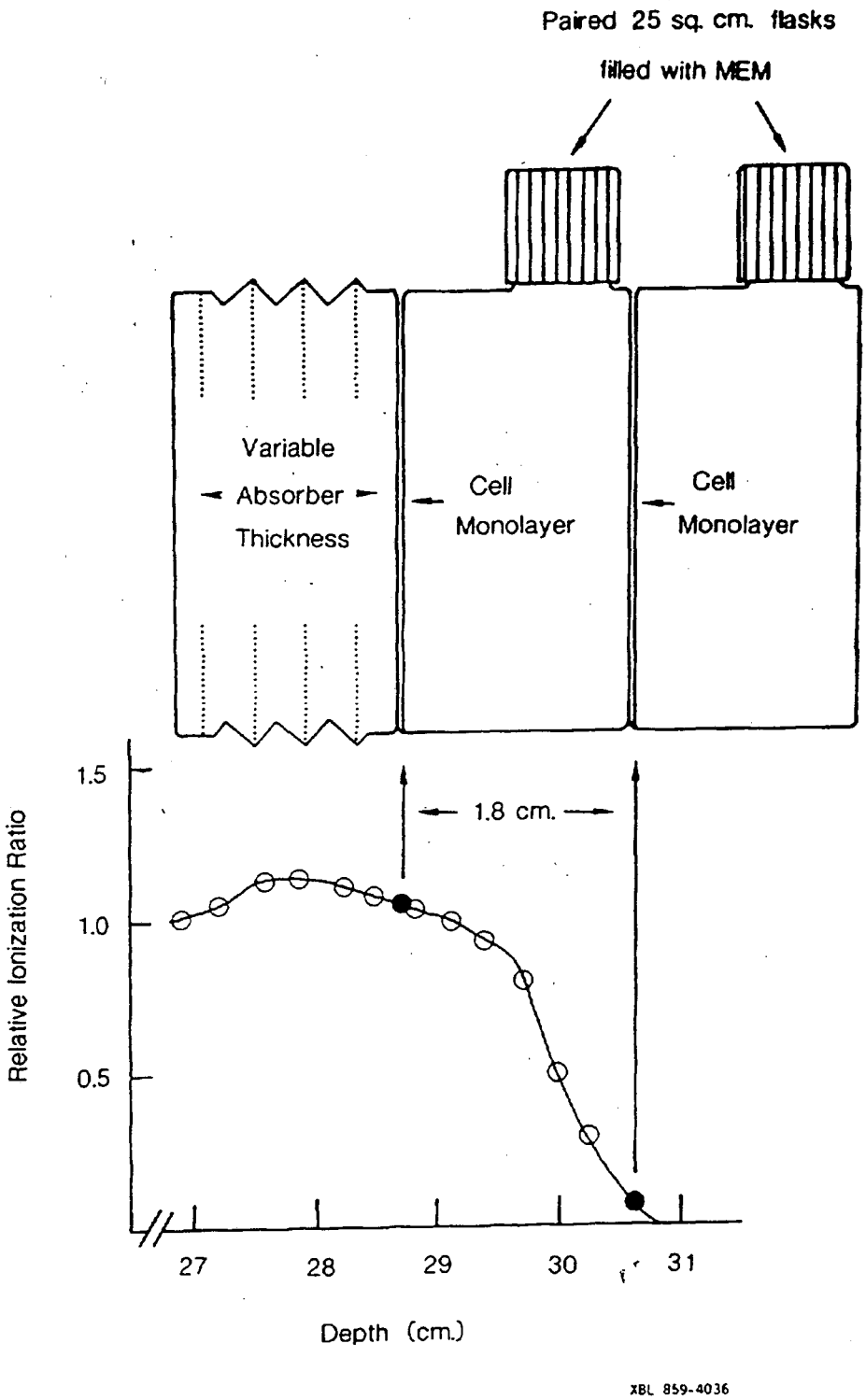
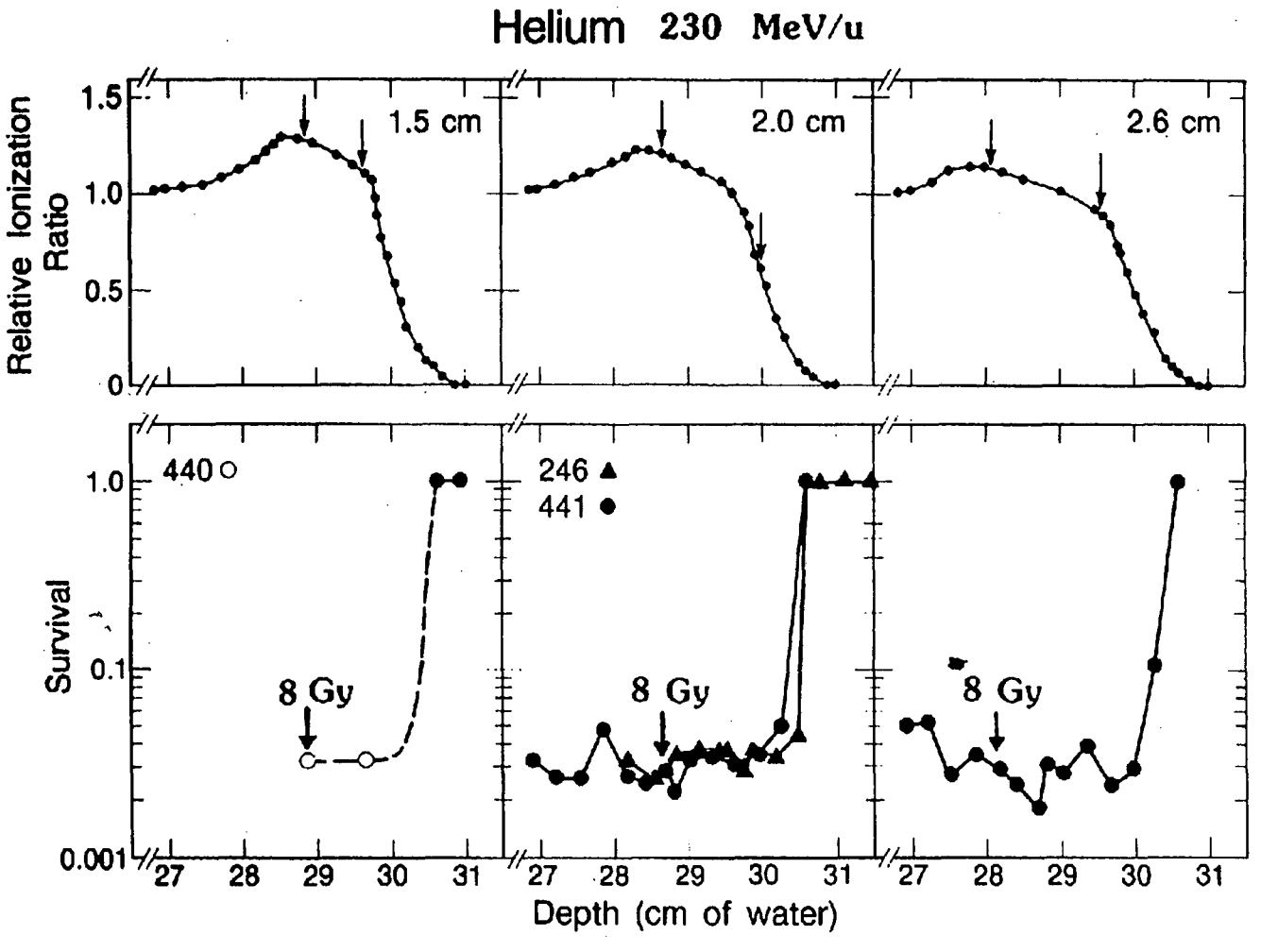
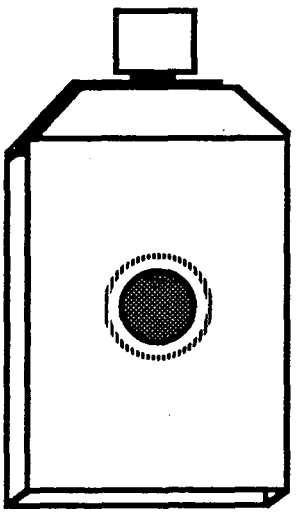


