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Research Proposal Submitted to the Atomic Energy Commission

by

712435

The University of Texas at Dallas
P. O. Box 30365
Dallas, Texas 75230

(AC 214) 231-1471

Beam Line Studies and Radiobiology of Pion Beams and Organization of the LAMPF Biomedical Steering Committee

Name:	Principal Investigator Chaim Richman
Title:	Professor
Social Security No.:	[redacted]
Department:	Pion Radiobiology Project

This is a continuation proposal to the AEC. The proposed starting date is August 1, 1970. The amount being requested is $138,025.00. The proposed duration is 12 months.

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Endorsements

C. Richman
Principal Investigator
Extension 386

Francis S. Johnson
Acting President
Extension 201

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PROPOSAL

TO

THE ATOMIC ENERGY COMMISSION

FROM

THE UNIVERSITY OF TEXAS AT DALLAS

Beam Line Studies and Radiobiology of Pion Beams

Chaim Richman
Principal Investigator

June 2, 1970

Introduction

The pion facility at Los Alamos is progressing very well; indeed, at this writing, Louis Rosen and his staff are moving into the LAMPF administration building at the entrance to the facility. Furthermore, each group, such as the High Resolution Spectrometer group, the P^3 group, the Nucleon-Nucleon group, as well as the Chemistry group, and other groups, are developing their own plans, including beam lines and experimental areas. Of all the groups, the HRS group and the Stopped Muon group seem to be the furthest along, and the HRS group is either ordering its magnets or about to do so.

There is a great deal of work that needs to be done now to plan the biomedical facilities in every respect. This planning should begin as soon as practically possible. Of first importance are two beam lines which need to be

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studied and designed from the point of view of biomedical problems. The first is the Burman-Jakobson channel which is now planned as a stopping pion channel for physics and will probably be in operation a year or more before the second channel, a purely biomedical channel of large aperture, is available.

Specific Considerations Regarding the Treatment of Human Cancer Cases with the Negative Pi-Meson Beam From LAMPF

To get some ideas on the channel requirements for radiobiology and radiotherapy, a discussion is presented here, written with Dr. Max Boone, on specific lesions that should be considered. The beam sizes and beam shapes needed can best be arrived at by this kind of study of the location of these lesions and what problems are encountered in the treatment planning.

For the purposes of this discussion, we are assuming that the principal advantages of a negative pi-meson beam are that it can be exquisitely shaped in three dimensions to fit the required treatment volume, as well as being able to be shaped to irregular dimensions so that it does not necessarily treat only regular cubic geometrical volumes. Although it is true that additional advantages should derive from the fact that the entering beam is of low LET and therefore low RBE and high OER, while the high dose volume is of higher RBE and lower OER, these considerations will await further confirmation in clinical material before one can be certain of their full therapeutic usefulness. As a consequence, only the dose localization factor will be considered in projecting which tumors should advantageously be treated with pi-mesons.

Tumors of the Head and Neck

Tumors of the head and neck offer immediately evident advantages as the case material with which to evaluate a new therapeutic modality because they

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are accessible in most cases to inspection and palpation, they are surrounded by normal tissues whose reaction can be gauged in the case of skin and mucosa by direct observation, and are also immediately adjacent to various vital structures such as the eye, brain stem, etc. The histological varieties occurring in each site and their routes of spread are well established, and the treatment results to be expected with modern radiotherapy, combined with surgery and in some cases with chemotherapy, are fairly well established. For the most part, these tumors are squamous cell carcinomas of various grades of anaplasticity, lymphosarcomas, and in some sites glandular carcinomas. In many cases, the lymph nodes in the neck are also involved early, and must be treated along with the treatment to the primary tumor. Disadvantages of head and neck tumors are that they are fairly rare. As a total group, they comprise 7 to 8 per cent of all malignant diseases, and in some series, even less than this total percentage of all malignancies.

Lessons from the Use of High Energy Electrons

Experience derived from high energy electron radiotherapy should be useful in planning for treatment with the negative pi-meson beam. The principal advantage of high energy electrons has been the capacity to confine the high dose zone to a superficial volume with sparing of underlying normal tissues. In addition, the negative pi-meson beam gives us the capacity to spare normal tissues located nearer to the skin than the treatment volume. A second advantage of high energy electrons is that through the choice of an appropriate E_o, it is possible to uniquely define the depth of penetration required depending upon the depth of tumor involvement. With the negative pi-meson beam, the highest pion energy will correspond with the E_o for the high energy electrons,

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and selection of an appropriate momentum spread will, in addition, enable us to spread the high dose zone over the desired depth interval with sparing of the more superficial and more deep-lying normal tissues. A possible disadvantage of this exquisite dose localization is also introduced by analogy with high energy electrons. In any radiotherapy, it is possible to have geometrical miss through not having the portal large enough, or having it extend an insufficient distance in a given dimension perpendicular to the beam direction. In the case of high energy electrons, it then became possible to have geometrical miss by placing the zone of rapidly decreasing dose too superficially so that deeper-lying portions of the tumor received inadequate dose. This was particularly true in the case of treatment of tumors of the tonsillar area where the interposition of the mandible was shown to attenuate the dose somewhat greater than an equivalent thickness of unit-density tissue. In the case of negative pi-mesons, to these other dimensions of possible geometric miss must be added that of the superficial zone. If the high dose zone does not extend sufficiently far toward the skin surface to include the entire tumor bearing region and its first echelon of spread, it will be possible to have geometric miss due to inadequate tumor dose delivered to more superficially-lying portions of the tumor complex.

Treatment Considerations for Specific Sites

A. Oral Cavity and Oropharynx

Tumors here are classified as T_1 if they are less than 2 cm. in diameter, T_2 if they are 2 to 4 cm. in diameter with minimal extension to adjacent structures, T_3 if they are more than 4 cm. in diameter with limited or moderate extension to adjacent structures, and T_4 if they are massive primary tumors.

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They may also be accompanied by spread to lymph nodes throughout the neck region, or to only a limited portion of the neck; they may involve the neck either unilaterally or bilaterally. Each of these considerations will call for different shaping of the negative pi-meson beam. It is felt desirable in order to encompass the full range of situations, a beam should have a high dose zone 10 cm. in depth with an appropriate momentum spread to achieve this. This would be required for the largest tumors in this site. If portions of the neck are to be irradiated along with the primary tumor in a single field, beam sizes up to 15 x 15 cm^2 should be provided. It should be noted that beam adjacency will not present the problem with negative pi-mesons that it has in the past with other beams utilized for radiotherapy. All radiotherapy beams are divergent beams in which it is virtually impossible to adequately match the beam margins without high dose overlap in depth and "cold spots" near the surface. With the negative pi-meson beam, the fact that it is essentially parallel should make beam adjacency problems much less difficult. Accordingly, if the lower neck must be irradiated along with the upper neck and primary tumor, adjacent beams may be utilized for this purpose without serious problems created by field adjacency if patient motion is minimized, and a jig is used for setup.

The technique of "boost" irradiation will undoubtedly be used. That is, a larger area including the primary tumor and probable routes of spread should be included within the irradiated volume for the first portion of the dose. After approximately 70% of the total tumor dose has been delivered, it is then often desirable to decrease the size of the high dose zone to encompass more precisely the area of primary tumor. This has been practiced in the past in order to achieve a higher tumor dose leading to greater probability of local control of the tumor while not greatly increasing the incidence of complications

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because the technique has excluded some normal tissues from the highest dose. This technique will in all probability also be applicable to pi-mesons. For this reason, the beam will probably be tailored after approximately 70 to 75 per cent of the tumor dose has been delivered so that the residual lower volume that is brought to a very high dose can be as small as possible. This will require still further exquisite beam shaping in three dimensions. In this respect, the negative pi-meson beam may be expected to adequately replace interstitial insertion of radioactive sources (as for floor of mouth and tongue lesions) which are presently practiced. A submental pi-meson beam portal, combined with lateral portals, could be used, for example, to treat the floor of the mouth with good control of the total volume brought to a high dose. Such a technique would lead to greater dose homogeneity than achievable with interstitial sources and should produce the same or -- as we expect -- better results.

In order to adequately treat residual lymph node masses in the neck after an initial course of therapy to larger fields, it should be possible to adjust the energy of the negative pi-meson beam so that the lowest energy represented is quite low in order to boost residual lymph node masses. The high dose zone should thus start only a few millimeters under the skin surface, probably not more than 3 to 4 mm., and may than extend 1 to 4 cm. in depth to include the lymph node masses. Here it should be noted that the use of negative pi-mesons to treat the neck will enable high doses to be delivered to the lymph node bearing areas with essentially no dose delivered to the spinal cord. This will be highly advantageous in head and neck radiotherapy where often the spinal cord and brain stem receive rather large doses verging on the normal tissue tolerance of the central nervous system.

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B. Nasopharynx

The nasopharynx only measures 1-1/2 by 2 by 2 cm^3. However, it is customary in treating tumors arising in this area to use a high dose volume extending from one side of the patient's head to the other and often, through use of anterior angulated fields, to have the high dose zone extend forward to the skin surface of the cheek and posteriorly even into the brain stem. The incidence of complications in successful treatment of nasopharynx cancers has been rather high. These complications include central nervous system damage, difficulties in motion of the jaw due to high dose irradiation of the tempero-mandibular joints, hearing loss due to high dose irradiation of the auditory mechanism, loss of taste and dry mouth, and many others. Through use of the negative pi-meson beam, it should be possible to start out with a high dose zone which is somewhat more generous than the size of the nasopharynx itself, but not so generous as the high dose zone involved in conventional treatment. Again, this could be carried to doses approximately 75% of the final tumor dose, at which time the fields could be tailored more closely to the nasopharynx and adjacent portals could be used for this purpose (that is, more than one field could be used with fields being adjacent to one another). The entire neck should be irradiated bilaterally, but this can be accomplished through use of negative pi-mesons with sparing of the spinal cord.

C. Larynx and Pyriform Sinus.

Tumors of the larynx vary from those involving the vocal cord and having dimensions of only a few millimeters in size to extensive tumors which extend essentially from the base of the skull to the thoracic inlet. Therefore, great control of beam size would be advantageous in treating this variety of tumors. Identification of exact placement of the high dose zone in the patient through tracing by mesic X-rays, annihilation radiation from induced radioactivity,

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or other techniques should be valuable in correlating with the precise localization of the tumor through tomography, direct contrast laryngography, and various other techniques. The control frequency in tumors in this group range from 90% for T_1 tumors of vocal cords to essentially 0% for advanced pyriform sinus tumors and tumors of the extrinsic larynx. In the earlier tumors, the capability for exquisite dose localization might be hoped to produce the same sort of survival presently obtainable with conventional methods but with fewer complications and morbidity. At best, it might produce improved survivals even in these cases. In the more advanced cases, one would hope and expect that improvement and percentages of cases surviving would be obtained with an exceptionally low complication frequency.

D. Paranasal Sinuses and Nasal Cavity

This group of tumors is very interesting in that they ordinarily lead to the death of the patient in approximately 2/3 of the cases with no evidence of distant spread of tumors; that is, they destroy the patient by invading locally. Therefore, if local control of these tumors could be achieved by neuroradiation modality, one could expect to salvage the patient since distant metastases is not the principal problem. Exquisite localization of the high dose zone is important here, not only to include the primary tumor and its routes of spread, but to also spare surrounding vital structures, such as the eye and the brain. The capability of shaping the beam [negative pi-mesons are very easy to stop and therefore irregular shaped fields may be easily obtained in counterdistinction to fast neutrons which are quite difficult to shape to irregular fields] should be especially useful in the case of tumors in this area.

E. Tumors of the Middle Ear and Mastoid

High energy electrons have not proven as useful in these tumors as had been expected. This is partially due to the marked influence of tissue

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heterogeneity and the occurrence of air spaces leading to great distortions in dosage delivery. With negative pi-mesons, it may be possible to achieve dimensional control of the high dose zone and therefore spare brain tissue while achieving an adequate control of the tumors. If this proves to be the case, this would represent an improvement over the present techniques using conventional irradiation and wedge-filtered fields in order to confine the high dose zone to that requiring treatment.

F. Thyroid Carcinomas and Miscellaneous Head and Neck Tumors

Thyroid cancers include a range of malignant potential going all the way from very benign malignancies in which patients often survive 15 or 20 years or more to one of the most malignant tumors known in man, the giant and spindle cell, cancer of the thyroid. For those tumors not amenable to radio-iodine therapy and where local irradiation in the neck is required, negative pi-mesons should offer the advantages of good localization of the high dose volume. The same is true for various tumors of the head and neck, such as solitary plasmacytoma, malignant melanoma, etc.

G. Pelvic Tumors

The decision as to whether pelvic tumors can be advantageously treated with negative pi-mesons will await careful evaluation of the possible effect of negative pi-mesons on the bowel. One will need to clearly establish the sort of shoulder widths in the survival curves of gut cells under negative pi-meson irradiation, as well as the recovery capabilities of gut cells with negative pion irradiation. Thus, it will be necessary to establish the D_q, D_o, and do various split dose experiments in an attempt to define the Elkind type recovery curve for negative pi-mesons. Although this will be somewhat difficult with the low intensity beam presently available at Berkeley, certainly attempts should be made to define as a minimum the D_q for negative pi-mesons, the RBE

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in the vicinity of the shoulder and in the exponential portions of the survival curves for negative pions versus conventional radiations, and if possible the OER values applying to gut cells. This is because the normal tissues as usual represent the limiting factor in radiotherapy, and one cannot conscientiously plan for applications of negative pion beams to the pelvis without first exploring this question. If it should prove feasible to treat pelvic tumors with pions, one may then consider irradiation of bladder tumors in which there is presently a very high local recurrence frequency with conventional irradiations, advanced pelvic tumors in which the survival rate is certainly less than optimal, and anoxic cells very definitely represent a problem, and possibly one might also consider preoperative irradiation for carcinoma of the rectum. Prostatic carcinoma might also advantageously be treated with negative pi-mesons because of the exquisite capacity to localize dose. One would probably hesitate to apply this new radiation modality to early cases of carcinoma of the cervix because of the high control frequency obtainable with present radiation modalities. However, if the bowel presents no radiobiological problem, in the future one ought to consider exploring the possibility of negative pions even in early carcinomas of the uterine cervix because it might be possible to still further increase the control frequency but with a lower incidence of complications because of the excellent control of the high dose zone obtainable with negative pi-mesons.

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The Burman-Jakobson Channel

The Burman-Jakobson channel is the low energy pion channel which has been designed for physics with pions from 50 to 150 MeV. It is shown in Figure 1. This channel, we have come to realize, deserves a great deal of consideration as a biomedical channel, and Louis Rosen once proposed moving this channel temporarily to the biomedical area.

The beam from this channel has a nominal size of 3 x 4 cm^2, which would be too small for radiotherapy; however, the adjustments on the quadrupoles are such that one can fairly easily go to 15 x 15 cm^2. This is ample for the kinds of tumor radiobiology and radiotherapy that one would want to start with; namely, head and neck tumors.

This channel would, however, have to be changed considerably for radiotherapy. For one thing, the momentum spread of the beam is small ($\frac{\Delta p}{p} = \pm 5\%$) and studies need to be made to see how this can be increased by making reasonable changes in the beam optics compatible with the physics requirements of the channel. An obvious technique is to introduce a variable absorber into the beam; however, this produces multiple scattering which will be evaluated.

A serious drawback of the channel is the fact that the electrons are not removed from the beam. A number of ways will be examined to do this; the usual separator is not favored by Burman and he suggests an r.f. separator. Two other methods will be looked at--if the channel were to take pions at 90° to the proton beam, the electron background would be quite low. Another procedure would be to take pions of much higher energy than would be needed, something like 150 MeV; the background here would also be low and then the pions would be slowed down to the required energy for radiobiology and radiotherapy. Here again, the scattering will be studied. In this area, therefore, a number

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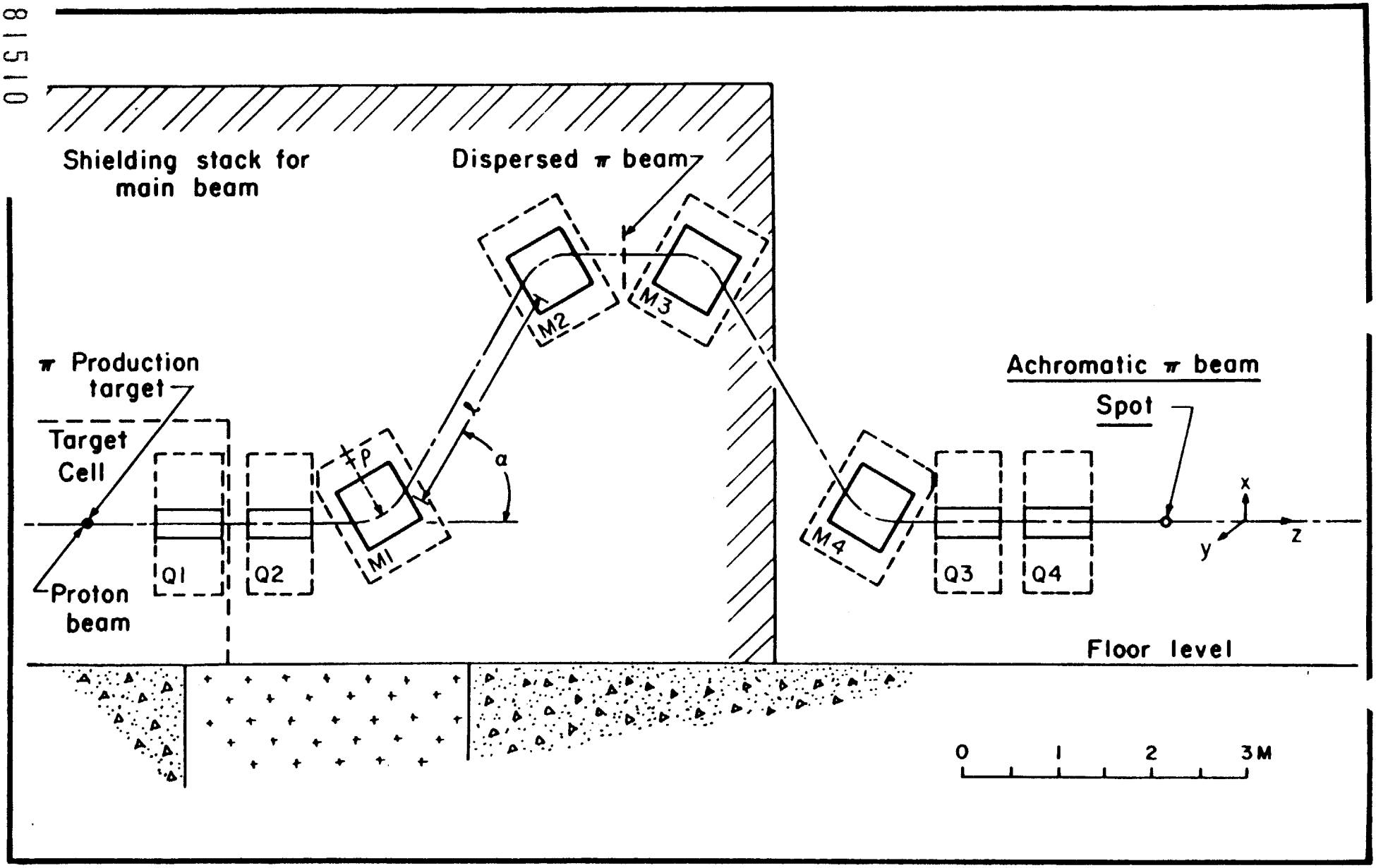

FIGURE 1: THE FOUR-BEND BURMAN-JAKOBSON BEAM LINE

of studies will be made to determine how this channel can be utilized for biomedical work.

