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LOS ALAMOS SCIENTIFIC LABORATORY
of the
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LOS ALAMOS • NEW MEXICO

Proceedings of the

Biomedical Sessions

of the

Fourth LAMPF Users Meeting

October 30-31, 1970

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held at the

Los Alamos Scientific Laboratory

Los Alamos, New Mexico

October 30-31, 1970

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TABLE OF CONTENTS

Foreword

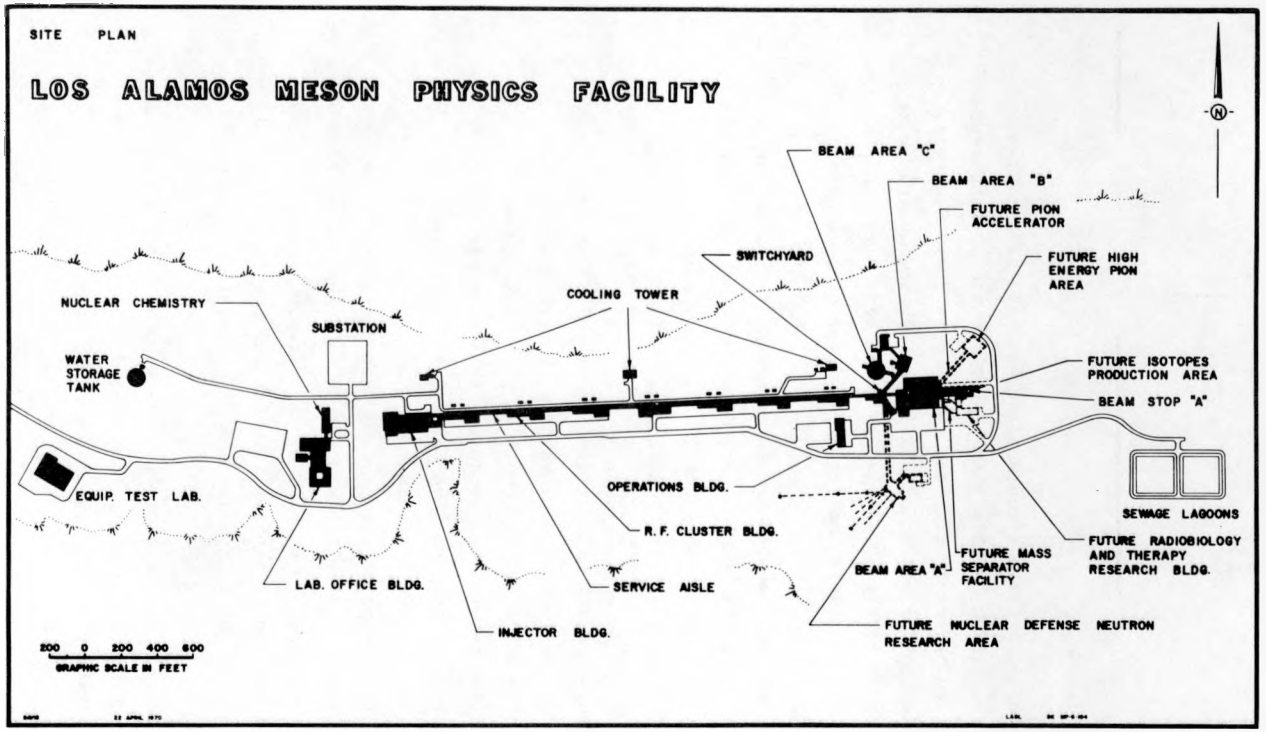
The Fourth LAMPF Users Group Meeting was held at Los Alamos on October 30-31, 1970. Within this general meeting, three separate sessions, under the general chairmanship of David E. Groce, were devoted to LAMPF biomedical activities. These meetings were attended by approximately 60 people representing a sizeable portion of the 144 LAMPF Users indicating an interest in biomedical activities.

These proceedings constitute the permanent record of the biomedical portion of the LAMPF Users Group Meeting. Some of the presentations are given in their entirety, i.e., edited versions of tape recordings; other less formal presentations have been summarized.

The business meeting held during the second biomedical session resulted in the formal adoption of a Charter establishing a Biomedical Steering Committee whose purpose is to guide biomedical activities required to establish a therapeutic program utilizing negative pi mesons. The Charter for this Steering Committee is given in the Appendix.

Much credit must go to Lewis Agnew, the Users Group Liaison Officer, and to Mrs. Billie Miller, the Users Group secretary, for helping to arrange the details of the various sessions. And special credit must go to Stanley L. Whetstone for helping to organize the biomedical activities and plan the biomedical programs.