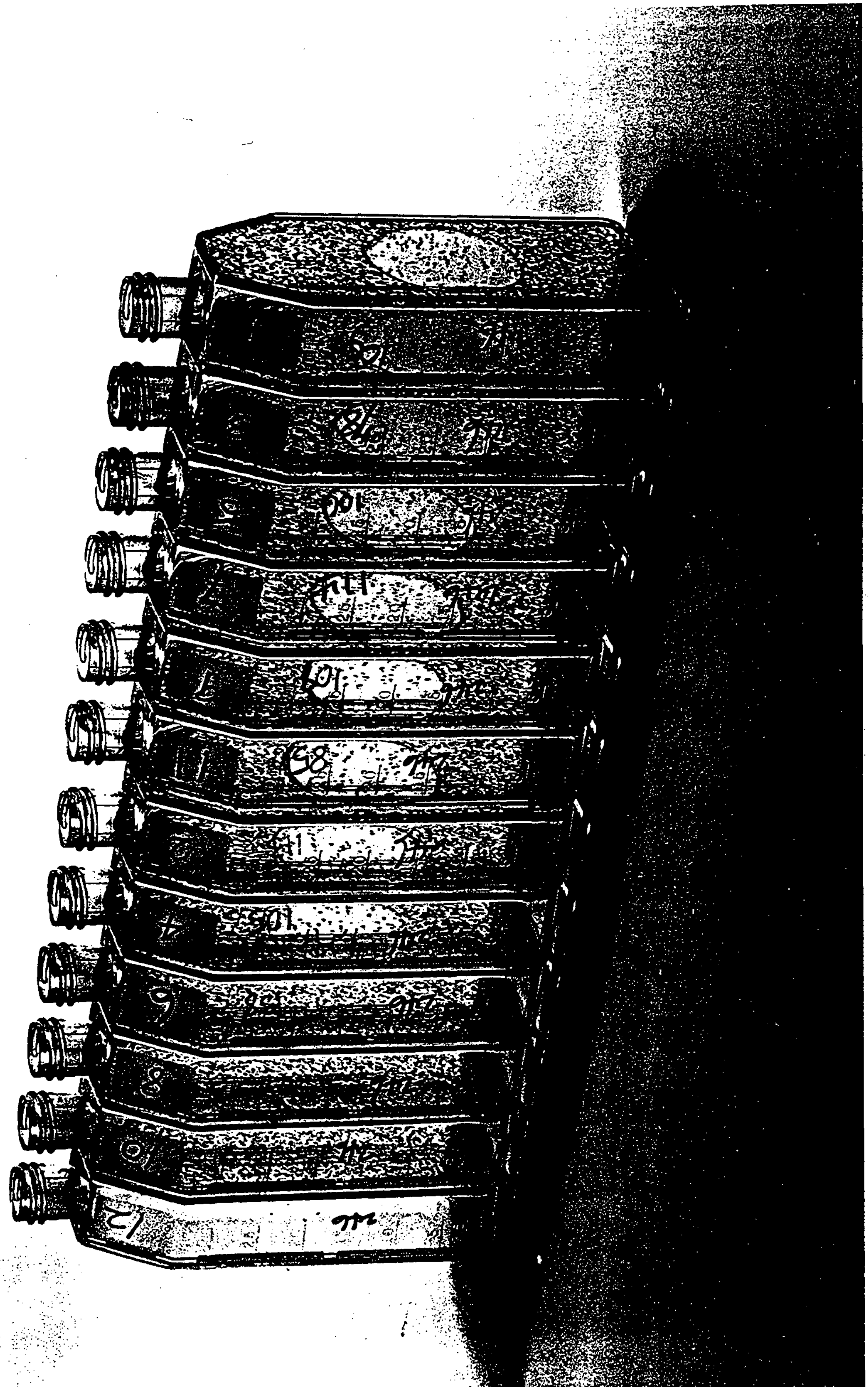



Paired 25 sq. cm. flasks
filled with MEM
Variable
Absorber
Thickness
Cell
Monolayer
Cell
Monolayer
1.8 cm.
Relative Ionization Ratio
1.5
1.0
0.5
27
28
29
30
31
Depth (cm.)