It will be important to consider if a beam can be made to irradiate a volume like a spherical volume with a minimum of bolus. Most of the time a beam line is designed for achromaticity; that is, there is no correlation between position and momentum of the particles. Symmetric beam lines satisfy this condition. For physics this situation is quite satisfactory. For radiotherapy it is clear that chromatic distortions or chromatic aberrations of a certain kind will be desired. Studies will be made as to how a beam line should be made to include desired aberrations so that various kinds of tumor regions can be irradiated. From the discussion above of various irradiations, it is clear that this will turn out to be a question of great importance.

It will be important for radiotherapy to know how to handle low energy pions. The lowest energy that the Burman-Jakobson channel can handle at present is 50 MeV. At the same time, pions as low as 8 MeV. (with a range of ~ 3.6 mm. in tissue) are needed for subcutaneous and superficial tumors. A bolus can always be used, but some of the advantages of pions are lost thereby. It would be much more desirable to have the channel handle such low energy pions. This question will be studied. To some extent this is a region of pion beams quite different from those envisaged up to now because not only is the energy low, but the momentum spread required is very high. What will probably turn out is that some bolus will be used but, in addition, to preserve the characteristic advantages of the pion beam, changes in channel design will be desirable in the Burman-Jakobson channel and especially in the Biomedical channel.

The methods of the TRANSPORT code will be very useful in these questions, but it is also clear that for radiotherapy we are concerned with a different set of problems and different kinds of beams from what physicists want (like

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small momentum spread). The code will be utilized therefore and the changes will be made in it for therapeutic beam requirements.

It should be mentioned that the Burman-Jakobson channel ends up in a horizontal beam. Such a beam is very good for head and neck work and there is no disadvantage here in radiotherapy. For chest and pelvic neoplasms, as well as certain other tumors, a vertical beam is much more desirable. Most radiotherapy centers do about 90% of their treatment with a vertical beam. The biomedical beam should end up in a vertical beam. It is a rather fortunate situation that we may have if all works out well that the Burman-Jakobson channel could end up being used for horizontal beam work and the Biomedical channel for vertical beam radiotherapy.

This channel has been funded through physics and its design is not yet frozen. We have time therefore to put into it the needs of radiobiology and radiotherapy, especially since the physics group at Los Alamos is very sympathetic to our requirements. We can look forward therefore to making it possible to start biomedical investigations as early as possible.

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WORK AT THE 184-INCH SYNCHROCYCLOTRON IN BERKELEY, CALIFORNIA

Proposed Research

I. Physical and Dosimetric Studies

We now have pion beams of dose rates 0.5 rad/min. and 1 rad/min. (over an area of 3 x 3 cm.^{2}) with an electron contamination of about 10% and 20% respectively. The muon contamination is 10% for both the beams. With these beams it is possible to make significant improvements in physical as well as biological experiments that would be of value for the biomedical work at LAMPF.

1. Physical Measurements

A beam with a low contamination of electrons will be used to obtain information on depth dose distribution of mesons.

Dosimetry of heavy charged particles can be done using parallel plate ionization chambers without worrying about the wall material of the ion chambers since the ionization is mainly in the gas. This will be true for pions except in the stopping region where the wall material is important since pion capture reactions occur mainly in the wall. Dr. Francis Shonka made a special plastic taking the pion interactions into consideration. Our measurements with a π^- beam of 25% electron contamination so far did not indicate any significant differences in the depth dose distributions as measured by thimble type ion chambers made out of ICRP muscle equivalent and the special plastic. However, our preliminary measurements of depth dose distributions of π^- mesons with parallel plate ionization chambers (with very thin aluminized mylar windows) that are commonly used with heavy charged particles show the dose at the peak is much lower when compared to thimble type ionization chambers. This needs to be studied further.

These types of investigations are very important in deciding the wall material

needed to be used for the dosimetry of negative pi-mesons. The peak of the pion depth dose distribution can be broadened using a variable absorber. Depth dose distribution with such broad peaks are necessary for most of the therapeutic applications. We propose to do these studies.

These physical measurements can be carried out quite well with the beam at Berkeley and this experience will certainly be useful and save a considerable amount of time in getting the biomedical work started at LAMPF.

2. Improvements in the Pion Beam at the 184-inch Synchrocyclotron
(in association with Mr. John Sperinde and Dr. Victor Perez-Mendez)

The cyclotron operation group, headed by Mr. James Vale, increased the beam current by nearly 50%. It was accomplished by pulsing off the Dee bias during the acceleration period. The beam had been previously increased by using carbon tetrachloride to neutralize the beam space charge in the central region. With this increase in beam current and by focusing the beam we get a π^- dose rate of the order of 1 rad/min over an area of 3 x 3 cm.^{2}

A 2" Beryllium target is commonly used for π^- production; a 4" Beryllium and a thick tungsten target were also tried to see whether we can improve the pion intensity. Preliminary results indicate that no significant improvements in intensity could be obtained for the beam geometry in the meson cave.

However, the intensity of the pion beam and the electron contamination is found to vary significantly with the position of the target. By sacrificing 50% intensity, the electron contamination is reduced from 25% to nearly 10%; that is, we are at present able to get a pion dose rate of 30 rads/hr with an electron contamination of 10%, or a dose rate of 1 rad/min with nearly the same electron contamination as before.

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3. A Method of Observing a Stopping Pion Region
(in association with Mr. John Sperinde and Dr. Victor Perez-Mendez)

Our preliminary measurements of locating the stopping negative pion region by detecting the gamma rays emitted following the capture process are very promising. A report on these measurements accepted for publication in Physics in Medicine and Biology is herewith enclosed.

II. Radiobiological Studies

1. Experiments with Cultured Cells (T_1)

The present dose rate of 1 rad/min is roughly equivalent to 2 to 3 rads/min of ^{60}Co gamma radiation. This dose rate is fairly close to the acute exposures and hence the information of RBE and OER will be more applicable to the therapeutic situations.

The conventional tissue culture technique is modified to suit the conditions for pion exposures at the cyclotron. The maximum period of exposures are four and six hours in the presence of air and nitrogen respectively to bring the surviving fraction to about 1%.

Experimental Procedure

a) The cells from an overnight culture are plated on 35 mm. plastic dishes one day before the pion exposures. To reduce the dose variation within the sample, the cells are plated in the central part of the 35 mm. plastic dish by placing a drop of medium containing cells. The dish is then incubated for an hour and additional medium is then added. Most of the cells are within 1-1/2 cm. to the central part of the plastic dish. Pion dose variation in that area is less than 10%.

b) Just before pion exposure the medium in the dish is removed and the Cells are then kept in contact with two thin layers of gauze wetted

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with medium containing a phosphate buffer to keep the pH at about seven.

c) Soon after the exposure, the cells are trypsinized and plated onto 5 to 10, 35 mm. plastic dishes after proper dilution depending on the dose given to that sample.

d) Plating efficiencies of 25 to 50% are obtained when the cells are kept in such experimental conditions up to eight hours.

Our preliminary experiments with ^{60}Co gamma rays and negative pi-mesons indicate that this technique works well and we hope to obtain RBE and OER for this cell line which has been studied extensively with neutrons by Dr. Barendsen and for heavy ions by Dr. Todd.

These types of investigations will not only give useful preclinical radiobiological data but also help in keeping up the momentum of physical and preclinical radiobiological work for π^- mesons so that it can effectively be transferred to the biomedical facility of LAMPF.

2. Experiments with Lymphocytes

Mr. U. Madhvanath is working on radiation response of human lymphocytes with ionizing radiations of different LET using heavy ions from Berkeley HILAC. This work will form his Ph.D. thesis in biophysics.

This system is being used because of its high sensitivity to radiation. Lymphocytes were separated from freshly drawn human blood and were maintained in short-term culture. After a day of culture preparation, they were exposed to the radiation. The cells were then incubated at 37°C (Air + 4% CO_2) for six days. On the sixth day the cell viability was determined using Trypan blue dye (viable cells exclude the dye).

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The results with ^{60}Co gamma rays indicated (as reported by others) that there are two major groups of lymphocytes of different radiation sensitivity. The D_{37} values were 80 rads and 300 rads. The D_{37} value of 80 rads of the sensitive group was found to be independent of dose rate.

Figure 2 shows the results of ^{60}Co and π^- mesons. For the sensitive fraction of lymphocytes, an RBE of about 2 was obtained for π^- mesons and this value will be applicable for acute dose rates of π^- mesons.

The mechanism of death of the non-dividing lymphocytes could be different from that of other mammalian proliferating cells. RBE measurements for mesons will be extended for the less sensitive fraction of lymphocytes.

3. Experiments with Yeast--Reverse Mutations in Saccharomyces Cerevisiae BZ-34

This system was found to be very practical for measuring the OER for mesons. This system has an OER of 2.5 for both the dose rates of 40 rads/hr and 40 rads/min of ^{60}Co gamma rays.

Our experiments with pions gave an OER of 1.8 and an RBE of 1.5. A report on these measurements is enclosed.

RBE and OER for this strain as a function of LET is being measured using heavy ions (Helium, Carbon, Neon) from the Berkeley Heavy Ion Linear Accelerator. The results of these experiments are being analyzed and written for publication. Figure 3 shows the summary of the results. It was found that the induction of mutations saturates with increasing LET, resulting in a lower mutation induction efficiency for Neon ions. This trend has also been found in the yeast (strain X841 used by R. K. Mortimer et al[1]). With BZ-34 the OER values obtained approach the limiting value of unity with increasing LET as is the case with mammalian cell systems.

1. R. K. Mortimer, T. Brustad, D. V. Cormack, Influence of Linear Energy Transfer and Oxygen Tension on the Effectiveness of Ionizing Radiation for Induction of Mutation and Lethality in Saccharomyces Cerevisiae, Radiation Research, 26, 465-482 (1965)

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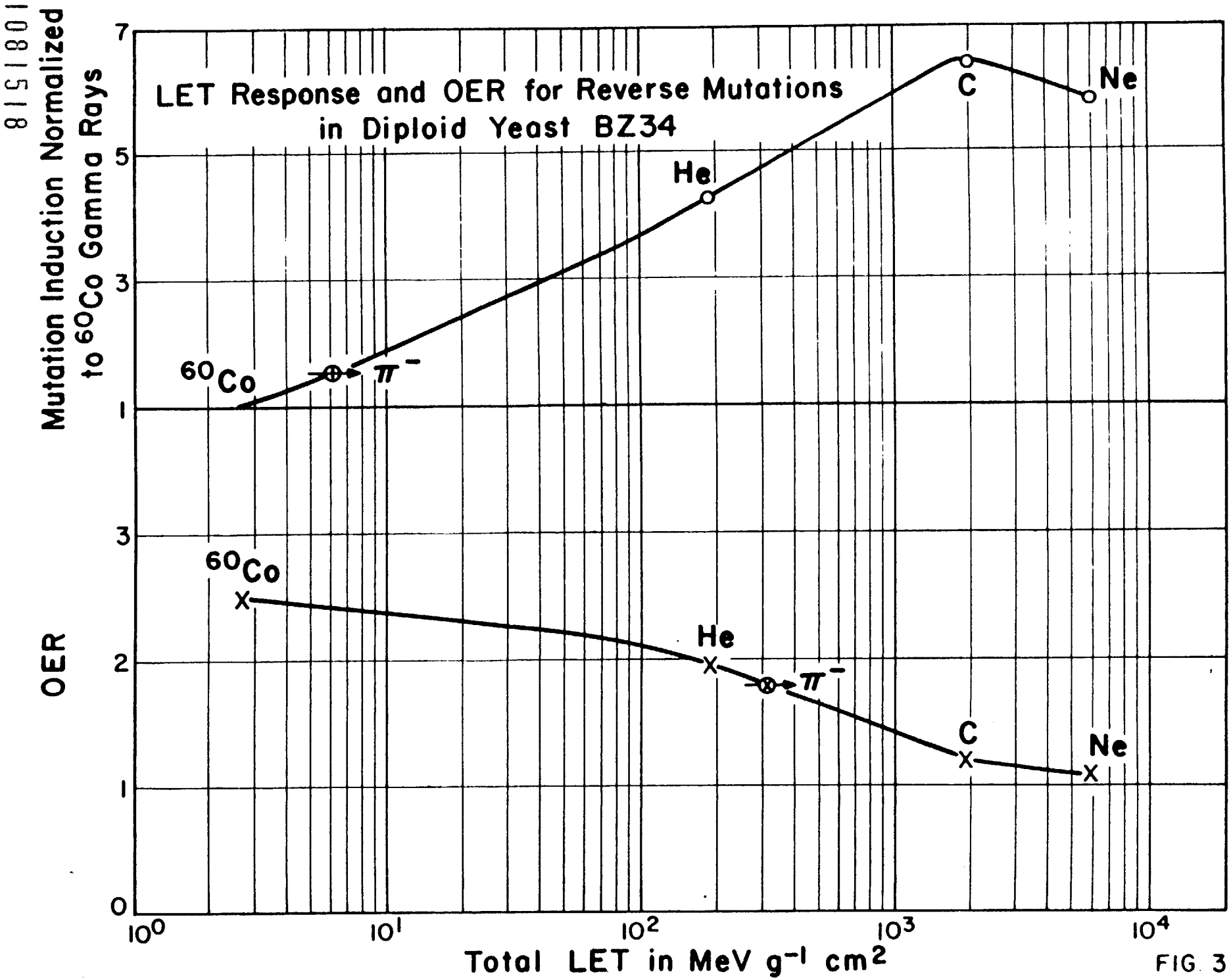

FIG. 3

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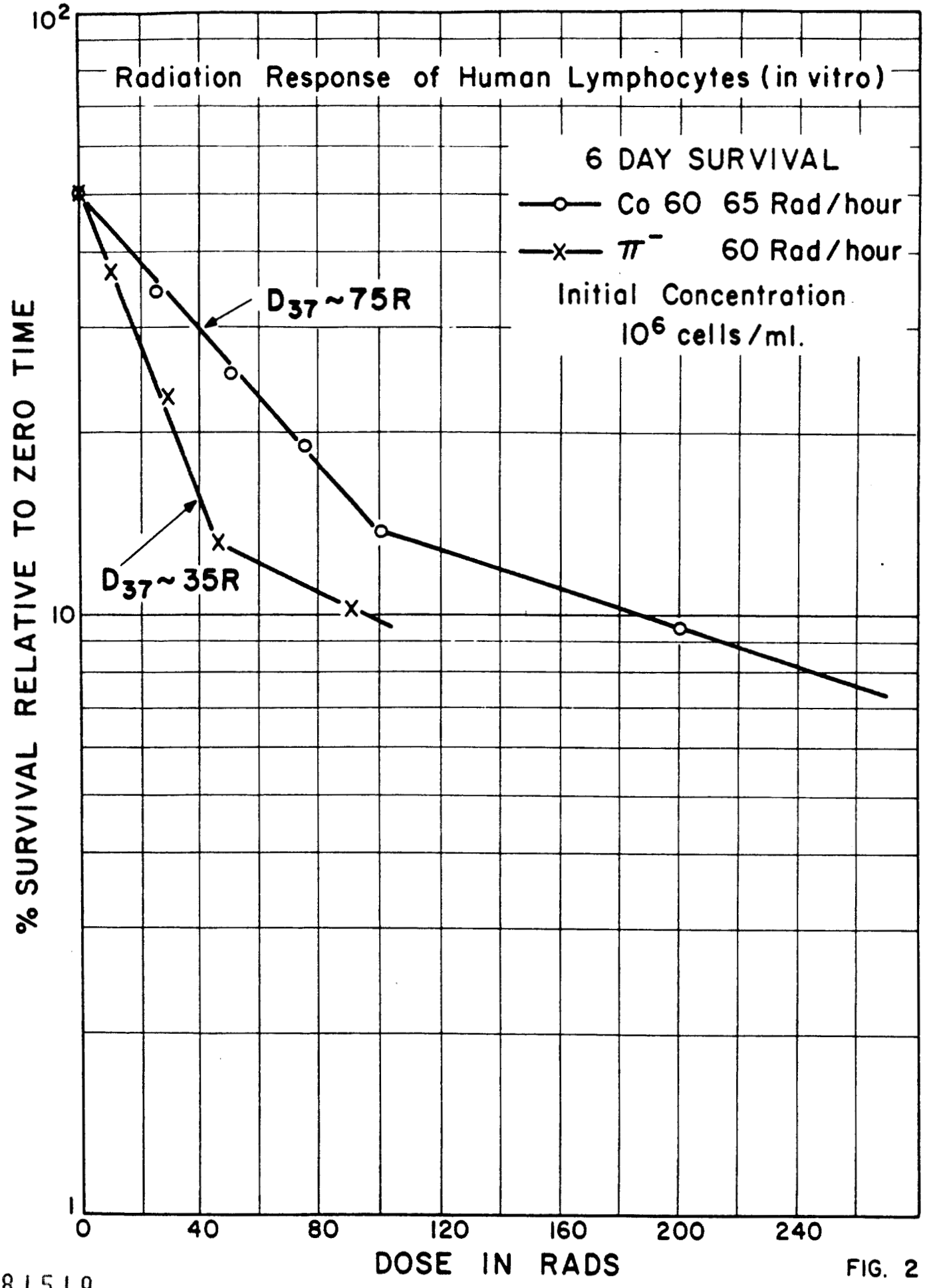

FIG. 2

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4. Experiments with Bone Marrow Cells

There is general agreement among the experts we have consulted with, that it would be of interest to obtain the RBE with a sensitive in vivo assay such as the spleen colony forming technique developed by J. E. Till and E. A. McCulloch.

Mr. J. Feola and Dr. Y. Maruyama -- from the University of Minnesota -- will be doing these experiments.

Procedure:

Bone marrow cells (BMC) will be drawn from the femur of several donor mice. BMC will then be irradiated in vitro in a special container of about 10 cm^3 at the π^- peak and plateau regions. Samples will be taken out after different doses are given to the BMC suspensions, and the cells will then be injected IV into recipient mice, previously irradiated with a dose of ^{60}Co γ-rays sufficient to knock out their immunological resistance. Medium will be added to the container to keep the volume constant, and consequently, the effect of secondary radiation will be the same. The cells will be stirred during irradiation to keep them under normal conditions of oxygenation. After nine days, recipient animals will be sacrificed, their spleens excised, and the colonies counted. By comparison with control groups, survival curves will be drawn.