Further details of the biomedical aspects of LAMPF will be found in "A Proposal for a Biomedical Addition to the Los Alamos Scientific Laboratory's High-Flux Meson Physics Facility," by W. H. Langham and D. E. Groce (LA-4490-P) which is available upon request.



Site Plan for LAMPF

BIOMEDICAL
SESSION I

1. W. H. Langham (LASL-HRL)
   "Radiotherapeutic Potentialities of Pi Mesons at LAMPF"

2. M. M. Elkind (BNL)
   "Radiobiological Considerations in the Application of Mesons to Radiotherapy"

Introductory Remarks on Radiotherapeutic Potentialities of Pi Mesons at LAMPF

W. H. Langham

Los Alamos Scientific Laboratory

These remarks will primarily be an introduction to Dr. Elkind's talk and will be a short summary of what Louis Rosen has been saying for the last three or four years.

The LAMPF accelerator will be the most intense beam of protons in the world or even contemplated for the next several years. The biologist's interest lies not in the protons, per se, although they may have biological implications, but in the secondary radiations, or beams, that can be derived from the proton accelerator. If a proton beam of sufficient energy impinges on a thick target, one gets all manner of radiations, including positive, negative, and neutral pions. The negative pion, of course, is the one of primary interest to the biologist.

By virtue of the fact that the negative pion is a charged particle, one can use magnetic optics and focus these charged particles, more or less as a pure beam on a target that can be anything from biological cells to a patient in need of radiation therapy for a malignant condition. The physicists assure us that they can use magnetic optics to focus and tailor the beams to fit the needs of the user. It may be possible, then, to have a relatively large diameter beam of negative pions capable of delivering 50 to 100 rads per minute to treatment volumes as large as 10 x 10 x 10 cm and possibly even larger if scanning techniques are used. Primarily, then, here is a beam of a radiation which has unique properties and that has never before been used for therapy.

When the negative pion comes to rest, it forms a pi mesic atom, either of oxygen, nitrogen, or carbon (oxygen being the predominant one, of course), ever present substances in both normal and malignant tissue. In this respect it doesn't have the shortcomings of the boron-neutron therapy technique which depended on whether the tumor would take up the boron. In the case of mesons, the capturing nuclei are ever present substances of the biological material to be irradiated. However, the same nuclei are present in normal tissue also, so one does not have the advantage of being able to kill cancer cells only, unless the stopping region of the beam can be carefully controlled.

When the pi meson comes to rest, it exhibits its most unique properties. It cascades down the Bohr orbits, giving off mesic x rays. These have a uniqueness to them too for therapy. It is possible, if one is clever enough at detecting these mesic x rays, to be able to actually delineate the stopping region of the pion beam.

When the meson cascades down to where its wave form overlaps that of the capturing nucleus, it spends part of its time inside the nucleus, and this results in an exploding of the capturing nucleus itself, in which the rest mass of the pi meson is converted to energy. About 40 MeV of this energy goes to overcome the binding energy of the capturing nucleus. About 30 MeV goes into kinetic energy of particles with a Z of 1 or greater. Unfortunately, a major part of the energy (about 70 MeV) is carried off as neutrons, which, of course, are not absorbed in the treatment volume itself. The charged particles to which the kinetic energy is given are short range and most of their kinetic energy will end up in the treatment volume. The total energy conversion then is on the order of 140 MeV, 30 MeV of which is deposited in the tumor as high LET radiation.

The pions, on the way into the tumor, are essentially like high-energy electrons. When they come to rest, the star contribution adds to the dose, giving a peak in the dose distribution curve in the stopping region. So one now has a way of delivering low LET energy, something of the order of a high energy electron, on the way into the tumor mass, and at the end of the beam one has an enhanced dose contribution which is made up largely of high LET irradiation, that is, particulate radiation.

Theoretical calculations by Curtis and Raju for a 96 ± 5 MeV meson beam show that protons give about 33 percent of the dose, helium nuclei about 14 percent, and heavier nuclei some 11 percent. The pions themselves in the Bragg region give about 35 percent of the dose. Obviously one has a very complex radiation, which means many radiobiological and dosimetry studies must be conducted before one can feel confident in using a pion beam on a living human being.

Dr. Raju has made actual measurements of the relative dose distribution as a function of depth which support the theoretical depth dose calculations. The measured peak-to-plateau ratio is probably not as high as theory would predict. However, Dr. Raju has been working under great difficulty with weak and impure beams. It is possible that part of the difficulty still lies in our ability to make such measurements with the weak beams currently available.