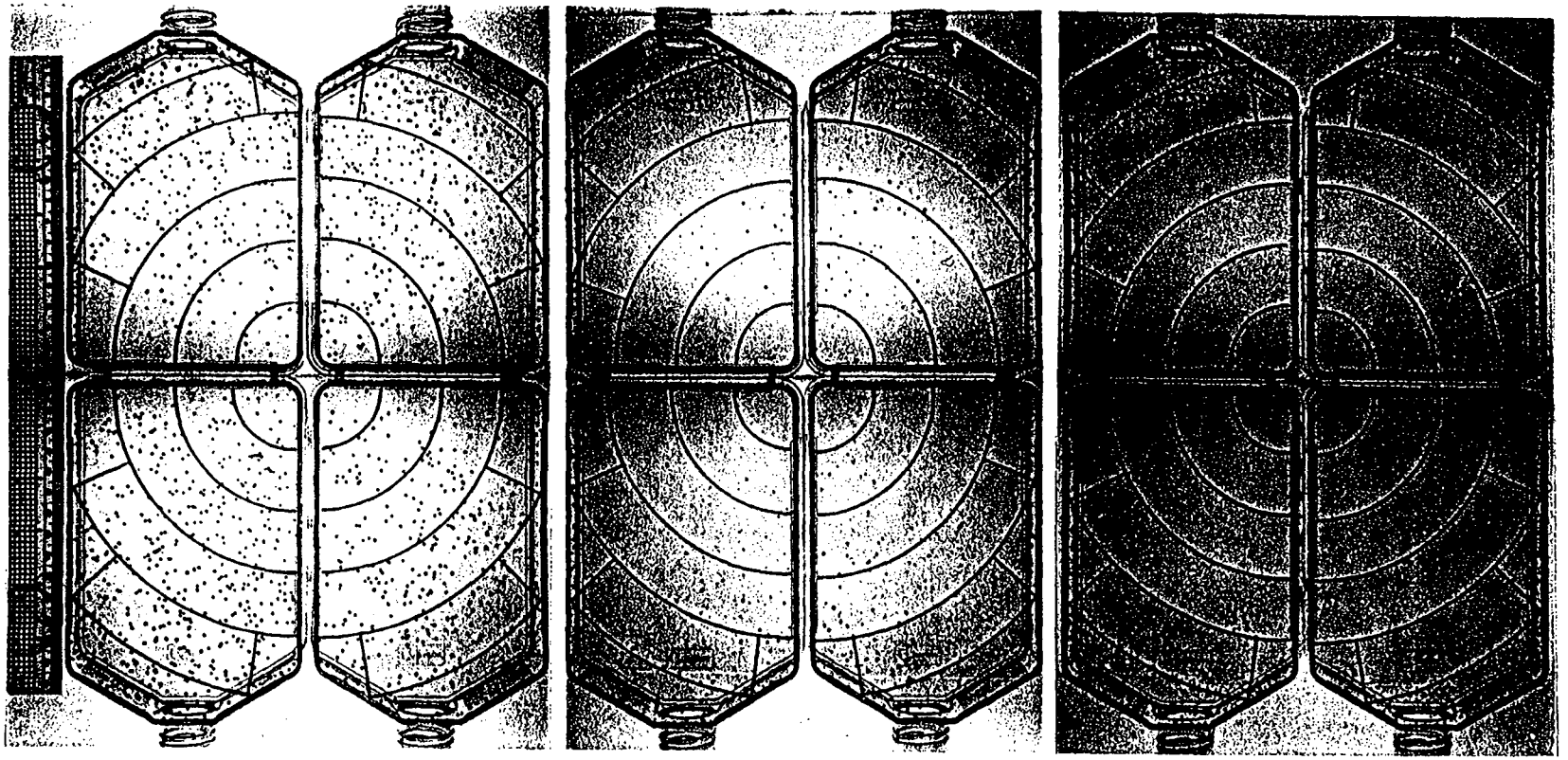
XBL 859-4036


Helium 230 MeV/u
Relative Ionization Ratio
1.5
1.0
0.5
0
1.5 cm
2.0 cm
2.6 cm
Survival
1.0
0.1
0.001
440 ○
246 ▲
441 ●
8 Gy
8 Gy
8 Gy
27
28
29
30
31
Depth (cm of water)
XBL 859-8486





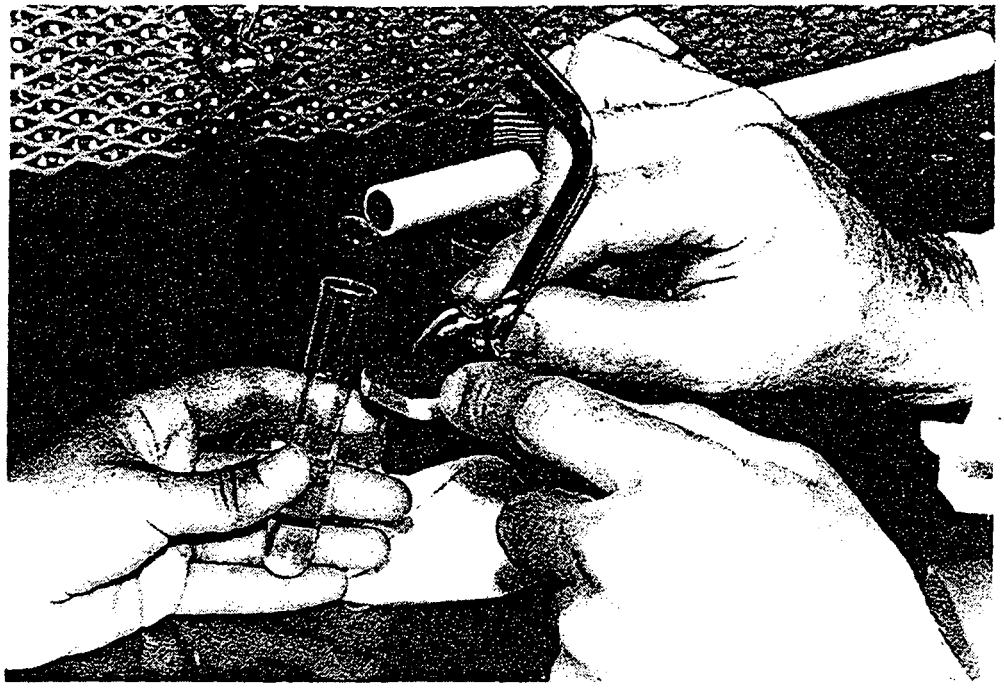
HUMAN T1 CELLS - RASTER FIELD - NEON 580 MeV/u



Control

1.5 Gy

3.6 Gy



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