Experiments with X-rays will be performed a posteriori, with dose rates equivalent to those used with the π^- beam, multiplied by 5 (value of the RBE obtained with in vivo systems), and also with acute exposures. Values of the RBE will then be estimated.

It is expected that a complete survival curve -- down to the 0.01 level of survival -- will be obtained, since the D_0 for aerated BMC irradiated with X-rays is about 100 rads. If the D_0 for π^--irradiation at the peak is about 50 rads, a dose of 200 rads ($\sim$ 4 hours irradiation time) would be enough to reduce survival to about the 0.01 level.

AEC BUDGET

August 1, 1970 through July 31, 1971

			AEC	UTD	TOTAL
A.	Direct Costs				
	1. Salaries and Wages				
	a. Principal Investigator Chaim Richman (academic mos)	20%		4,200	4,200
	b. Associate Investigator Mudundi R. Raju	100%	15,889		15,889
	c. Research Scientist	100%	17,000		17,000
	d. Research Engineer	20%	2,630		2,630
	e. Programmer	20%	2,272		2,272
	f. Secretary	50%	2,615		2,615
	g. Secretary (part-time)		250		250
	Total Salaries and Wages:		40,656	4,200	44,856
	2. Supplies and Expendable Equipment		4,000		4,000
	3. Project Equipment				
	a. Pulse Height Analyzer		15,000		15,000
	b. Dosimetry Equipment		6,000		6,000
	4. Employee Travel		2,000		2,000
	5. Consultants Fees		1,000		1,000
	6. Postage, Communication and Reproduction		1,000		1,000
	7. Books and Scientific Journals		250		250
	8. Computer Costs		3,000		3,000
	Total Direct Costs:		72,906	4,200	77,106
B.	Indirect Costs (70% of Total Salaries and Wages)		28,459	2,940	31,399
		TOTAL:	$101,365	$7,140	$108,505
		%	93.4	6.6	100.0

1081521

UNIVERSITY OF CALIFORNIA

LAWRENCE RADIATION LABORATORY
BERKELEY, CALIFORNIA 94720

August 22, 1969

Dr. C. S. Shoup, Chief
Research Contracts Branch
Laboratory and University Division
United States Atomic Energy Commission
Oak Ridge Operations
Post Office Box E
Oak Ridge, Tennessee 37830

Dear Dr. Shoup:

It is a pleasure for me to send you six copies of our completed proposal. We are very happy with the work over the years and I look forward to carrying out some interesting new ideas that are contained in this proposal.

With best regards,

Dr. Chaim Richman
Principal Investigator
Pion Radiobiology Project

Enclosures:
As stated

CR:br

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SOUTHWEST CENTER FOR ADVANCED STUDIES
POST OFFICE BOX 30365
DALLAS, TEXAS 75230
214 ADAMS 1471

27 August 1969

Dr. C. Shoup
Chief, Research Contracts Branch
Laboratory and University Division
U. S. Atomic Energy Commission
Oak Ridge Operations
P. O. Box E
Oak Ridge, Tennessee 37830

RE: Renewal Proposal - Contract AT-(40-1)-3343
Our Account 1480; SCAS proposal #5469

Dear Dr. Shoup:

We are pleased to forward on behalf of Professor C. Richman six copies of a proposal entitled "Pretherapeautic Studies with Negative Pions". The work proposed is an appropriate extension of the research now being conducted under the referenced contract. Continuing support for these significant tasks is sought for the period 1 November 1969 - 31 October 1970.

By separate correspondence, the Commission has been notified of our change of entity on 1 September 1969. On that date, we officially become the University of Texas at Dallas. This change will in no way affect our carrying out our contractual obligations in connection with our research.

Sincerely,

D. W. Canham, Jr.
Director of Research Support

DWC/skg

cc: Dr. Robert Wood/AEC

1081523

BUDGET

November 1, 1969 - October 31, 1970

A. Direct Costs			
1. Salaries and Wages			
a. Principal Investigators			
C. Richman	(40%	11 mos.)	$11,790
M. R. Raju	(45%	6 mos.)	
	(70%	5 mos.)	8,870
b. Associate Investigator			
J. Feola	(85%	9 mos.)	
	(100%	2 mos.)	11,700
c. Graduate Student	(65%	12 mos.)	2,980
Total Salaries and Wages			$35,340
2. Staff Benefits			1,020
3. Expendable Supplies			5,000
4. Purchased Services			1,400
5. Project Equipment			
a. X-ray unit and Dosimetry Equipment			6,000
6. Consultants Fees and Travel			3,500
7. Employee Travel			3,000
Total Direct Costs			$55,260
B. Indirect Costs (70% of Salaries and Wages)			$24,740
Total Cost			$80,000

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AUTHENTICATION

Submitted by: _____

C. Richman
Principal Investigator

Approved by: _____

S. C. Fallis
Director, Fiscal Affairs

Southwest Center for Advanced Studies*
Dallas, Texas

*To become the University of Texas at Dallas effective 1 September 1969

1081525

PROPOSAL

TO

THE ATOMIC ENERGY COMMISSION

FROM

THE SOUTHWEST CENTER FOR ADVANCED STUDIES

Pretherapeutic Studies With Negative Pions

Chaim Richman
Principal Investigator

August 15, 1969

* * * * *

SCIENTIFIC BACKGROUND

Over the past seven years or so, work with negative pions both experimental and theoretical has shown that they constitute a type of radiation that has very good promise for the therapy of neoplastic disease. In the first instance it was verified experimentally that the physical dose distribution is as good as was expected from the fundamental data on pions. The beams penetrate without excessive attenuation to depths of as much as 20 cm. and at that depth there is good energy deposition in a region of the order of 5 cm. or so. This radiation can reach therefore any region of the body and deposit energy in a

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AUG 25 1969

specified region. On the exit side of the beam, only the background in the beam consisting of electrons and muons is present. Both of these backgrounds very probably can be reduced to negligible proportions in a therapeutic beam. On the entrance side, the beam is of low LET and gives a dose of much lesser effect than in the peak.

The radiobiological work with ascites tumor cells, Vicia faba and other systems has confirmed the fact that the peak region is highly effective with an RBE between 2 and 5. Furthermore the OER is also reduced in this peak region to values of around 1.5 compared to about 2.7 for Co-60.

The combination of high LET in the tumor region and low LET in the entrance region plus practically no exit dose indicates the pions have a strong peak in the tumor region for both oxygenated and anoxic cells. This peak will differ in height depending on the histology and the type of cells being irradiated.

It has also become clear that working with a charged particle beam has a number of advantages and unusual possibilities since electromagnetic methods can be used to bend, shape and focus the beam and also to remove background. In addition, in the production of negative pion beams, the positive particle background never passes through the negative magnetic channels. Thus a very good control system of the beam can be built, a fact which will play a much greater role in the future work.

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The deeper radiobiological picture has only been begun: a few very important facts can be discerned at this time which will be well worth exploring. In the peak region repair processes in the irradiated cells are much less than in the entrance region. This has already been observed. In addition when the treatment is given in fractions the differential of repair of surrounding normal tissue over the tumor tissue will be further enhanced. Without any doubt, it can be stated that skin reactions will be minimum for a given tumor effect compared to any other radiation. It will follow, therefore, that the post-treatment comfort of the patient will be much better for a given cure rate or putting it another way pions may improve the cure rate considerably for a given post-treatment response.

There lies before us therefore a most promising field which contains many questions. The problems that need to be solved can begin with the beam optics of the therapeutic beam at LAMPF. The full dosimetry that is necessary for therapy still lies before us and finally the radiobiology of this new radiation will need to be uncovered.

The use of negative pions for radiobiology and therapy makes many unusual demands in the sophistication and complexity of the entire system; however, by the same token it makes possible an entirely new approach to these problems.

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SCIENTIFIC SCOPE OF THE PROPOSED RESEARCH

I. Improvements in the Pion Beam at the 184" Cyclotron

In pion radiobiology the intensity of the beam has played a determining role. This has been apparent for a long time. First of all in the experiments on the survival of ascites tumor cells for different doses only points in the early part of the survival curve could be obtained. The total doses given were in the neighborhood of 300-400 rads.

A second result of the low dose rate is the necessity of making long exposures with the attendant complication of the presence or absence of repair processes in comparing the pion peak with Co-60 effects of the same duration.

A third problem of long exposures exists in the comparison of oxygenated and anoxic states of cells to pions. Here long exposures in the anoxic state can lead to damage to the cells outside of the effects of the radiation.

It has been assumed for a long time that the pion beam at the 184" cyclotron was as good as it could be. Over the last few years two experiments have been done -- one at CERN and one in Berkeley on the production of pions from different targets and at different angles which shed some new light on this question. The experiment at Berkeley was done by Arch Thiessen and his group from Los Alamos. This data makes it possible to redesign the pion beam. Victor Perez-Mendez at Berkeley believes that redoing the beam may lead

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to an increase of as much as a factor of 2 to 4 in the beam flux. It is proposed to study this problem in detail. In addition to the data on yields, it seems that the small meson quadrupole which is next to the cyclotron tank should be replaced by a more suitable one. This magnet has an aperture of 8"; here a 12" aperture would be better. In redesigning this magnet it would help to change the shielding on that side of the cyclotron to accommodate a larger unit as well as to change the meson wheel to a larger aperture.

Any new equipment needed for the improvement of the beam will be provided by the physics group at the cyclotron.

Three computing programs exist at this time for calculating the beam optics of taking the pions out of the fringing field of the cyclotron and through the transport system into the pion cave. These programs will be used with the new information to improve the beam.

A significant increase in the pion beam intensity would make it possible to get good values for the RBE which are not dose rate dependent. A factor of 2 to 4 in intensity would enable us to get a more detailed picture of the RBE for wide beams. This kind of information is important now as we start to design the beam for therapy at Los Alamos. Indeed, while the general picture looks encouraging, it is necessary now to come to the actual details of the therapeutic installation at Los Alamos.

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II. Physical Measurements

We propose to continue the necessary work on dosimetry for carrying out the radiobiological experiments.

Special plastic was obtained from Dr. Francis Shonka which takes into account the interactions of stopping negative pions. Dr. Shonka has kindly sent us a set of small size (0.17cc.) ion chambers made out of this plastic and another set of ion chambers made out of ICRP muscle equivalent plastic. The aim is to find out how important it is to use special plastics as ion chamber material to measure pion doses. Preliminary measurements indicate no significant changes in the depth dose distribution of negative pions as measured by the ion chambers made out of ICRP muscle equivalent plastic and the special plastic. This point needs further study.

A Los Alamos group headed by Dr. Robert Burman is planning to set up a pion beam at the 184" cyclotron at Berkeley starting around November 1, 1969. This beam will utilize the external proton beam in the proton cave instead of the internal beam that we now use for the pion beam in the meson cave. This new beam setup will therefore be quite similar in its optics to the beams at Los Alamos and TRIUMF in Vancouver. There is a good possibility, therefore, for working here with therapeutic-like beams in terms of the momentum distribution and the control of the penetration. We plan to measure the depth dose in different LET intervals of these beams such as 0-10 Kev/μ, 10-100 Kev/μ and $>$100 Kev/μ using conventional proportional counters.

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III. Experiments with Cultured T-1 Cells

The established T-1 cell line has been derived from normal human kidney cells. Experiments by Barendsen in Rijswijk, and by Todd in Berkeley, have established the dependence of the RBE and OER of different types of heavy charged particles with respect to impairment of the proliferation capacity of these cells, assayed by the clone technique. Furthermore, Barendsen has obtained extensive data with various beams of fast neutrons of different energies with these cells. The investigation of effects of π^--mesons with this cell system will provide, therefore, a comparison with most of the existing types of directly and indirectly ionizing radiations of interest.

In the present facility, irradiations must be carried out which last 10 or more hours in order to decrease the fraction of surviving cells to about 30 percent; consequently the cells may proceed through a considerable portion of their life cycle during irradiations, if they are exposed in normal conditions, i. e. at 37° C. In abnormal conditions, e. g. at room temperature or in the absence of oxygen, necessitated by part of the experiments, they may be stopped in a particular, as yet unknown, portion of their cycle. If the exposure time is kept to less than 10 hours, the effects may not be too disturbing, however.

Dr. Barendsen initiated these experiments last summer here and he was successful in measuring the RBE. The measured RBE for stopping pions was

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found to be 2. However difficulties developed in measuring the OER. Since the exposures lasted for hours, we had to keep the cells in an anoxic medium throughout this time. The OER value obtained for CS^{137} gamma rays at acute dose rate under nearly the same experimental conditions gave a value of 1.6. This suggests that the cells were not completely anoxic during exposure, since the correct value here is 2.7.

We are continuing these experiments with a view to measuring the OER for stopping pions. A modified exposure setup is being made with a glass deoxygenation unit instead of the glass and rubber unit that was used previously. The unit will be checked first with conventional radiations and later on the OER will be measured for stopping pions.

IV. Experiments with Yeast - Reverse Mutations (Arginine) in *Saccharomyces cerevisiae* Z-34

Roman and Jacob[1] have described an extremely radiosensitive effect for diploid yeast that is heteroallelic for mutations at a biochemical locus. Relatively small doses of ultraviolet radiation result in a large increase in reversion to the wild type of these cells. This is presumably due to intra-allelic recombination. This effect also is inducible with X-rays and is perhaps the most radiosensitive effect known in yeast.[2]

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1. H. Roman, F. Jacob, Comptes Rendus, Vol. 245, 1032-1036 (1957).

2. R. K. Mortimer, Radiation Research Supplement I, 394-402 (1959).

1081533

Mortimer suggested Z-34 strain for measuring OER for pions because of its sensitivity. No data on OER is available with this strain.

Experimental procedure:

1. Subculture the Z-34 yeast cells in about six flasks for two days at 30° C.
2. Select the flask that has a minimum frequency of spontaneous Arginine reverse mutants. A typical minimum frequency is about 2×10^{-5}. (This is done by plating the cells from each flask on -Arginine plates and incubating the plates for about 3-5 days at 30° C. The number of colonies formed on the -Arginine plates give the number of spontaneous mutations per total number of cells plated.
3. During exposure to ionizing radiation the cells from the flask that has minimum reverse mutation frequency are placed on non-nutrient phosphate buffered agar discs. Special holders were made so that the temperature of the cells could be kept about 5° C. during exposure; the exposures can be carried out either in the presence of air or nitrogen. The cells need not be kept at a lower temperature during acute exposures.
4. The cells are plated on -Arginine plates and YEPD plates and reverse mutations frequency is determined after incubating the plates for about 3-5 days.

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Preliminary measurements indicate that doses as low as 50 rads can be detected. The OER for Co-60 gamma rays is found to be about 2.5 and is independent of dose rate. This result is very important because the OER value measured for pions at the presently available dose rate (25 rad/hour) will be applicable to acute dose rates as well.

We propose to measure OER for pions as well as for Co-60 gamma rays, acute as well as chronic levels similar to the dose rate available for pions.

No information on variation of OER as a function of LET is available for this strain. We propose to measure the OER as a function of LET using heavy ions (He, Li, C, Ne) from the HILAC.

V. Lymphocytes for Radiation Response Studies with π^--Mesons

Progress Made: Because of the high sensitivity of lymphocytes to radiation, the short term *in vitro* culture system was taken up for use with π^--mesons. Starting with freshly drawn blood, methods were standardized to separate lymphocytes and maintain them in culture. Preliminary results were obtained with X-ray exposures (survival after six day incubation following exposure) and the system is ready for use with π^--mesons.

Experiments Planned for this Year: Survival curves will be obtained for π^--beams (oxygenated as well as anoxic conditions) for doses ranging

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from 20 rads to 200 rads. Part of the samples will be used, after treatment with phytohemagglutinin, to collect mitotic figures for chromosome aberration studies. Phytohemagglutinin initiates a certain fraction of the original population of cells to transform to blastoid forms and divide. Inhibition of this transformation will also be studied for the order of doses mentioned above.

Experiments Planned for the Next Year: Depending on the preliminary results and the sensitive parameters obtained as indicated above, these studies will be extended to enable better quantitative analysis.

It is intended that the experiments with yeast and with lymphocytes will be of limited scope and will not be continued unless the beam intensity is increased.

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VI. Work on a Biomedical Beam in Area "A" at LAMPF

The future of biomedical work with pions will have to be at LAMPF. Here there will be the pion intensities that will make all the experiments possible as well as therapy itself possible. The first and probably for a long time the most useful area for this work will be the physics area "A" which is now being planned and prepared. This area will have the pion beams and muon beams for the various experiments in physics. The physics groups as well as the group in radiochemistry are now actively preparing their experiments for that area. Their equipment and facilities are being designed and built so that when LAMPF goes into operation they are ready to begin their work. Such an active program should also be pursued by Biology and Medicine.

The importance of area "A" is that without a large investment, work can get under way with the added advantage that much of the physics equipment for beam control can be used. In this way biomedical workers can concentrate their efforts and their funds on the particular problems of their discipline.

The program here is to work along with the beam designers to make the low energy pion beam (50-150 Mev.) the kind of beam that is needed for biomedical work. These needs are sometimes different from those in physics. Biomedical beams must be large (at least 10 cm. x 10 cm.). Shaping must be provided as well depth control of the beam by simultaneously changing all the currents in

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the magnets. Much thought and calculation and finally construction and testing needs to be put in on how far one should go in eliminating the electron and muon backgrounds. It is an important fact that the electron background can be removed entirely by means of an electron separator and it appears further that much of the muon background (which isn't too large in the first place) can be removed by the beam transport system. The drawback in having a long separator is the cost plus some loss in intensity.

There is a question of whether the biomedical beam should be horizontal or vertical or whether to have two beams. It appears that for therapy as well as for many experiments in radiobiology the vertical beam is preferable. At the same time physical research is usually carried out with horizontal beams.

In the fashioning of the beam where we work along with the Los Alamos groups, the final work of building the facilities will rest with Los Alamos. (Dr. Louis Rosen has stated that these facilities will be provided by LAMPF).

To take the next step it is necessary at this time to start planning, building and testing some of the dosimetric units that Los Alamos will not provide and that will be needed by practically all the biomedical workers. These systems are the dose measurement units for pions, the profile of the beam unit, the time-of-flight system and an LET distribution system for studying the biomedical beams with peaks of different widths. This is a very large program. It is also the minimal program that needs doing and we must make every effort to see that it gets done.

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VII. A Method of Observing the Stopping Pion Region (With a Patient in Therapy)

A suggestion has been put forth by a number of people including Dr. Victor Perez-Mendez and Dr. Louis Rosen which seems to have a lot of merit. The idea is simple and offers a way of observing where the pions are stopping and therefore the region where therapy is being done.