How could one take advantage of the depth-dose distribution of a pion beam for cancer therapy? If one wished to treat a tumor of 10 cm thickness, at a depth of 10 to 20 cm, then one would pick an energy or momentum spread of the pion beam which would range somewhere between 52 - 80 MeV initial energy. In other words, one can treat tumors at different depths, and tumors of different thicknesses, and volume by selecting the appropriate initial energy spread. This, of course, is feasible, by means of magnetic beam optic systems. If one wished to treat a small tumor at shallow depth, the ratio of the peak-to-plateau region dose is higher than it is if one is treating a large tumor at greater depth. Unfortunately, that happens to be just what would be predicted theoretically; that the advantage of the depth dose distribution with respect to pi mesons is influenced by the depth and the size of the tumor volume being treated.

There are other properties of pions which make them interesting for therapy. The oxygen enhancement ratio (OER) and the relative biological effectiveness (RBE) are a function of the linear energy transfer. One can immediately see that this offers certain advantages in tumor therapy. For large tumors, however, one actually has a variability in the RBE and OER through the treatment volume because of the variability of the dose ratio of the star contribution and the Bragg peak contribution of the unstopped pions. One may actually find himself faced with a new problem of shaping the beam with respect to dose equivalent and effective dose. One can see, therefore, many complicated and sophisticated biological and dosimetry studies that must be done before a meson beam can be adequately understood and used for cancer therapy. This all justifies lots of good radiobiological and dosimetry research.

In summary, the unusual properties of negative pions offer a number of attractive potential advantages for the therapy of deep seated tumors. However, these same properties pose an equal number of important and difficult problems in radiation biology and dosimetry that must be solved before the treatment of patients can begin. Among the potential advantages offered by a pion beam are the following:

1. The depth-to-entrance dose ratio (in rads) appears favorable, perhaps of the order of 2 to 3:1, depending on size of the treatment volume.

2. Exit dose is highly favorable as it is dependent largely on muon and electron contamination of the beam, which can be reduced to very low levels by physical means.

3. The relative biological effectiveness (RBE) of the terminal portion of the beam is favorable, probably of the order of 2 to 3, again depending on size of the treatment volume.

4. The RBE of the plateau region of the beam is favorable, being 1 or less and quite comparable to high-energy photons.

5. The oxygen enhancement ratio (OER) of the terminal region of the beam is favorable, perhaps of the order of 1.6, comparable to that of high-energy neutrons.

6. The OER of the plateau region of the beam is favorable, perhaps about 2.7, comparable to high-energy photons.

7. Beam control is highly favorable in that the charge on the pion permits beam manipulation by means of a computer-driven magnetic optical system. Additional beam control is feasible by use of variable absorbers and specifically shaped cross-section collimators.

8. Beam tailoring with respect to dose, dose-equivalent, and effective dose appears possible once RBE and OER as a function of beam energy spread are known.

9. In situ monitoring and visual display of the terminal region of the beam through detection of characteristic π mesic X rays, nuclear gamma rays, or positron production may be possible.

10. A dose rate approaching 100 rads/min to a 10 x 10 x 10-cm treatment volume will be available. Higher dose rates to smaller volumes will be possible, and irradiation of larger volumes at lower rates may be feasible employing multiple-field or scanning techniques.

Radiobiological Considerations in the Application of Pi Mesons to Radiotherapy

by

M. M. Elkind

Brookhaven National Laboratory

The purpose of my being here is to tell you about some of the radiobiological considerations that enter into the use of pi mesons in radiotherapy.

To begin with, to discuss factors specific for pi mesons requires that I discuss those which are of general importance in radiotherapy as a whole as far as radiobiological considerations are concerned. So what I will try to do is outline some of the principal phenomena that we believe play a major role in the effectiveness of radiation in general in the treatment of tumors.

I will draw upon some work in the literature, some of my own experiments, but in the main, experiments of other people. Pertinent information does not necessarily have to come from experiments dealing with pi mesons, as I think you will be quick to recognize. Also, I won't try to rank order the points that I'll make as they relate to pi mesons, because such an ordering requires careful evaluations if it is to be done on a rational basis.

For historical reasons I start with a figure showing a survival curve for a line of cells known as Hela 53 cells. They came from biopsy tissue derived from a woman who had carcinoma of the cervix and were put into culture by Gey some 20 years ago. This curve (Fig. 1), produced by P. T. Puck and P. Marcus, was the first mammalian cell survival curve for cells irradiated and assayed in culture. It has historical interest and also helps me to define some of the terms I will use.

Figure 2 represents a curve similar to Fig. 1 with surviving fractions on semilog coordinates. The dose D_0 is the dose required to drop survival in the exponential region of such a curve by a

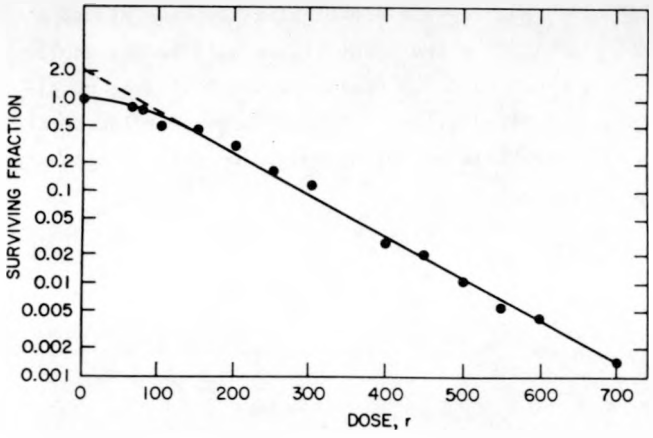
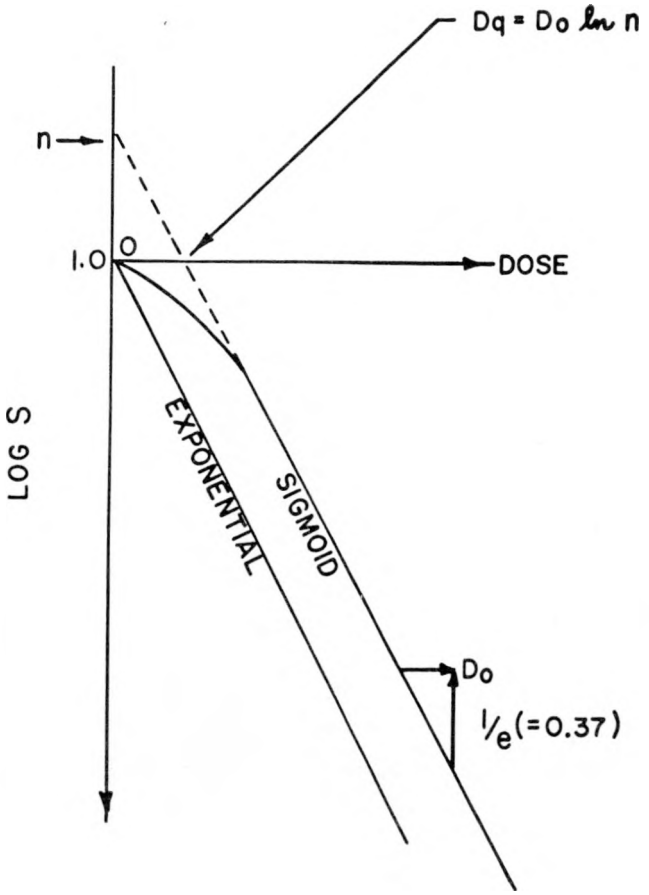


Figure 1.

factor of 1/e, or a factor of 0.37. This is a term commonly used in radiobiology. A second useful parameter is the extrapolation number of such a curve and is the value of the ordinate to which the exponential portion of the curve extrapolates. A parameter which is a measure of the threshold, or shoulder width of the curve, the D_q dose, or threshold dose, of course, is related to the other two parameters by the equation $D_q = D_0 \ln n$. In general, a sigmoid curve is one which also shows that damage has to be accumulated before an effect is produced.

My story begins with the HeLa cell curve in Fig. 1. A number of investigators, including myself, became interested in the potential of mammalian cells for quantitative radiobiological study, and we developed a context which has helped develop a rational basis for radiotherapeutic studies today. I hope this doesn't sound like too grand a general-



SURVIVAL CURVES

Figure 2.

ization, and some of you who are therapists may take issue with it, but I believe that this is the case and I think many of you may be here because it essentially is the case.

One of the principal phenomenon which play a major role in the use of radiation in treatment of tumors is, therefore, very simply this dose effect curve. The fact that, with increasing dose, a decreasing portion of cells survives is by itself very important in the use of radiation in the treatment of tumors. We accept implicitly that we can carry over a finding which deals with individual cells irradiated in dishes to a continuous mass of tissue and apply the same kind of probability statements that are evident on the ordinate of this curve to the likelihood that varying proportions of cells in the tissue will survive. So the dose effect curve, the survival curve, is one of the principal foundation stones upon which a radiobiological rationale of radiation therapy is based.