The technique is as follows:

When the π^--meson stops, it is captured in the outer pion orbits of the atom. It cascades from one level down to another until it reaches the lowest orbit from which it is captured into the nucleus causing the nucleus to explode and yielding the high LET fragments. Now in the cascade process X-rays are emitted in the region of 50-160 kev. These X-rays have been studied extensively for many years now and their characteristics are well known. It is possible to observe these X-rays by the usual scanning techniques, thus observing the stopping of the pions. Perez-Mendez has suggested using a spark chamber to look at the X-rays but more conventional techniques are available.

Besides being an interesting technique, it offers a way of making sure in a patient that therapy is being done in the proper area as determined perhaps by a separate X-ray radiogram where the organs can be seen.

We hope to work with Dr. Victor Perez-Mendez's group to study this technique with the pion beam at Berkeley.

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PROGRESS REPORT

The work on the OER with Vicia faba has reached a satisfactory state of completion, and the first report appended describes the experiement and the results obtained. The OER is shown to be definitely reduced to a value of around 1.5 in the pion peak of dosage. This is to be compared to the value of 2.7 for Co-60.

The study of the aberrations is continuing. This work is quite long and tedious. A comparison of the different kinds of aberrations found is shown in Figure 1:

a) Normal cell in metaphase

b) Isochromatid aberrations in two S-chromosomes

c) Cell with multiple aberrations produced by π^--mesons

d) Cell with many fragments produced by π^--mesons

The second paper enclosed in this report is of a continuing study of the response of ascites tumors to π^--mesons. In this case well-oxygenated two-day-old tumors were used. These results are interesting first for the RBE value obtained and second, for the light shed on the recovery processes that can be expected with this radiation.

The third report summarizes the groundwork being laid for work with lymphocytes with π^--mesons. This short summary describes the system and the endpoints that are being studied before the runs are made with π^--beam.

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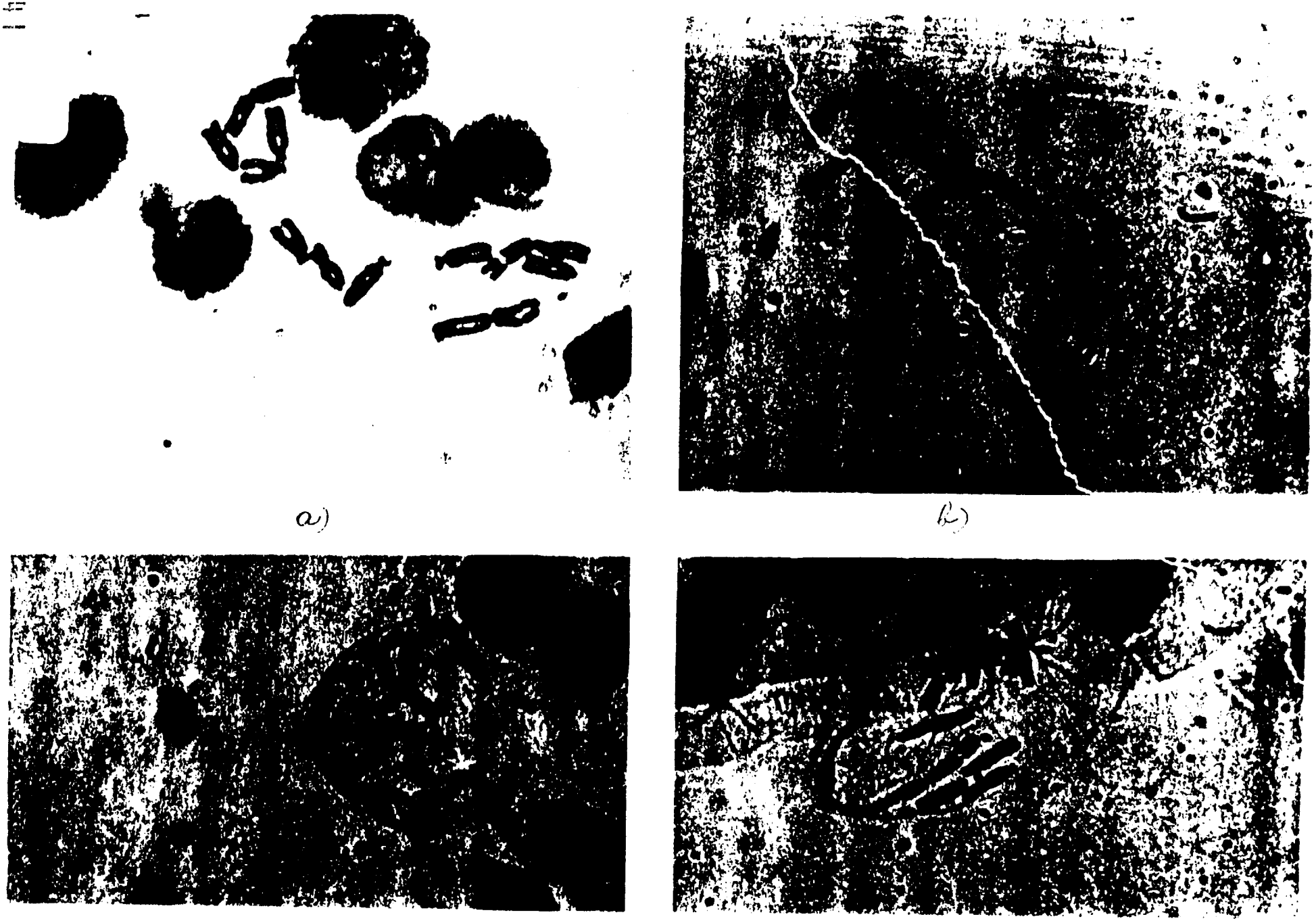

Fig. 1

Proposal No. 2663-4
Renewal of Contract
AT-(40-1)-3343

PROPOSAL

TO

THE ATOMIC ENERGY COMMISSION

FROM

THE SOUTHWEST CENTER FOR ADVANCED STUDIES

The Dosimetry and Radiobiology of Negative Pions

Chaim Richman
Principal Investigator

June 25, 1968

* * * * *

I.

INTRODUCTION

Negative pions were discovered in cosmic rays in 1947 and were recognized in those days by the large star that they produce in nuclear emulsions at the end of their range. After they were produced in the laboratory and their properties were fully appreciated, it occurred to a number of people that this particle might have therapeutic applications in cancer therapy. We discussed this possibility with C. A. Tobias in Berkeley, and Hill at Illinois wrote a memorandum on this possibility. Fowler and Perkins were the first to make calculations of dose distributions in tissue. The problem, of course, has been that no therapeutic beams existed. Even so, we at Berkeley, a group at Brookhaven and a group at CERN undertook the dosimetric studies of these particles. So far only

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our group has carried out radiobiology with such beams.

It is fair to say, at this time, that although we were all attracted to the possibilities of pions because of the favorable dose distribution, it is the radiobiology which is proving to be of first importance. The advantages for therapy that lie in this area far outweigh the simple but useful peak of dose in the tumor region. The study of this particle has taken on new significance with the fact that a pion factory is being built and a therapeutic beam will be available. The goal of these experiments has become, therefore, no less than the complete evaluation of this radiation, both as to the nature of the dose and the radiobiological effects to the extent that the presently available beam intensities permit.

II.

SCIENTIFIC BACKGROUND

The dosimetric studies at Berkeley and at CERN have shown as expected that negative pion beams are very penetrating and, in addition, produce a favorable dose distribution in tissue. In a region (tumor) as large as 3 to 5 cm. in diameter, embedded in tissue as much as 25 cm., the dose is 2.5 to 1.5 times what it is throughout the tissue in front of the tumor.

Studies of the size of the pulses in a Lithium-drifted silicon detector, calibrated with various sources, have also shown that in the peak region high LET fragments constitute an appreciable fraction of the dose. Thus in the peak the dose is not only greater but of an advantageous quality for the irradiation of tumors.

There are distinct advantages to having a region of high LET that can be superimposed on the tumor region and that region only. The studies of the

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effects of the peak on the survival of ascites tumor cells irradiated in vivo give an RBE of around 4. The effectiveness of the dose in the peak region is then 6 to 10 times what it is in the healthy tissue. This point was emphasized by Fowler and Perkins in their first paper although at the time they had no numbers to work with.

The second effect of the high LET component in the peak is to reduce the OER. It is well known that the OER, for a great many systems, is around 2.5 for X-rays and Co-60 γ-rays. For the anoxic cells in tumors this means that it takes about 2.5 times as much dose to sterilize them as it would the oxygenated cells. This means that these cells constitute a highly radioresistant component in therapy. Recently, therapy with neutrons has been inaugurated based on this fact and the fact that neutron recoils have a higher LET than γ-rays. The OER for neutrons is about 1.6 over a wide range of neutron energies. The peak of dose should clearly have a low OER comparable to that of neutrons.

The following properties make pions a very real candidate for therapeutic work:

a. Good dose distribution

b. Little exit dose

c. High RBE in the tumor region

d. RBE of ~ 1 in the overlying healthy tissue

e. Low OER in the tumor

f. High OER in the overlying tissue

g. Good control of the beam since the particles are charged particles

h. Repair is expected in the overlying tissue and very little in the tumor for fractionated regimes

i. Skin reactions will be less than for any radiation for a given tumor effect.

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III.

SCIENTIFIC SCOPE OF THE PROPOSED WORK

LET SPECTRUM OF π^--MESONS

The physical character of the radiation is now well known. The depth dose under various conditions has now been measured, and we are able to handle the beam quite well.

There is one very important piece of information, however, lacking and that is the LET distribution of the fragments in the peak. It has been shown by Barendsen and his co-workers that with neutrons it is the high LET fragments from nuclear recoils that are so effective in lowering the OER at higher neutron energies. Thus it has been found that the OER for neutrons is fairly independent of neutron energy from about 2 to 15 Mev. To compare pions with neutrons, as well as to understand the radiobiological effects of pions, a good measurement of this distribution will be made.

The technique that is used most often at present that of a TE proportional counter with TE walls, will be used to begin with. However, a study must be made to see how this chamber reacts to several prongs of a pion star. To make good measurements, the chamber must not see two fragments of a star as one track of a higher LET. It has been suggested that the wall-less chambers utilizing TE gas might be more suitable. The experiments will utilize both kinds of chambers, and should, therefore, give a good picture of the LET distribution.

Such measurements have been made for neutrons; this work will give, therefore, in addition, a direct comparison of the two radiations on this important point.

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RADIOBIOLOGICAL EXPERIMENTS

The aim of these studies is to measure values of the relative biological effectiveness (RBE) and the oxygen enhancement ratio (OER) of π^--mesons in the plateau and peak region with a view to assess their potential value for radiotherapy. This aim implies that interest is centered around a particular radiobiological end-point; namely, impairment of the capacity for unlimited proliferation of mammalian cells since it is this capacity that we want to destroy in all tumor cells without producing too severe damage to normal tissues. Other biological end-points (e.g. growth delay and chromosome aberrations) are of interest in order to obtain a better insight into radiological mechanisms which in turn can support conclusions to be drawn from experiments involving cell killing.

In view of the low dose rate of about 10 rads/hour* attainable with π^--mesons, and the necessity to restrict the length of the irradiation, effects of rather low total doses have to be measured. Although it is in principle simplest to measure accurately RBE and OER values at doses which are sufficiently large to produce surviving fractions of cells of between 0.1 and 0.0001, measurements at low doses which produce surviving fractions of cells of between 0.50 and 0.10 can yield significant results if the experimental conditions are well-controlled.

In addition, since radiotherapy in patients is usually given as a series of low doses spaced by 24 hours or more, sufficient to allow complete recovery of sublethal damage, experiments with rather low doses may provide the most relevant information required.

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*In our most recent experiments, the dose rate has been 30 rads/hour.

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It can be stated with a good deal of confidence that with the experience gained from the previous biological work and with the use of some new approaches with cells and with Vicia Faba, three new experiments will be carried out which promise to shed much light on the OER of negative pions. These experiments are as follows.

EXPERIMENTS WITH ASCITES TUMOR CELLS

Mr. J.M. Feola et al[1] using L#2 cells (lymphoma) transplantable in mice, and assayed by the serial dilution technique has obtained a D_{37} of about 65 rads for π^--mesons in the peak region. Thus a dose of 50 rads should correspond to a surviving fraction of 0.5 and a dose of 150 rads should correspond to a surviving fraction of 0.1. It seems that the dose rate can be increased to 20-30 rads/hour which will enable us to obtain a surviving fraction of about 0.1 with an irradiation of 8 hours.

This earlier work attempted to find a difference of the peak dose on ascites tumor cells of different ages, three- and five-day-old tumors. No difference in surviving fractions was observed. Two reasons probably account for this fact: 1) The errors were large and the experimental points were few. 2) The oxygen pressure inside of the tumor fluid was not known.

Since then we have studied the pO_2 in the tumor fluid with a microelectrode and it has become fairly clear that in a two-day-old tumor, the pO_2 is $\sim$40 mm, which is normal and well oxygenated while by the fifth day the tumor is almost anoxic. This is for an inoculum of 10^6 cells. The equipment used was a Beckman

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1. J.M. Feola, C. Richman, M.R. Raju, S.B. Curtis, and J.H. Lawrence, Radiation Research, 34, 70 (1968).

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microelectrode and a Beckman readout system. Two and six-day-old tumors will therefore be irradiated in vivo. The animals will be sacrificed, the number of cells will be counted and serially diluted. The irradiated cells will then be injected into 4 groups of 10 animals each.

Points will be obtained at 100, 200, 300 and 500 rads. This experiment should give then a value of the OER in vivo.

EXPERIMENTS WITH CULTURED T-1 CELLS

The established T-1 cell line has been derived from a normal human kidney. Experiments by Barendsen in Rijswijk, and by Todd in Berkeley, have established the dependence of the RBE and OER of different types of heavy charged particles with respect to impairment of the proliferation capacity of these cells, assayed by the clone technique. Furthermore, Barendsen has obtained extensive data with various beams of fast neutrons of different energies. The investigation of effects of π^--mesons with this cell system will provide, therefore, a comparison with most of the existing types of directly and indirectly ionizing radiations of interest.

In the present facility, irradiations must be carried out which last 10 or more hours in order to decrease the fraction of surviving cells to about 30 percent; consequently the cells may proceed through a considerable portion of their life cycle during irradiations, if they are exposed in normal conditions, i.e. at 37° C. In abnormal conditions, e.g. at room temperature or in the absence of oxygen, necessitated by part of the experiments, they may be stopped in a particular, as yet unknown, portion of their cycle. If the exposure time is kept to less than 10 hours, the effects may not be too disturbing however. Furthermore, in long exposures, repair of sublethal damage produced by the low LET component of

the energy deposited, may occur. In order to assess the effect of π^--mesons in conditions where no changes occur during exposure, it is proposed to irradiate cells both at room temperature and frozen in liquid nitrogen at -196° C. These experiments will be complicated by the fact that in freezing mammalian cells, dimethyl sulfonide or glycerol must be added, which may influence radiosensitivity.

Thus the experiments will consist of two series:

1) Measurements of survival curves at rather low doses involving exposures of up to 8 hours, possibly to be extended later to 12 hours. The cells will be kept at room temperature, 22-26° C. Cells will be irradiated in equilibrium with air or nitrogen to estimate the oxygen enhancement ratio.

2) Measurements of survival curves of cells exposed at -196° C may provide a survival curve over an extended range of doses, since exposure time is not limited. Cells can be kept indefinitely at this temperature. Before an estimate of the OER can be made, experiments may be required concerning the influence of DMSO and freezing.

Comparison of the curve obtained at -196° C with the data obtained for the cells at room temperature for the low dose region will provide some insight in the properties of damage produced by π^--mesons.

All the experiments with π^--mesons must be compared with equivalent data measured for X-rays or γ-rays applied in identical conditions.

It should finally be mentioned that experiments carried out until now have been performed at the center of the beam, at the position where the maximum number of π^--mesons are stopped. Further data should be obtained with respect to the RBE and OER in other positions within the beam, especially before and beyond the maximum.

1081549

EXPERIMENTS ON OER USING VICIA FABA

Vicia faba is well known to be a very useful and meaningful system for the study of radiobiological effects. The OER found for acute irradiations is closely the same (2.7) as is observed for mammalian systems. Furthermore, Hall[2] has shown that the seedlings can be kept anoxic for a period of 24 hours at 3° C without any apparent damage to subsequent growth. He has shown, in addition, that at 3° the OER found for chronic irradiations (46 rads/hour) was the same as for acute irradiations (64 rads/min).

This system when irradiated at 3° C is, therefore, quite suitable for measurements of OER with negative pions. Work is now well underway on growing the roots and cooling the roots. Exposures have also been made already with Co-60.

In view of the fact that a higher dose rate is now available, a measurement of the OER at room temperatures can also be made. The problem in such measurements is always the length of time that the roots can be kept anoxic; it seems now that the roots can be kept hypoxic for 8 hours at room temperature without apparent permanent damage. The OER at room temperature is dose rate dependent which is an interesting fact in itself. All the necessary control experiments with conventional radiations will be carried out.

Detailed cytological studies will also be made of the root tips after irradiation in the plateau and the peak. Dr. Sheldon Wolf of the University of California Medical School in San Francisco is collaborating in this work.

---

2. E.J. Hall, Br. J. of Rad., 40, 128 (1967).

1081550

IV.

WORK ACCOMPLISHED

DOSIMETRY

The dosimetry has evolved over the last several years. It turned out that all of the electronics was faithful and in good order except for the final step of summing all of the pulses to give the total dose. The dosimetry used with pions is a single particle dosimetry; each particle is detected alone and the pulses are amplified and finally summed. The technique which has now been worked out, uses a small computer, the PDP-5, for the final summation. Figure 1 is a photograph of the complete particle analysis and dosimetry electronics with the computer in the center. To accomplish the faithful summation, the pulses from the amplifier are digitized by an analog-to-digital-converter (ADC), then stored in the computer. From here on, advantages accrue from the fact that the pulses are in a memory; any kind of calculation can now be made with the computer. The teletype prints out the pulse distribution as well as partial sums and the total energy deposited in the detector. In figure 1, the time-of-flight equipment is on the rack on the left, and the rack on the extreme right contains the number-of-particles-versus-range equipment and dosage equipment with the ADC at the bottom.

It is possible to identify the pions by the time that they take to go from the cyclotron tank, through all the magnets and out through the shield, a total distance of about 25 feet. The background of electrons takes a shorter time to traverse this distance. The difference in the times is of the order of a few nanoseconds. By introducing a variable delay called a trombone in the circuitry and putting these pulses in coincidence with dosimeter pulses, it was possible

1081551

to obtain curves for the pions alone as well as for the pions with the electron background. The electron background has never been large; it constitutes about 25 percent of the total beam. Still in all, it is good to be able to say that we know exactly what the background does in all of the physical measurements.