An experiment by Jim Belli (Fig. 3) shows Chinese hamster cells irradiated in the presence of air, as were the cells of the preceding figure and the same cells in the absence of air, or in the presence of a very small percentage of air. For practical purposes, these curves are related by a simple dose modifying factor; that is, their extrapolation numbers noted here as $\bar{N}n$ values, are almost equal, and this means that the curves have essentially the same shape. The dose modifying factor is 3.1. Another term used to indicate the sensitizing effect of oxygen is oxygen enhancement ratio (OER). When curves are functionally similar, as these almost are, the two terms are equivalent. Generally, the OER is taken as the ratio of doses to some particular level of survival. If we took the ratio of doses at the 10% level, we would come up with a factor of 3.1, and similarly at lower survivals, simply because these curves are functionally related.

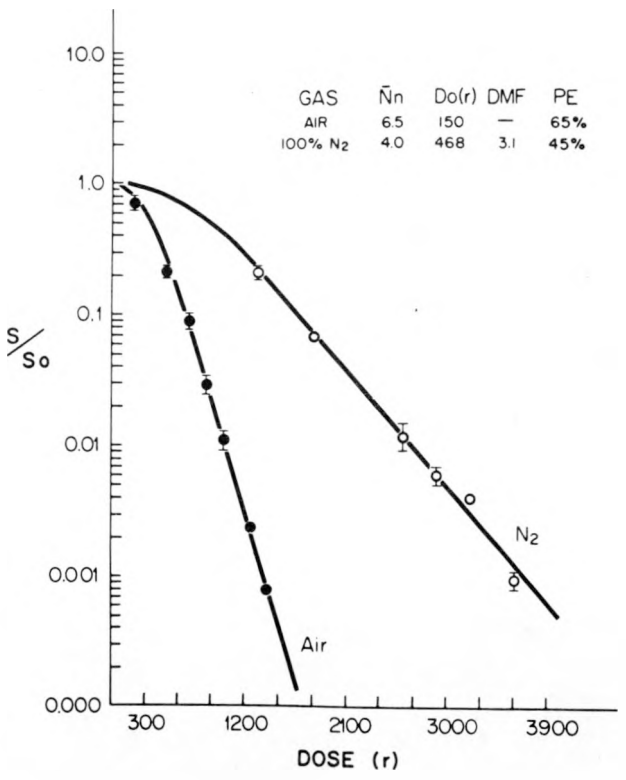


Figure 3.

Now here you see the result when the difference in oxygen concentration is fairly extreme, and Fig. 4 shows the graded effect when varying levels of oxygen are mixed with nitrogen and CO_2 (the CO_2 maintains the proper pH of the medium). When these cells, also Chinese hamster cells, are irradiated in the presence of air or the concentrations of oxygen shown, progressively there is a shift of the curve to the right and an increase in the D_0. The curves become shallower, but they all extrapolate to about the same value on the ordinate. In this instance the value on the ordinate is not just the extrapolation number but, as in Fig. 3, represents the multiplicity of the cell groups irradiated times the extrapolation number. The main point is that only D_0 is a function of the level of oxygen present in the gas mixture. The effect sets in at about 0.01% oxygen and is essentially completed in the region of 1% oxygen.

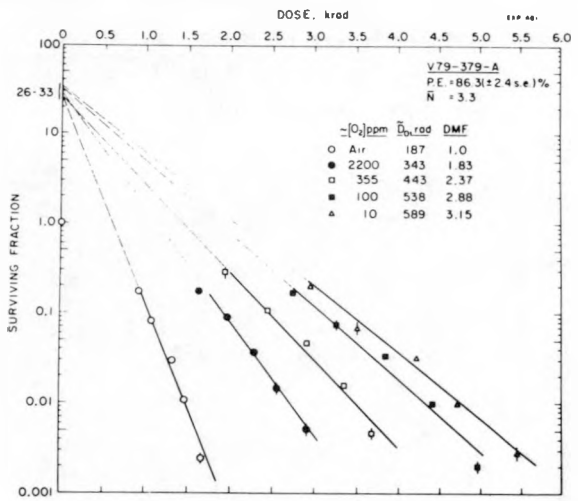


Figure 4.

You may ask, since these experiments were done with cultured cells under fairly ideal conditions, do they also apply to tumor cells? Let me show you some examples which answer this question affirmatively.