The top diagram in Figure 2 shows the electronics in block form. The various detectors and the various signals are shown. The bottom drawing shows the geometry of the scintillators and the silicon detector together with the variable absorber.

Figure 3 shows spectra from the time-of-flight system. A spectrum with electrons and without electrons is shown. The relative number of the two curves is not important here.

Figure 4 is the differential range curves for two energies of negative pions, for pure and contaminated beams. It is clear that the pions stop in a clearly defined region of about two inches of lucite. It is also clear that the penetration is excellent.

Figure 5 is a plot of the dose distribution of a 65 Mev π^--beam in water. It is clear that the peak is high and also broad. On the same graph is a plot of the number-of-particles-versus-distance-curve. These latter curves give one a feeling for the loss of particles as the beam traverses water. It also shows the momentum spread of the beam in terms of its range.

Figure 6 is a comparison of the dose distributions for 67 and 91 Mev negative pions for contaminated beams and pure beams. It must be added that even in a "pure" beam there is still about a 10% negative muon contamination.

Figure 7 is data which is very important because it shows clearly that the total dose distribution is not the whole story by any means. The character of the dose is equally important. What was measured here was the percentage dose

1081552

above a certain threshold in different regions of the π^--peak, and it is compared with π^+-mesons; π^+-mesons have a dose distribution similar to π^--mesons but with a smaller peak. They have no star effect. By changing the threshold energy of the pulses, we see the contributions due to the large pulses produced by the star fragments. It is clear then that in this high LET region, the π^--peak is much more effective. These high LET effects do not appear in total dose but make themselves known in the biological experiments.

Figure 8 is the isodose distribution for a 65 Mev π^--beam with contamination. There is a tail of low dosage that is seen here in two dimensions.

Figure 9 is an isodose plot of a 65 Mev π^--beam with the background removed. It can be seen that it is a very interesting distribution. The drop-off dose on the sides and in the back of the tumor region is very rapid. The peak of dosage, at the present time, is over a limited region. In the future, for therapy, it will be necessary by means of a more sophisticated magnetic system to spread the peak more. These isodose curves also show that the biological experiments have to be put in place carefully. The build-up of dose from entrance to the tumor region is truly unique and shows how different and effective pions may turn out to be in saving the healthy tissue in front of the tumor.

Figures 10 and 11 are the same type of distributions for π^+-mesons. Since there are no stars produced, these serve simply as an interesting comparison for the two kinds of beams.

The final curve, Figure 12, repeats the integral dose distribution of Figure 7 and adds the differential pulse distribution for a 65 Mev π^--beam. It can be seen that there is a low but significant distribution of pulses beyond 10 Mev and extending beyond 50 Mev. The final spike is the dose due to pulses giving an energy over 50 Mev in the silicon detector.

1081553

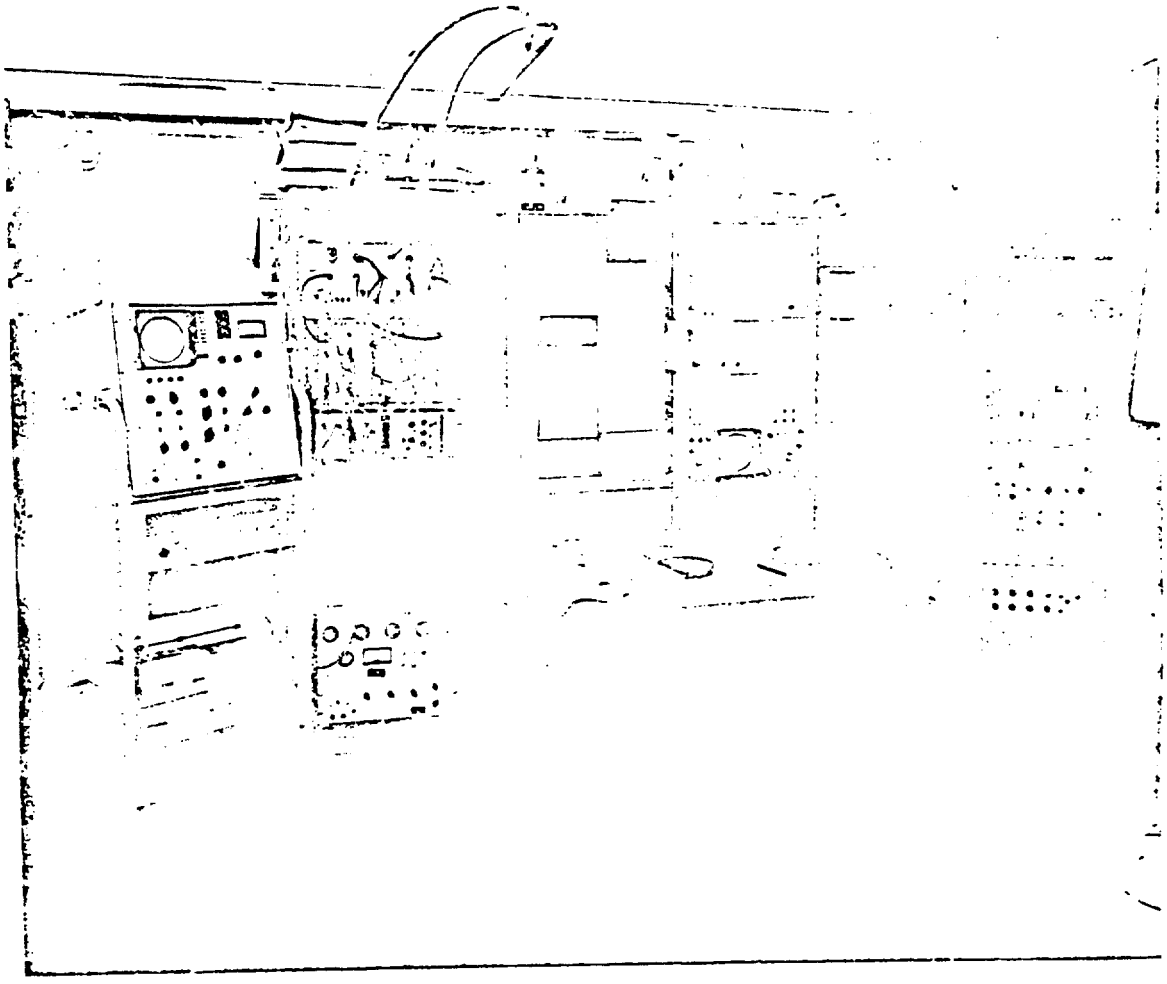
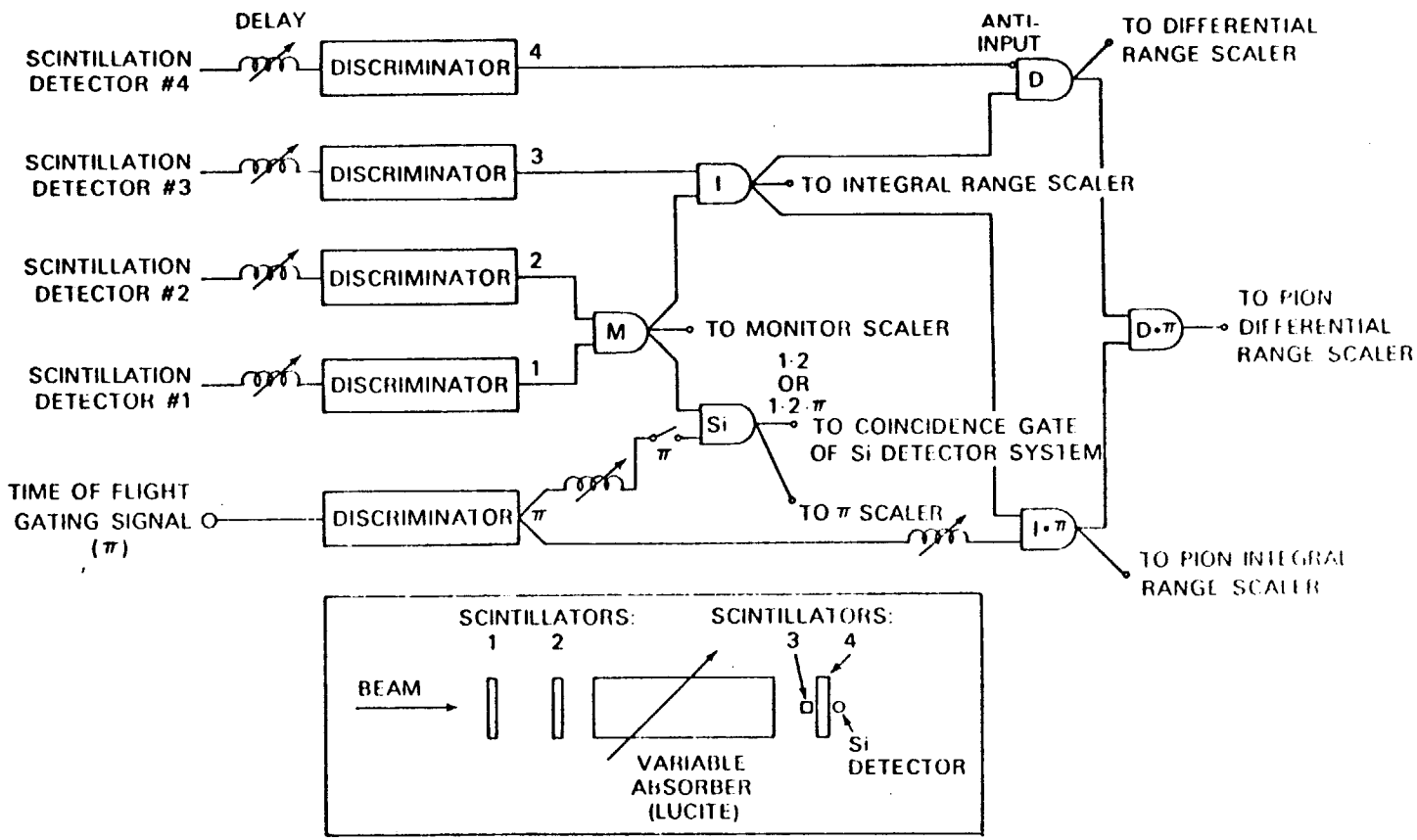


Figure 1.

Photograph of the electronics and the on-line computer used for the dosimetry of the π^--beam.

1081554



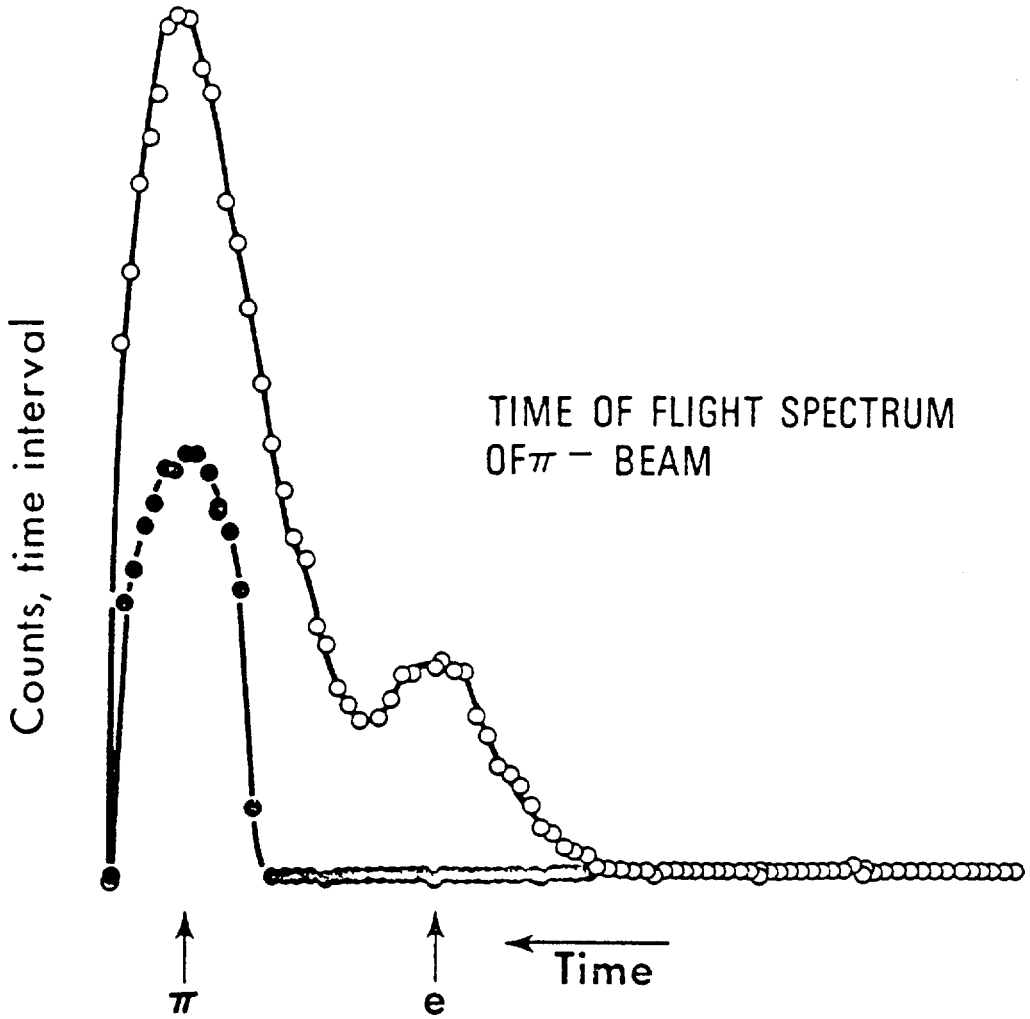
DBL 678-1729

Figure 2.

Top: Block diagram of the electronics used in the dosimetry.

Bottom: Geometry of the scintillation detectors, the silicon detector, and the absorbers.

1081555



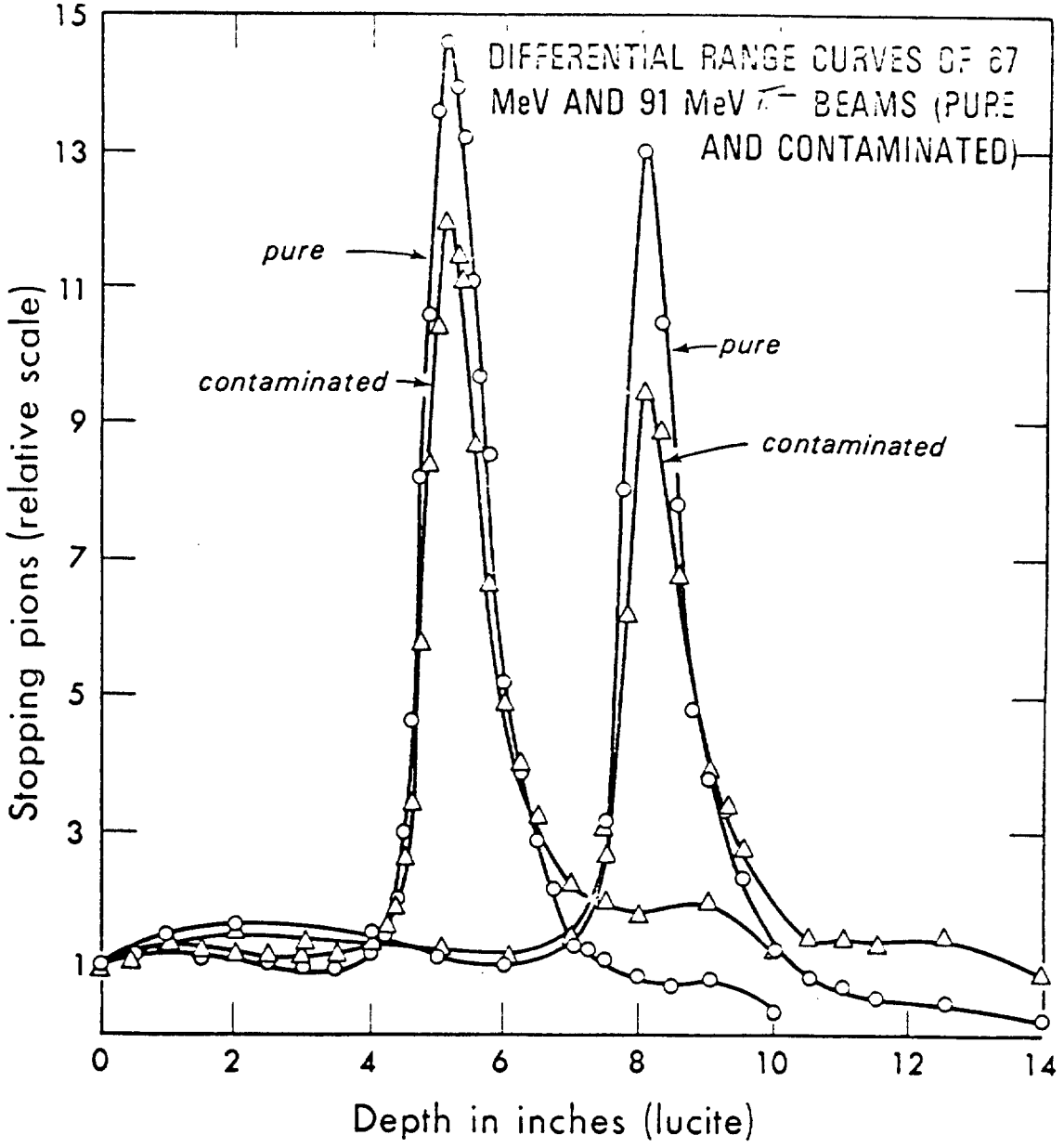
DBL 677-1696

Figure 3.

o Total beam of electrons, muons, and pions.

● Beam without electrons.