This experiment, performed by VanPutten and Kallman, shows cells from a mouse mammary carcinoma, put into suspension, and irradiated <u>in vitro</u>, either in the presence of oxygen or nitrogen. The results of several experiments are shown (Fig. 5). Treated cells were then inoculated back into isologous mice . The assay of the viability of the cells is not simply colony formation, as in the

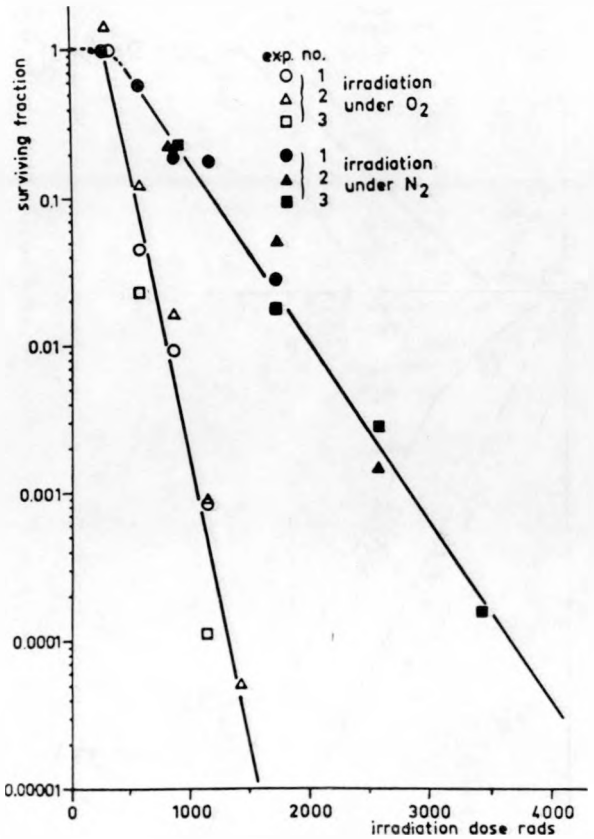


Figure 5.

previous experiments, but the ability of these cells to grow into a tumor. The data show a marked decrease in cell sensitivity when irradiated in the absence of oxygen.

Figure 6 shows some results of James Belli again, dealing in this case with a line of cells known as P-388 mouse leukemia cells. These cells were grown and irradiated in the peritoneum of a mouse. The closed circles trace the survival curve obtained, with cells extracted from donors one day after they were inoculated with 1×10^6 cells each. If an initial inoculum is grown for 7 days, it produces a population of about $2\text{-}3 \times 10^8$ cells, and at that time the peritoneum is filled with fluid. The survival curve for such cells is one characterized by a distinctly smaller slope; its D_0 value has increased by something like a factor of 3. In view of this we can infer, with considerable justification, that between day one and day seven, at least one principal factor has changed, that is, the level of oxygen concentration present. There is also a graded effect which Belli demonstrated with regard

to oxygen concentration and the sensitivity of these cells. In this instance, the variation in oxygen concentration was brought about by consumption of oxygen by the cells themselves. If these cells are allowed to grow after inoculation, in 2 days the slope of the survival curve has shifted somewhat but is not quite as shallow as the curve for 7-day cells. The curve for 3-day cells is just about as shallow as the 7-day curve but has a somewhat lesser shoulder; and the curve for 4-day cells is essentially coincident with the 7-day survival curve. What is seen here then is a demonstration of the fact that as these cells grow and divide, they outstrip the oxygen supply available to them from the tissue surfaces around them. They also very likely consume the nutrient supply to the point of exhaustion and in so doing they progressively render themselves hypoxic and as a result, their sensitivity to radiation is progressively decreased. Four days after they were inoculated, they survive as though they are anoxic cells. If such cells are then inoculated into a new host, they rapidly develop a sensitivity characteristic of 1-day cells. That oxygen depletion is responsible for the reduced sensitivity on day seven is very reasonable since $\sim 10^8$ cells per millimeter is a concentration that will deplete the oxygen present in a few minutes or less.

P-388 cells are free-living cells; that is, they are loose in the fluid in the peritoneum of a mouse. Let's consider now the case where the cells are in a solid tumor. Figure 7 has to do with lymphosarcomas irradiated in donor mice and assayed in isologous recipients. When Powers, Palmer, and Tolmach did this with many tumors, each indicated by a different symbol, and put the data together, the curve appeared to be bi-basic. The intial portion of the curve drops off rather rapidly with a D_0 similar to "oxic D_0's", and the terminal portion of the curve rather more slowly, the D_0 more characteristic of "hypoxic D_0's". This bi-basic curve implies that some proportion of the cells in this solid tumor were hypoxic at the time of irradiation. An estimate of that proportion can be made by extrapolating the terminal portion of the curve back to the ordinate which yields a value of 1-2%. From this we might infer that 1-2% of these cells were hypoxic. In spite of the fact that this is a very small percentage of the population, it is these cells which very likely would dictate whether or not these tumors would be sterilized with radiation, as is clear from the following.

If we assume that a surviving fraction of 10^{-10} is needed to sterilize, with high probability, all the cells in these lymphosarcomas (10^{-10} is a surviving fraction consistent with the number of viable cells per tumor), then projections of the initial and final portions of the curve in Fig. 7 indicate that markedly different doses are needed. Thus 1% or 0.1%, or even 0.01%, can still represent a critical percentage of the cells in a tumor treated with ionizing radiation. From the sketch in Fig. 8 we can visualize a solid tumor as a system of tissues in cylindrical geometry in which a blood vessel is at the axis. Cycling cells occupy a limited zone beyond which there is a zone of cells very likely not cycling although some of them may very well be viable. The reason for this is that at least their oxygen supply is limiting. There are theoretical considerations and a number of measurements which show that over distances of the order of 10-15 cell diameters, the oxygen concentration from a capillary drops to a level which will not support active metabolic activity in many types of cells. Therefore, beyond the oxic zone there is a zone where there may be relatively few cells but cells which, while not cycling, are also hypoxic. Beyond that zone, there would be very likely a zone of necrotic cells and cells which are lysing. Such material might be absorbed into the surrounding tissue and removed if the tumor dynamics and anatomy permit.

The survival curve and the oxygen effect are two principal phenomena in radiobiology. Another one is that concerned with the repair of sublethal damage, as demonstrated in Fig. 9. This experiment demonstrates the ability of mammalian cells to repair sublethal damage. The single-dose survival curve, again with Chinese hamster cells, is traced by the closed circles. The open circles show other groups of cells whose survival to graded second doses was assessed 18.1 hrs after 505 rad. When a given dose was fractionated, survival did not lie superimposed over the original single dose curve but was displaced upward. Therefore, dividing a

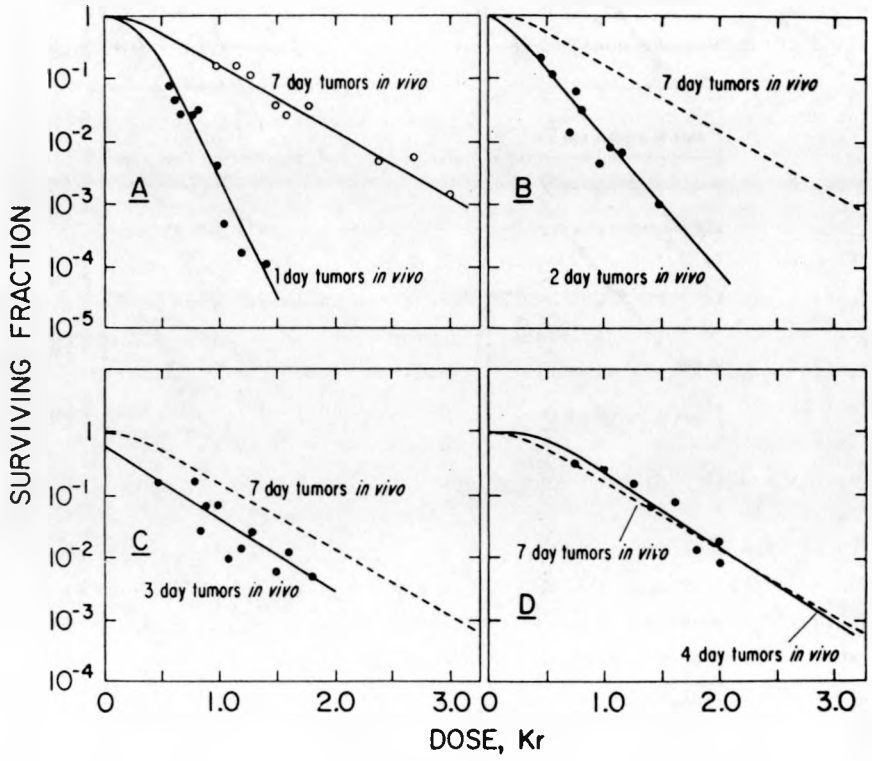


Figure 6.