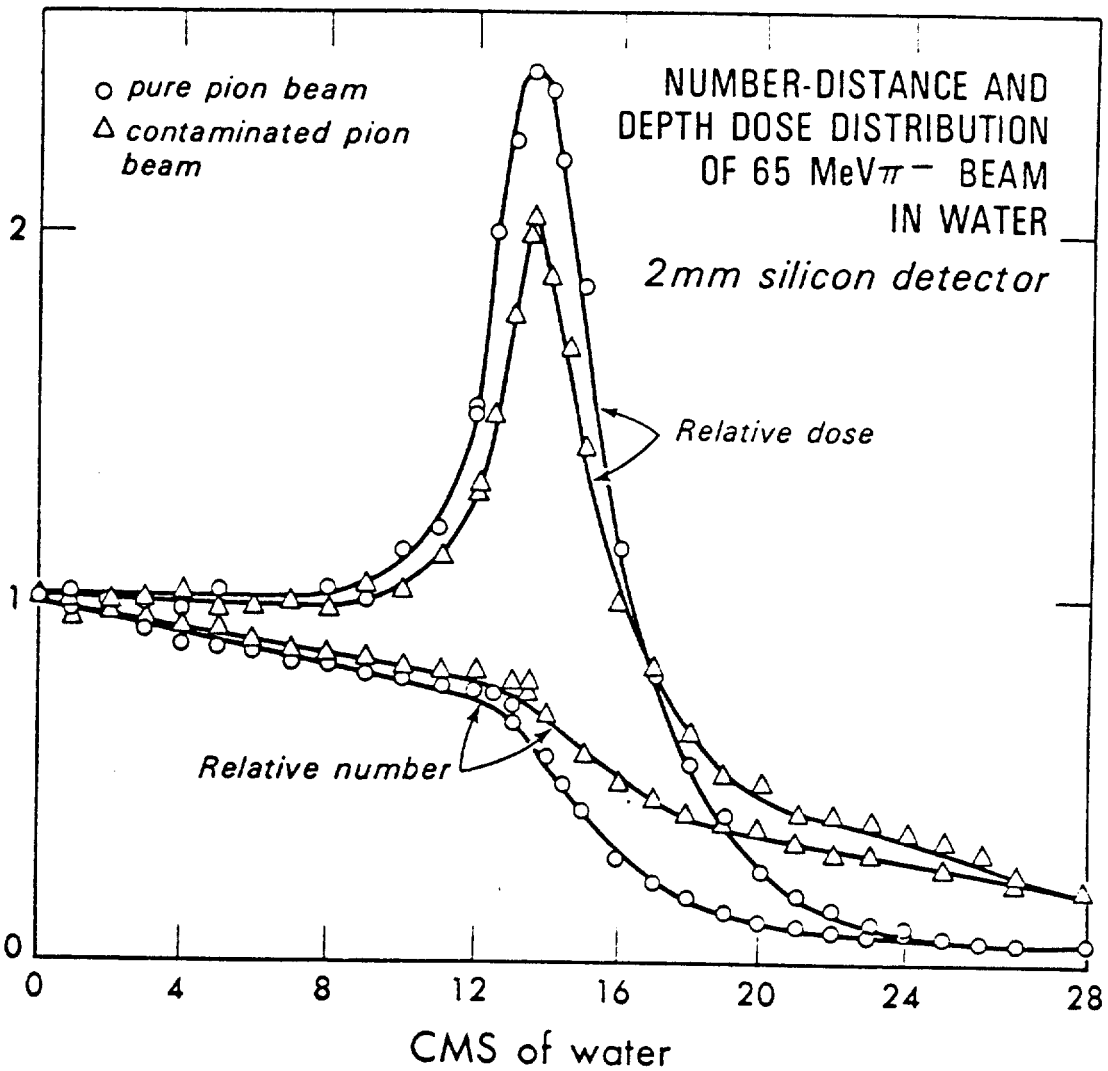
1081556



DBL 677-1706

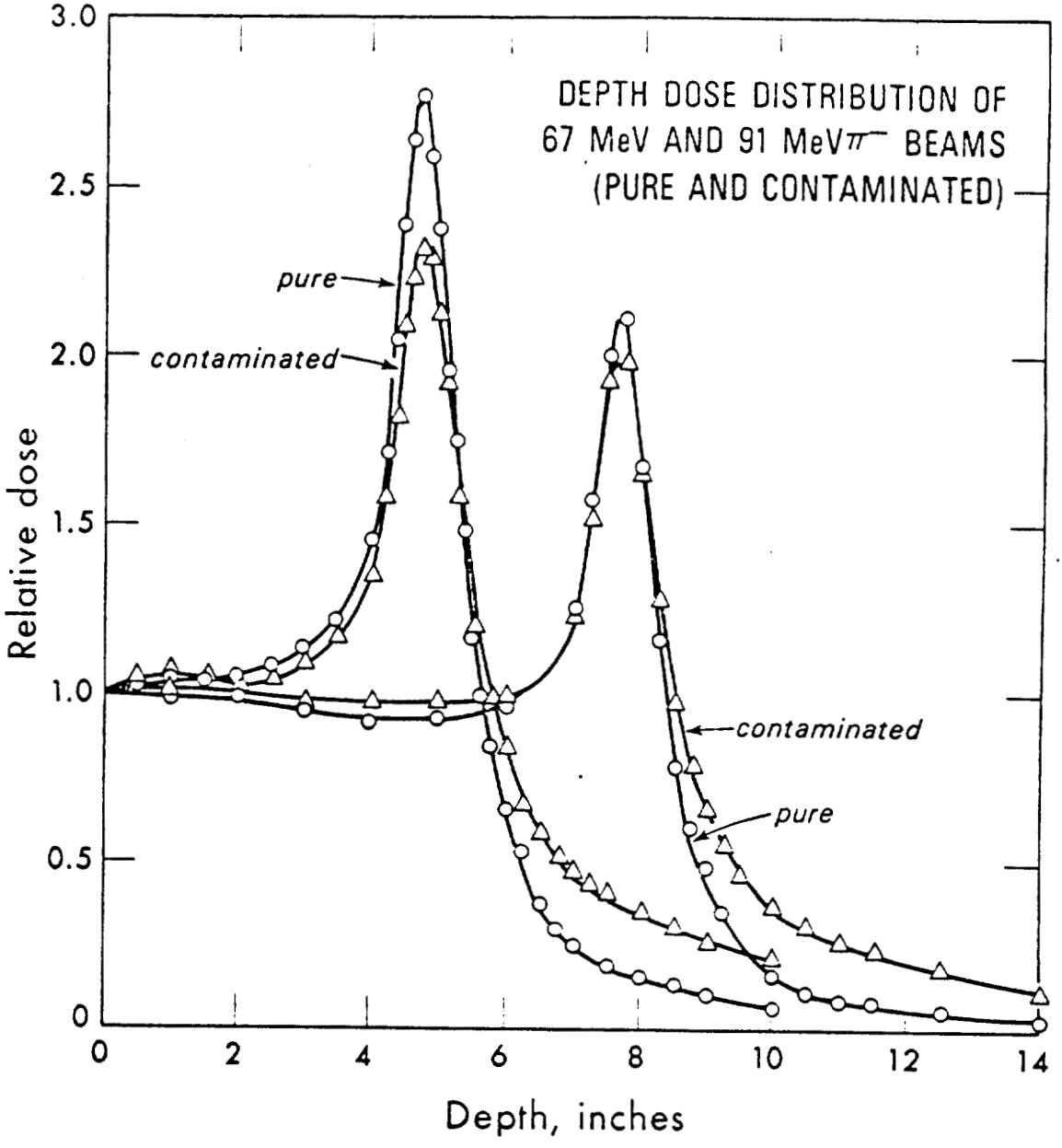
Figure 4.

1081557



DBL 677-1700

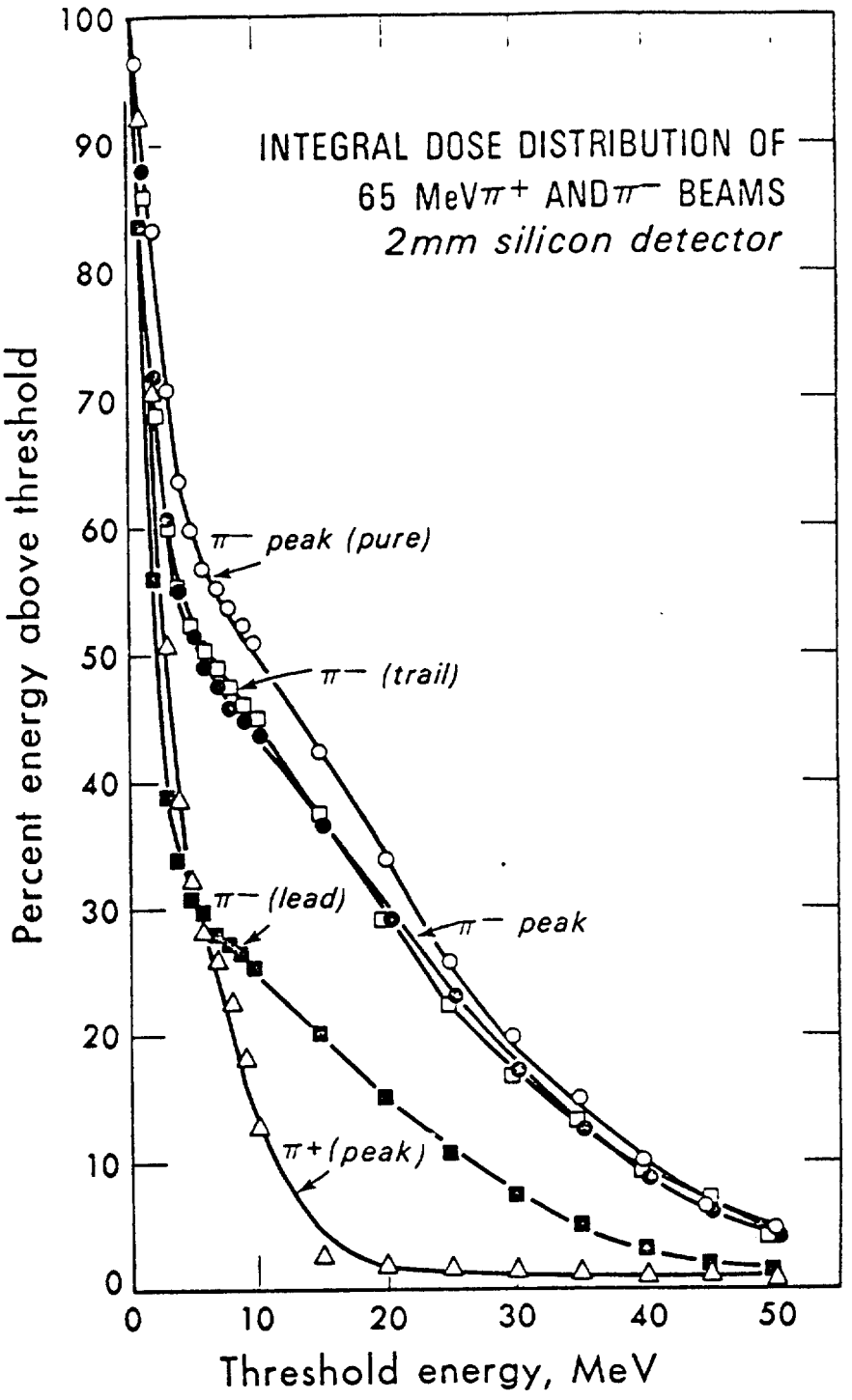
Figure 5.



DBL 677-1699

Figure 6.

1081559



DBL 677-1697

Figure 7.

1081560

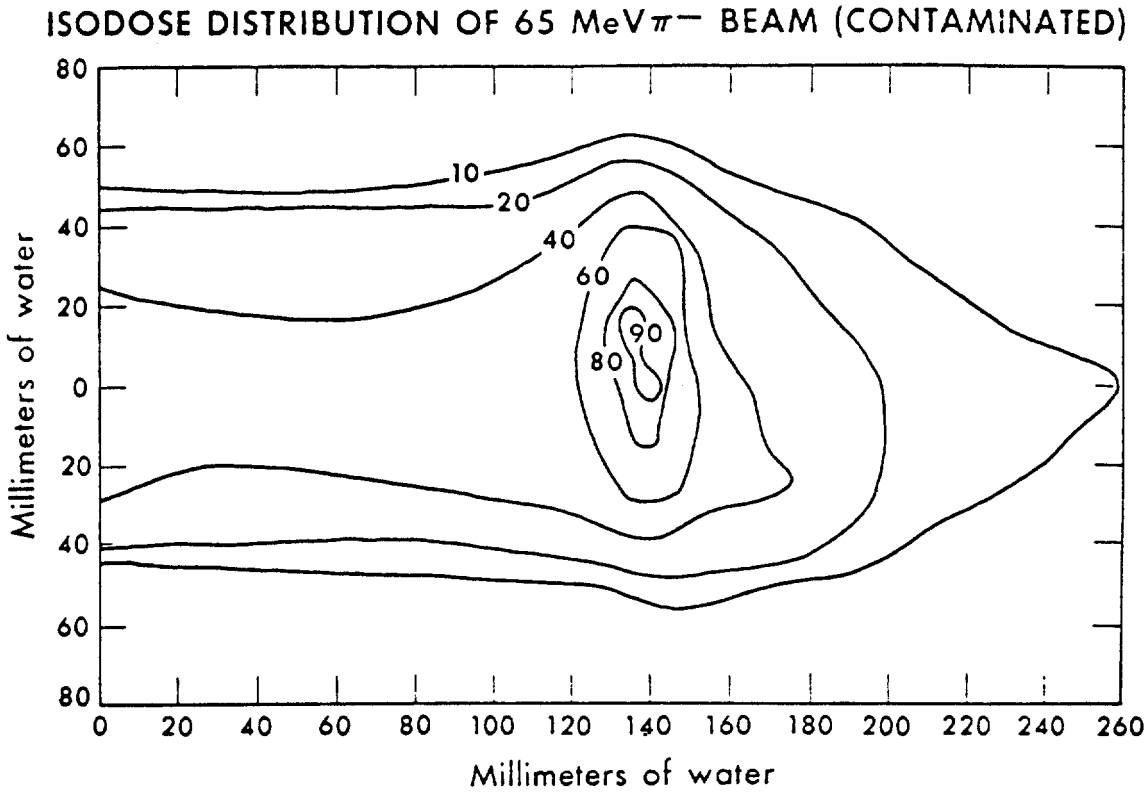
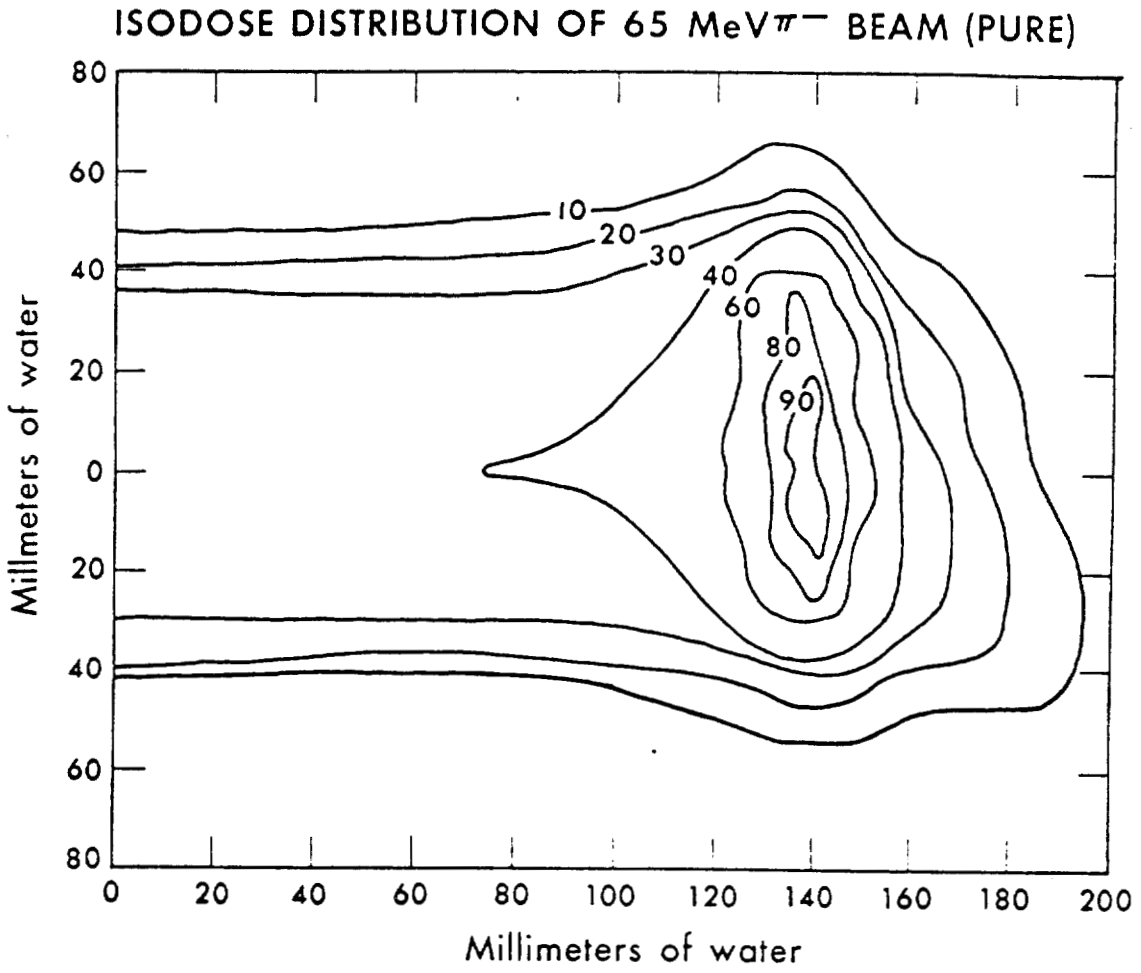


Figure 8.

1081561



DBL 677-1704

Figure 9.

1081562

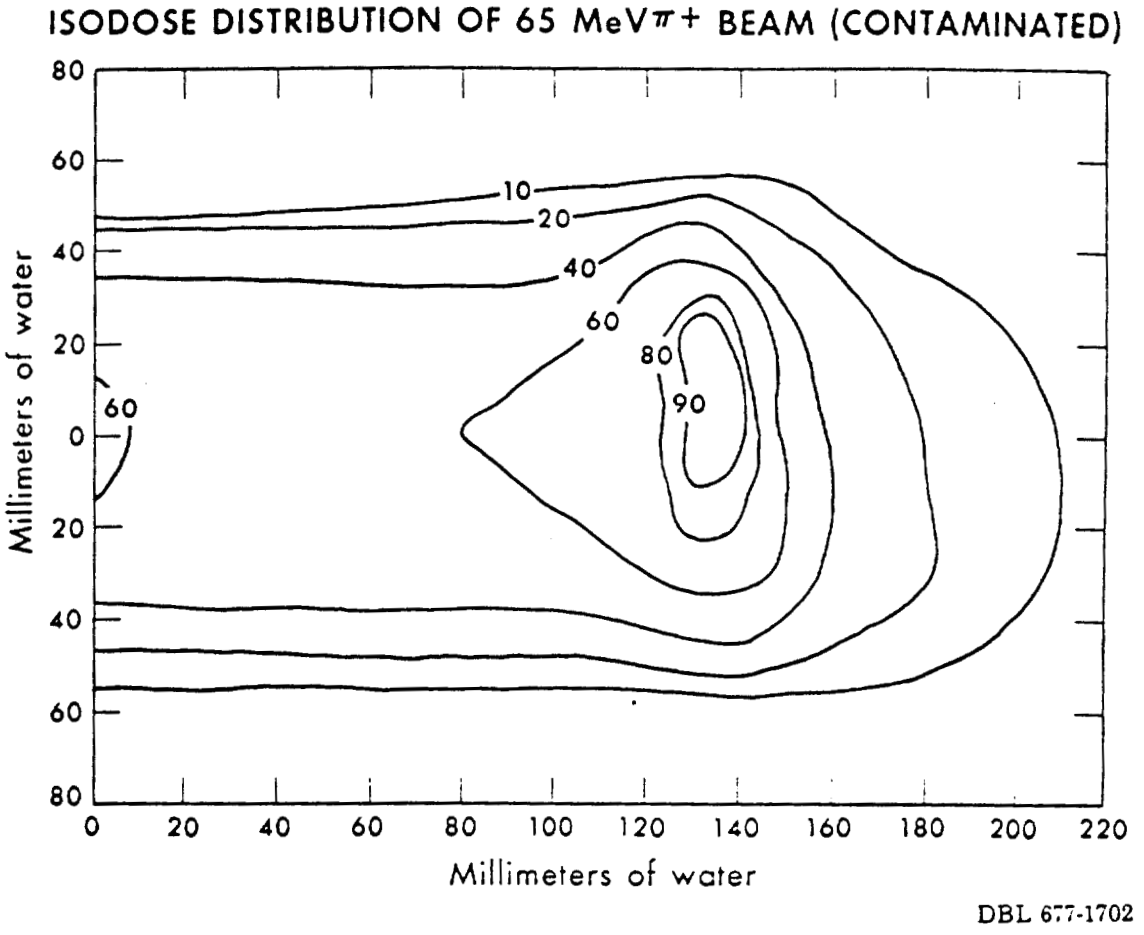
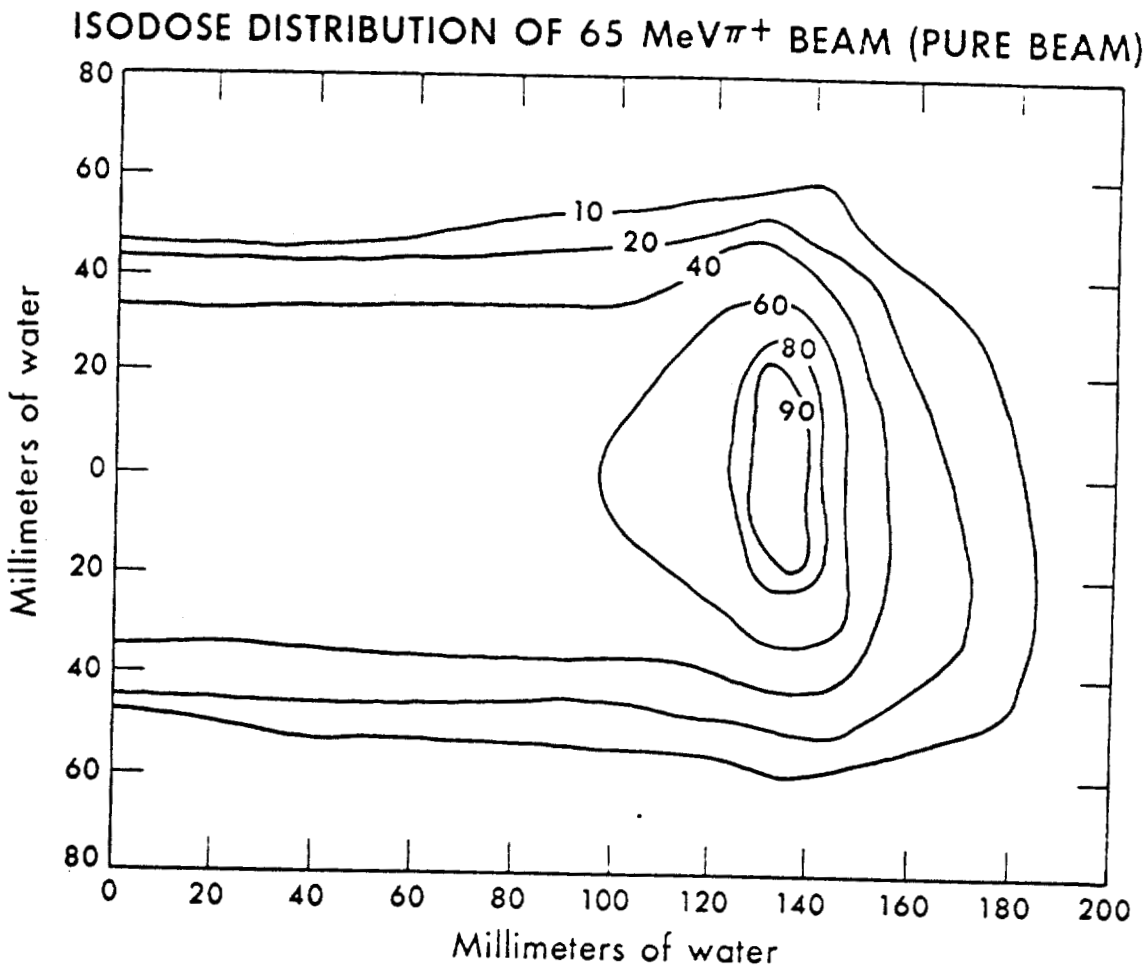


Figure 10.

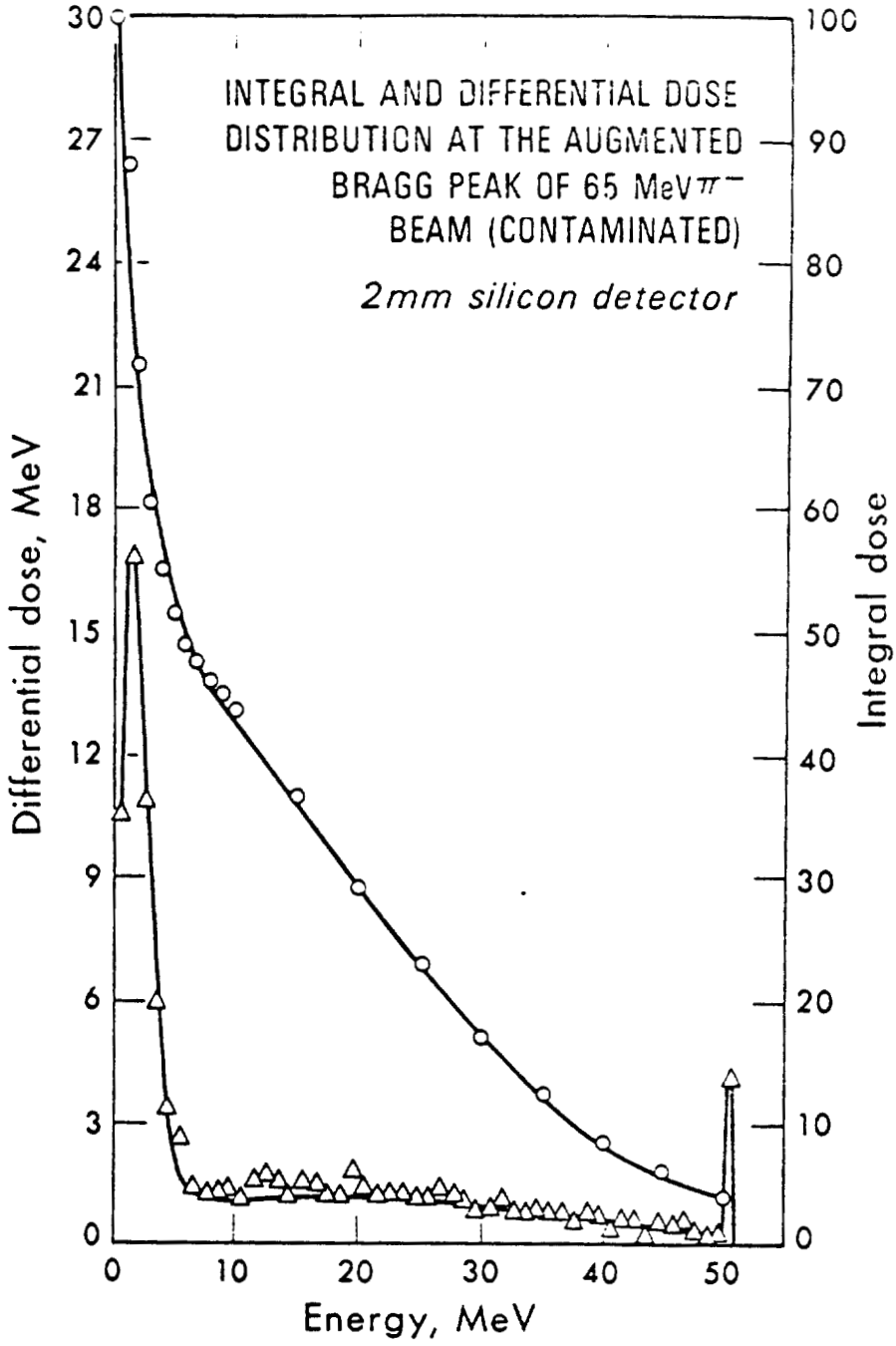
1081563



DBL 677-1703

Figure 11.

1081564



DBL 677-1701

Figure 12.

1081565

WORK ACCOMPLISHED

RADIOBIOLOGY

Preliminary measurements are now being completed on the OER for pions and these results are being compared with Cs^{137}. This entire area will be presented at the Pion Review Meeting in Washington on July 23.

1081566

AUGUST, 1968 THROUGH JULY 31, 1969

(1 year)

A. Direct Costs			
1. Salaries and Wages			
a. Principal Investigator			
Chaim Richman	(40%)	$9,600	
b. Associate Investigator			
M. R. Raju	(25%)	3,300	
c. Research Associate			
Tissue Culture	(33 1/3%)	4,000	
d. Research Assistant			
M. Gnanapurani	(100%)	6,840	
e. Secretary	(20%)	840	
Total Salaries and Wages			$24,580
2. Benefits, Sick Leave, etc.			
25% of Salaries and Wages			5,320
3. Supplies and Expendable Equipment			
oxygen, electronic spares, etc.			3,000
4. Project Equipment			
a. PDP8/I - for data handling of LET chambers			4,000
b. Coulter Counter - for cell counting			3,000
c. TLD Dosimeter			2,000
d. Readout Equipment for PHA			2,000
e. Microscope for Cytology (Vicia Faba)			5,500
5. Travel and Subsistence			
a. Dallas to Berkeley, 6 trips at $250		1,500	
b. Dallas to Wash., 2 trips at $250		500	
c. Berkeley to Wash., 1 trip		400	
d. Summer Stay in Berkeley		2,000	
			4,400
6. Page Costs, Drafting Exp. Repro. Costs			1,000
7. Telephone and Telegraph			100
8. Consultants - Electronic, 10 da. at $100		1,000	
Barendsen, 1 month		800	
			1,800
9. Books and Periodicals			300
Total Direct Costs			57,500 ~~$51,500~~
B. Indirect Costs - 85% of Salaries and Wages			20,893 ~~$73,193~~
			77,893

1081567

June 24, 1968

V.

AUTHENTICATION

Submitted by: Chaim Richman

Chaim Richman
Principal Investigator

Approved by: Ralph N. Stohl

Ralph N. Stohl
Vice President

Southwest Center for Advanced Studies

1081568

SOUTHWEST CENTER FOR ADVANCED STUDIES
FORMERLY
GRADUATE RESEARCH CENTER OF THE SOUTHWEST
POST OFFICE BOX 30365
DALLAS, TEXAS 75230

(214) ADAMS 1-1471

February 21, 1968

Dr. Robert Wood, Chief
Radiological Physics and
Instrumentation Branch
Division of Biology and Medicine
Atomic Energy Commission
Washington, D. C. 20545

Dear Bob:

Drs. Raju, Burke, Amer, and Curtis and Messrs. Feola and Loughma and I met in Berkeley last week and went over our plans for the biological runs scheduled for the next three months. I have wri ten down for you short resumes of the systems that will be used and the reasons for using them.

Our feeling at this time is that Vicia faba affords the best opportunity for measuring the OER in a system, and this is being pursued intensely. The second system is a lymphoma which is in the frozen state and is therefore anoxic. From a number of point of view, this is promising and the Co-60 runs are now being made.

In subsequent series of experiments, we are going to do grasshoppe neuroblasts which, as you know, is a very sensitive system. In addition, Mr. Loughman described for us the advantages of using lymphocytes and so this system will also be prepared.

As you can see, our endeavor here is to obtain a complete and as clear a picture as possible of the biological effects of pions with the present machine. It appears entirely possible that in these systems, the dose rate limitations can be overcome, and we look forward to learning a great deal from these systems.

CONTRACTS

1081569

A budget has been prepared for the three-month extension we discussed earlier and reflects, for the most part, our actual cost experience on the project.

Sincerely,

Chaim Richman

Chaim Richman

R. N. Stohl
Vice President

Enclosures

cc: Dr. C. S. Shoup
Atomic Energy Commission
Oak Ridge, Tennessee

1081570

BIOLOGICAL EXPERIMENTS BEING PREPARED FOR CYCLOTRON RUNS

Experiments on the OER Using Vicia Faba

Several systems have been considered for determining the OER with pions; however, the problem is that most biological systems are damaged when they are kept anoxic for long periods of time, such as would be necessary with the low intensity pion beam.

It has been shown that Vicia faba seedlings can be kept anoxic for a period of 24 hours at 3°C without any apparent damage to subsequent growth (Hall, Britis Journal of Radiology, 40, 128-133). It was further shown that the OER measured at 3°C is the same for both chronic as well as acute exposures. This makes this system particularly suitable for the low intensity π^--beam at the 184-inch cyclotron, and it is clear that the results obtained in the protracted irradiatio will be applicable for intense beams where the irradiation will be of an acute nature.

Cytological studies will also be made on the irradiated roots.

RBE Studies for the π^--Beam Using Cultured Mammalian Cells Irradiated at -196°C

Cultured mammalian cells are used in these experiments because of the quantitative nature of the results that can be obtained. Lymphoma (L5178Y) are frozen and exposed at liquid nitrogen temperature. At this temperature, the cells are in the anoxic state. The end point used is the survival of the cells, which simulates the experimental therapeutic situation; in this state the cells are more radioresistant.

The exposures to pions have to be made at low dose rate, and it is expected that with frozen cells, dose rate effects with be eliminated and the dosage will simply accumulate.

1081571

Studies are now in progress with Co-60 γ-rays to work out the experimental techniques. There are a number of technical problems relating to the exposure of a large number of cell suspensions and the dosimetry inside of the Dewar. The Co-60 runs serve not only to work out the techniques but also to compare acut with protracted irradiations at this temperature for a low LET radiation. The pion dose distribution in the plateau region behaves very much like X-rays.

Survival curves are obtained for the suspensions in the usual fashions with a Coulter counter. It should therefore be possible to obtain values for the RBE for anoxic cells for stopping pions.

Lymphocytes

We propose here to take whole blood from animals and extract pure lymphocyte Such lymphocytes are arrested in the G_1 state and are essentially dormant. The cells are put in suspension and irradiated at normal temperatures. This is a relatively sensitive system; about 100 rads gives a 50% reduction in survival. The cells are irradiated with different doses. Phytohemagglutinin (PHA) is then added and the cells are now sorted in the following way. The dead cells accept a stain and are counted and survival curves drawn. Certain cells may be alive but functionally impaired and will not grow. The remaining cells will grow and will give a mitotic index and permit chromosome studies.

Some effects of hypoxia can also be determined with this system. Hence, in a <u>single</u> mammalian cell system <u>three</u> separate parameters, with and without the <u>effect of oxygen,</u> may be observed.

1081572

PROPOSED THREE-MONTH BUDGET
May, June, July 1968

A. Direct Costs			
1. Salaries and Wages			
C. Richman	(33%)	$1,980	
N. Amer	(50%)	1,250	
Technician	(100%)	900	
Total Salaries & Wages			$ 4,130
2. Vacation, Sick Leave Accruals, FICA Retirement & Benefits 25% of A1			1,032
3. Supplies and Expendable Equipment			750
4. Electronic Counting Equipment		1,500	
On-line Data Handling Equipment		3,000	
			4,500
5. Purchased Services, Calibration, etc.			250
6. Communications, Telephone, and Telegraph			150
7. Publications and Page Costs			300
8. Professional Fees and Consultants			500
9. Travel: 3 trips Dallas/UCB at $300 w/subsistence			900
			$12,512
B. Indirect Costs			
85% of Salaries and Wages			3,510
Total three-month budget			$16,022

1081573

GRADUATE RESEARCH CENTER OF THE SOUTHWEST
POST OFFICE BOX 30365
DALLAS, TEXAS 75230

ADAMS 1-1471

November 12, 1965

U. S. Atomic Energy Commission
Research and Development Division
P. O. Box E
Oak Ridge, Tennessee 37831

Attention: Mr. C. S. Shoup
Chief, Biology Branch
Research and Development Division

Gentlemen:

Subject: Renewal of Contract No. AT-(40-1)-3343

In response to your letter of November 1, 1965, we are submitting the information required in satisfaction of contract requirements and for consideration of renewal.

We have already submitted to Dr. Nathaniel F. Barr, at AEC Headquarters, a summary account of progress in the program and preprints of technical papers which will appear either as Lawrence Radiation Laboratory technical reports or articles in professional journals. We are submitting an additional set of these documents herewith. The two letters addressed to Dr. Barr, six copies of which are also attached, are provided to meet, in part, the progress report requested in paragraph one (1) of your letter.

An expenditure statement is also provided which indicates current expenditures on the program, including both the Center's contribution to this specific contract and its costs for pion dosimetry studies incurred from its own funds in the first quarter of fiscal year 1966. This expenditure report does not include American Cancer Society funds which have also been expended for purposes which complement research carried on under AEC sponsorship.

As we point out in the letter to Dr. Barr, we regard the scope of work set forth in the contract as complete and have proposed that a new scope of work be prepared for any resulting contract. This scope or work description should include installation of an electrostatic separator in the existing pion beam for removing electron and muon contamination and rerunning previous dosimetry experiments. It is clear from the expenditure statement that no further funds remain available for performance of this second task.

1081574

NOV 15 1965

Our letters to Dr. Barr explain in reasonable detail what we propose to undertake in the subsequent period and the budget for accomplishing this work which, however, excludes any amounts which may be expended by the Lawrence Radiation Laboratory.

Dr. Richman at present has no Federal funding for his project although a proposal has been submitted for concurrent radiobiology work to the Office of Naval Research. We have been advised informally that this proposal has been approved but that funding is not yet available. As we point out in our letters to Dr. Barr, we are proposing that the Commission support essentially the costs involved in rerunning dosimetry experiments. We would expect that ONR funds and any renewal funds from the American Cancer Society would be devoted almost entirely to continuing the work with mice and bean roots which is described in the attached papers.

A summary of the proposed research is also enclosed, together with a voucher for the remaining 10 per cent of the consideration set forth in Article B-XI of Appendix B to the contract.

Although considerable equipment was developed to permit accurate dosimetry, advances were made primarily in techniques using known components. We conclude that no inventions, in the sense that this word is used in the U. S. Patent Laws, were made in the course of the work under this contract.

Sincerely,

Ralph N Stohl

Ralph N. Stohl
Vice President

1081575

November 2, 1965

Dr. Nathaniel F. Barr, Chief
Radiological Physics and
Instrumentation Branch
Division of Biology and Medicine
U. S. Atomic Energy Commission
Germantown, Maryland

Re: Contract AT(40-1)-3343
Our Account No. 1440

Dear Dr. Barr:

I understand that subsequent to your meeting in Berkeley last September with Dr. Richman, Dr. Raju, and Mr. Robottom, they submitted to you a draft letter which in effect stated that the scope of the referenced contract, as now written, had been substantially completed, though preliminary radiobiology studies could still be undertaken to advantage.

With respect to dosimetry, the most critical factor in Dr. Richman's program at present, we believe that only a pion beam relatively free from contaminants will permit definitive dosimetry. It is our plan that OMR funds, when received, will be used exclusively for radiobiology to supplement the work now being carried on by the Lawrence Radiation Laboratory staff. The funds requested from the Commission for the next 12-month period will be devoted in large part to installing an electrostatic separator to improve the pion beam, detector studies, and to repeating with somewhat improved techniques the dosimetry experiments which have already been performed.

The budget which accompanies this letter is for the most part self-explanatory in view of the work proposed. Mr. Stevens and Mr. Sperinde will be working at Berkeley primarily on the physics of the program. Mr. Hammack, an electronics technician, will be working in Dallas with Dr. Richman. The travel and subsistance costs are due largely to our remoteness from Berkeley and the fact that Dr. Richman plans to spend the summer of 1966 in Berkeley. Dr. Richman's letter of November 1 to you, is transmitted together with mine for convenience in review.

F11135

1081576

NOV 15 1965

Representatives of the Los Alamos Scientific Laboratory have approached Dr. Richman relative to his work in Berkeley and plan to visit Dallas later this month. There seems little doubt that initial design and planning for the linear accelerator (meson factory) to be constructed at Los Alamos will require dosimetry data whose reliability goes beyond what has been accomplished thus far.

We estimate that our present program funds will be exhausted sometime in the month of December 1965. We respectfully urge that this proposal be considered as soon as convenient. We would appreciate a beginning date of November 1, 1965, on any contract amendment which may result, or as soon thereafter as may be permitted under the Commission's administrative regulations.

Sincerely,

Ralph N. Stohl
Vice President

Enclosures: 6 sets transmittal & Richman November 1, 1965 letter to Barr
(3 sets only) Papers UCRL-16387
" 16071
" 16302
Budget

bcc: C. Richman (without 3 papers)
R. C. Peavey " "
J. S. Robottom (complete set)

1081577

REVISED AEC BUDGET

A.	Direct Costs			
	1. Salaries & Wages			
	a. Principal Investigator			
	C. Richman	(50%)	$ 8,250	
	b. Research Associate			
	L. Stephens	(75%)	7,000	
	c. Graduate Student			
	J. Sperinde	($200/month)	2,400	
	d. Technician			
	H. Hammack	(50%)	2,700	
	e. Secretarial			
	E. Raphael	(50%)	2,392	
	Total Salaries & Wages			$22,742
	2. Benefits & Accrual for Vac. & Sick Leave 25% of 1			5,686
	3. Electronics Equip., x-y plotter, Pico ammeters, semi-conductor detectors, oscilloscope camera			5,000
	4. Travel - Dallas to Berkeley & Return 5 trips @ $250			1,250
	5. Subsistence & Per diem; 90 days @ $10.00 (Summer, 1966)			900
	6. Expendable Equipment & Supplies			1,000
	7. Telephone & Telegraph			500
	8. Report & Page Costs			750
	9. Computer Rental CDC 1604 or equivalent 1 hour (rate subject to change)			225
	Total Direct Costs			$38,053
B.	Indirect Costs--80% of Salaries & Wages			18,194
	Total Budget			$56,247

1081578

GRADUATE RESEARCH CENTER OF THE SOUTHWEST
POST OFFICE BOX 30365
DALLAS, TEXAS 75230

ADAMS 1-1471

November 1, 1965

Dr. Nathaniel F. Barr, Chief
Radiological Physics and
Instrumentation Branch,
Division of Biology and Medicine
U. S. Atomic Energy Commission
Germantown, Maryland.

Dear Dr. Barr:

I will write down for you our present situation in the pion dosimetry program so that you can see where we stand and what we feel needs to be done.

The Dosimetry So Far:

We have finished about four different dosimetric studies of the 90 MeV pion beam at Berkeley. We have used ionization chambers for dosage, scintillation counters for the particle attentuation in lucite, semiconductor detectors for the pulses of pions in flight and stopping pions, and finally a time-of-flight set up for the composition of the beam.

Speaking broadly, we have found from these experiments the following:

1) As expected, pions are very penetrating particles that give a good peak of dose at the end of the range.

2) This peak is not as high as some people expected, at least not with the beams available at the present time.

3) The pulses obtained when pions stop are indeed very large and contain therefore a sizeable high LET component. The average energy of the star in silicon is about 20 MeV.

4) The beam contains a background of about 25% electrons and 10% muons; these contaminations obscure to a significant extent the dosimetry of pions.

5) The beams available on the 184" cyclotron are somewhat high in energy for bio-medical work, and the slowing down results in attenuation and scattering of the beams. Instead of 90 MeV, what would be best is a 60-50 MeV beam.

1081579

Excursion Into Radiobiology:

With this beam we have taken a look at the effect of the peak and plateau of the Bragg curve with stars on Vicia Faba, and with the help of a number of people in Berkeley, on the effects of the beam on ascites tumor cells in mice.

The peak has a remarkable effect over the plateau on growth rate of the roots, anaphase bridges and micronuclei of the root meristem in Vicia Faba. For example, we see about 2.4 times as many chromosome bridges for cells exposed in the peak relative to cells exposed in the plateau.

With the help of Dr. J. Feola at LRL, mice with ascites tumor cells were exposed in the peak and in the plateau. The results show a greater effectiveness of the peak dose over the plateau dose on cell viability. The probable errors are still large; however, the experiment can be improved a good deal. It is also becoming clear that the effects in the peak are not just due to the higher dose but also to the higher LET in the peak. Mr. W. D. Laughman and Dr. H.S. Winchell have studied the chromosome bridges and the polyploidy of the ascites tumor cells exposed to the beam; they find a ratio of about 5:1 for cells exposed in the peak to those exposed in the plateau. The probable errors are still large.

What Needs To Be Done:

The π^- - beam is a remarkable radiation and the background of electrons and muons should be removed as much as possible with an electrostatic separator. Then the dosimetry of pions will be much clearer. The focusing system will then be redesigned to go with the separator. With a separator it may also be possible to go down in energy from 90 to around 50-60 MeV. This may work out since one of the main difficulties of lower energy beams is an increased electronic background. I feel that all the dosimetry experiments that have been done should be repeated with a clean beam.

I trust that you will agree with us on the importance of continuing our excursions into radiobiology.

With reference to the pion factory, the facts that we are learning are of great importance to the shielding problem and also to the scope and lay-out of a bio-medical cave.

I am submitting with this letter a very reasonable budget for a year. Mr. Stephens and Mr. Sperinde are needed to help set up the separator and magnets and help with the alignment of the entire system, as well as with the experiments.

I am enclosing three of our papers which give details of our work.

Sincerely yours,

Chaim Richman

Chaim Richman

CR:er
cc: Jack Robottom
Ralph Stohl

Encl.

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S I EXCHANGE

The negative pion beam at the 184" synchrocyclotron in Berkeley has a contamination of about 35% electrons and muons. These contaminations obscure the peak to plateau dose ratio of pions as well as other dosimetric measurements of the beam. The radiobiological studies on bean roots and mice are also affected by this background. It is proposed to add an electrostatic separator in the beam handling system together with a further focusing magnet to produce a much purer beam which will then be used to restudy the dosimetry.

It is expected that the electrons will be easy to separate, but the muons will be more difficult since their mass is so close to the pion mass.

Besides this work, improvements will be made in the semiconductor detector electronics to enable us to measure not only the spectrum of the pulses but also the integral of the dose pulses.

For the study of the effects of pions on ascites tumor cells (Lymphoma) in mice a new system for the irradiation of the mice will be built which will control the environment and improve on the feeding of the mice. In the last irradiation trouble was encountered in both of these arrangements.

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Expenditure Report

Contract AF(40-1)-3343

Through September 30, 1965

A.	Direct Costs			
	1. Salaries & Wages			
	a. Faculty & Staff	$ [illegible]		
	b. Tech. & Grad. Students	1,711		
	c. Secretarial/ Clerical	305		
	Total Salaries & Wages		$ 9,330	
	2. Vacation/ Holidays & Staff Benefits		1,776	
	3. Purchased Services(drafting, calibration, etc.)		273	
	4. Project Equipment		11,014	
	5. Consultant & Professional Fees		3,491	
	6. Telephone & Telegraph		10	
	7. Printing, Reports, Repro. Costs		173	
	8. Travel		2,418	
	9. Computer Services		921	
	10. Supplies & Expendable Equipment, Materials, etc.		789	
	Total Direct Costs			$ 30,195
B.	Indirect Costs--30% of Total Direct Costs			9,059
	Total Costs			$ 39,254
	Contract Limitation			35,000
	GRCSW Contribution			$ 4,254
	Additional GRCSW Contribution (FY 1966 only) to Pion Dosimetry			$ 5,760

1081582

GRADUATE RESEARCH CENTER
OF THE SOUTHWEST
POST OFFICE BOX 8478
DALLAS 5, TEXAS

OFFICE OF THE PRESIDENT

EMERSON 3-5211

CABLES: GRADRESCEN

November 7, 1963

Dr. Nathaniel F. Barr, Chief
Radiological Physics and
Instrumentation Branch
Division of Biology and Medicine
U. S. Atomic Energy Commission
Washington 25, D. C.

Dear Dr. Barr:

I have learned with pleasure of your interest in Dr. Chaim Richman's current radiobiology research using a pi-meson beam for dosimetry studies. Enclosed is a proposal which Dr. Richman has drafted outlining the nature of the problem, his current experimental program, and the course of his future research.

As Dr. Richman has probably told you, his summer results were extremely encouraging; and he is moving toward the use of a more effective ionization chamber for his subsequent work.

At this stage, research costs are relatively modest; and we do not anticipate requirements for a major staff for some time to come. The American Cancer Society has given us a starting grant, which, together with the co-operation of Dr. Lawrence at the Donner Laboratory and the use of AEC facilities, has made possible the progress which has been made.

We have requested support for this program from the National Institutes of Health, but the success of this proposal is uncertain. We would also hope to maintain at a modest level our American Cancer Society support. In the event the National Institutes of Health elects to fund this work, we would withdraw this proposal, though in view of the Commission's interest in this field, we would provide you with current information as work progresses.

For my part, I consider Dr. Richman's program one of the most intriguing and potentially valuable of all which are now being pursued at the Center, and indeed we have supported it on our own unsponsored research funds for approximately two years.

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FEB 4 1965

I may say that Dr. Richman's standing and the intrinsic merit of this research commands my personal support as a scientist, and I am hopeful that the Commission will be able to assist him.

Very truly yours,

L. V. Berkner
President

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PROPOSAL

TO

U. S. ATOMIC ENERGY COMMISSION

FROM

SOUTHWEST CENTER FOR ADVANCED STUDIES

OF THE

GRADUATE RESEARCH CENTER OF THE SOUTHWEST

Investigation of the Dosimetry of Negative and Positive Pions and their Feasibility for Cancer Therapy

Dr. Chaim Richman
Principal Investigator

* * * * *

I.

SUMMARY

The purpose of this work is to explore from the dosimetric standpoint the nature of beams of negative and positive pions. These two radiations offer unusual possibilities for the treatment of radio-resistant tumors and cancer therapy in general. The distribution of dosage looks promising, as well as the possibility for overcoming the "oxygen effect," which we have good reason to believe is responsible for the fact that ordinary X radiation and gamma radiation are not effective for certain kinds of neoplasms.

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IMPORTANCE OF PROPOSED RESEARCH

At present, beams of pions are used to study various problems in pure physics. The most useful beams are produced by synchrocyclotrons as, for example, the one at the Lawrence Radiation Laboratory at Berkeley. Such machines yield protons of energy between 500 and 1000 Mev, which then impinge upon a target to produce the beams.

We can describe with some precision the behavior of a nagative pion as it traverses matter such as tissue: the pion loses energy throughout its path like any charged particle; that is, it interacts with the electrons in the atoms, producing ionization and this ionization is given by the familiar Bragg curve calculated for pions. At the end of its range, a new phenomenon is observed: the negative pion is captured by a nucleus such as carbon, oxygen, or nitrogen, and causes this nucleus to explode into α-particles, neutrons and protons. Most of the energy used to create the particle is now returned to us in kinetic energy of these fragments. About 30 Mev is given off in the α-particles, and protons, which are therefore of short range. A unique consequence is that the cubic centimeter of tissue where the pion stops receives an energy transfer many times what a cc of tissue receives by the traversal of the pion. This is the first of the phenomena by which one is led to think of the negative pion as a candidate for a therapeutic particle.

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The positive pion has not heretofore been considered in any way as having therapeutic possibilities. Our experiments, however, have shown that there is a large dosage available at the end of a positive pion. The positive pion decays into a short range muon of 4 Mev. This muon in turn beta decays into a positron and two neutrinos. The interesting feature in this case is that these positrons are highly energetic; and their range is such that they may be useful for large regions of involvement as occur, for example, in ovarian carcinoma.

The radiological treatment of cancer is at present greatly limited by the available tools, and the purpose of this work is to ascertain what these new radiations can offer for the treatment of many malignant diseases.

The cross sections for the production of pions, their angular distribution, and the energy spectra at the different angles are well known. The behaviour of pions in matter is well understood; furthermore, the energy spectra of the α-particles and the neutrons resulting from the capture have been measured in a number of materials. There are effective methods available for making beams of pions; and it is known what combination of mu-mesons, electrons, positrons, and neutrons can be expected. Thus, the differential physical background is well established.

The short range particles that are produced in tissue in the capture of the negative pion ionize heavily per unit distance; i.e., with a high LET. Such high LET's have an unusual importance

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for cancer therapy. This comes about in the following way: For many years, it has been known that large tumors outgrow their supply of oxygen; further, it has also been known for many decades that a low oxygen supply makes tumor cells unresponsive to X rays and gamma rays. In recent years, it has become clear that high LET radiation overcomes this so-called oxygen effect. However, we have not had available a wholly satisfactory form of such high LET radiation. The negative pion offers this possibility in a highly useful form since the LET in the healthy tissue remains low. This selective radiation with its high-LET terminal dose is the most important aspect of the work discussed here.

The penetrating quality of pions is most impressive; a 50 Mev pion will traverse 10 cm of tissue before stopping, while a 100 Mev pion will travel 30 cm in tissue before coming to rest. Such energetic pions are easily produced with several of the high-energy synchrocyclotrons now in operation. Such a particle can penetrate any portion of the body without giving an undue dosage to the healthy tissue. In therapy, the pion energy would be chosen so that the pions will stop at the site of the tumor. The ionization in the healthy tissue remains low because the pion is light and interacts weakly with the electrons in tissue, compared to a heavy particle with the same energy.

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III.

RESULTS OF PRIOR WORK

Under a modest initial grant from the American Cancer Society, AEC facilities made available at the Donner Laboratory, University of California, and support from the Center's own funds, Dr. Richman and his co-workers devoted the summer of 1963 to an intensive experimental program using the 184-inch synchrocyclotron. The results of this program appear in Enclosure A entitled "On the Dosimetry of Negative and Positive Pions." This paper also references other work which bears upon this problem.

IV.

SCOPE OF PROPOSED PROGRAM

Experimental results confirm that available pion beams are adequate for dosimetric measurements; indeed, there is a need for such studies wholly apart from the therapeutic aspects of this radiation.

Somewhat unexpectedly, it was observed that the positrons from positive pions produce a large terminal dose which merits study for other applications despite the low LET compared to the corresponding negative pion dose. Available ionization chambers were not adequate, during the summer program, to measure the dosage produced by the stars resulting from negative pion capture. The Investigator proposes, therefore, to use a high-pressure ionization chamber now under construction at Berkeley, or solid state detectors to increase the stopping power of the detectors.

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From the technological standpoint, it is planned to investigate alternative magnetic systems for producing beams of varying size and quality. Radiobiological studies will be begun with the co-operation of members of Donner Laboratory by irradiating tumors in mice if the dosage is sufficient.

V.

METHOD OF PROCEDURE

Enclosure A referenced earlier also describes the experimental techniques which have been used thus far. Substantially similar techniques will be pursued in the program here proposed.

VI.

SUPPORT AVAILABLE FROM OTHER SOURCES

The Principal Investigator has a small grant from the American Cancer Society for preliminary studies in this field, and there is some prospect that modest funds for a second year's work may be available.

The Center has supported this work from its own funds and will continue to underwrite the Investigators expenses to a reasonable limit, including one-half of his salary and approximately four thousand dollars in general purpose equipment.

A proposal was submitted on January 11, 1963, to the National Institutes of Health for support of this program. We have been unable to ascertain the prospects for approval or whether this proposal, if approved, will be funded. In the event the NIH should act favorably, we would expect to withdraw this proposal to the AEC.

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VI.

BUDGET

First Year

A.	Direct Costs			
1.	Salaries & Wages			
	a. Principal Investigator, C. Richman	(100%)	$8,250*	
	b. Co-Principal Investigator, M. Weissbluth	(20%)	4,800	
	c. Senior Physicist	(20%)	4,000	
	d. Research Associate (Postdoctoral)	(50%)	- o -	
	e. Mathematician--Programmer	(100%)	8,000	
	f. Graduate Students--2 (summer)		2,400	
	Total Salaries & Wages			$27,450
2.	Employee Benefits--15% of 1			4,110
3.	Travel (Berkeley & Dallas @ $200 round trip, 10 trips)			2,000
4.	Report and Page Costs			300
5.	Occupancy, Utilities, and Maintenance			2,000
6.	Shop Costs (instrument rework, fabrication, etc.)			500
7.	Consumable Supplies (electronic spares, tubes, wire, connectors, small tools, misc. lab materials)			450
8.	Major Equipment** Scintillation counters, photomultipliers, amplifyers, scalers, electrometers			8,000
	Total Direct Costs			$44,810
B.	Indirect Costs--30% of A.			13,440
	Total First Year Budget			$58,250

*One half of Dr. Richman's salary will be met by the Center

**In addition to costs estimated, the Center will contribute approximately $4,000 for such equipment as meters,

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oscilloscopes, testing equipment, and certain costs of fabrication. The Donner Laboratory at Berkeley has generously made available other equipment, personnel, and services; and, on the assumption that cyclotron time will be made available, we have not included such costs for future work.

Second Year

We do not believe that we have a sound basis for estimating second-year costs since these will depend in large measure on the results of our first-year effort and the co-operative role which the Donner Laboratory may wish to take.

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