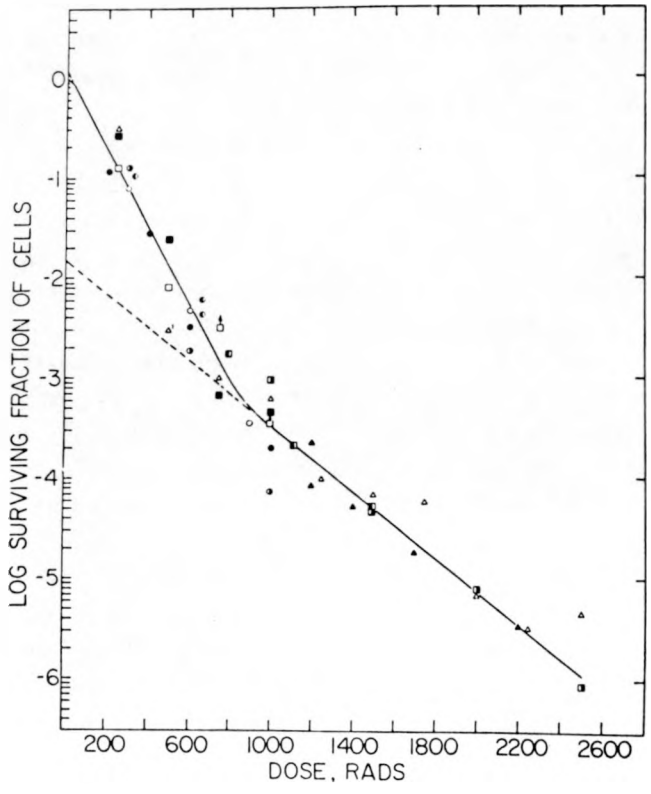


Figure 7.

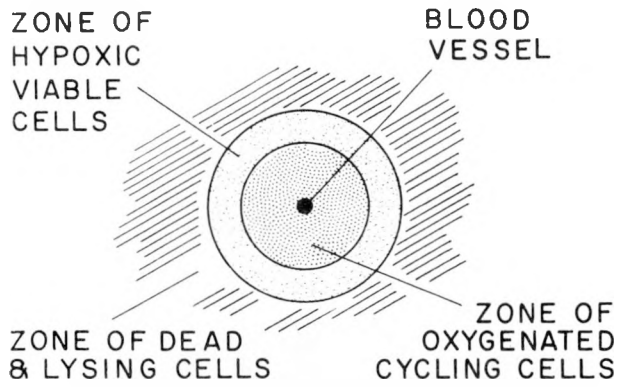


Figure 8.

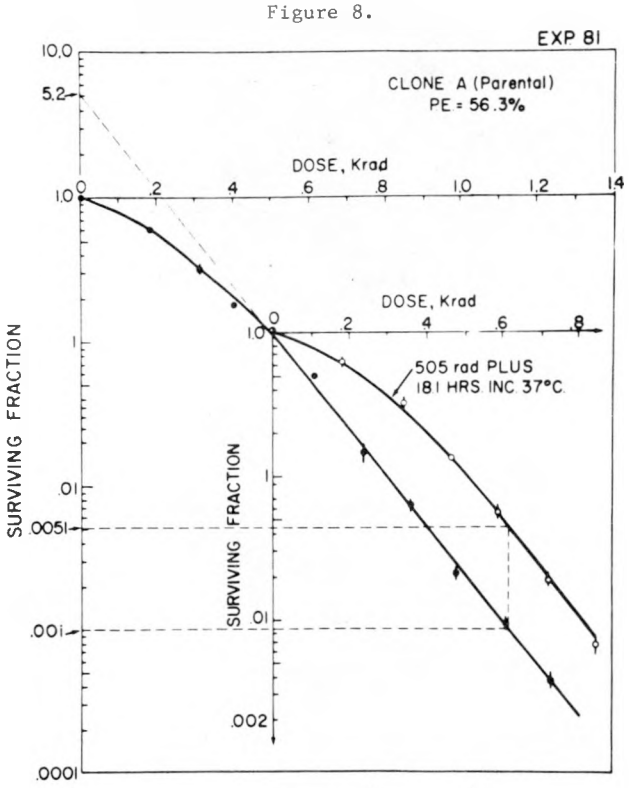


Figure 9.

given total dose into two parts results in increased survival. From this, it was clear that between the dose fractions, cells surviving a first exposure repaired damage, and, therefore, the effectiveness of a fractionated dosage schedule would be less than for the equivalent dose given in a single exposure.

It's important to know what the survival kinetics are between dose fractions. To get some impression of this, I show some data now in which the total dose was held constant while the interval of time between two dose fractions was varied. Figure 10 shows experiments with Chinese hamster cells again. The ordinate is still surviving fraction, but the abscissa is time between two doses. Cells kept in air between two doses in a metabolizing medium and at a temperature which would support active growth gave the result plotted by the open circles. There is a prompt increase in survival, a drop to a minimum, and a further increase. Now the fact that there is this prompt increase means, to begin with, that there is a repair process going on. The minimum has to do with the progression of cells in their growth cycle between the two fractions. The point to note, however, is simply that there is structure to this curve in the early part of a fractionation period--structure which reflects repair--plus the development of greater relative sensitivity in survivors of the first dose as they progress in their cell cycle toward division.

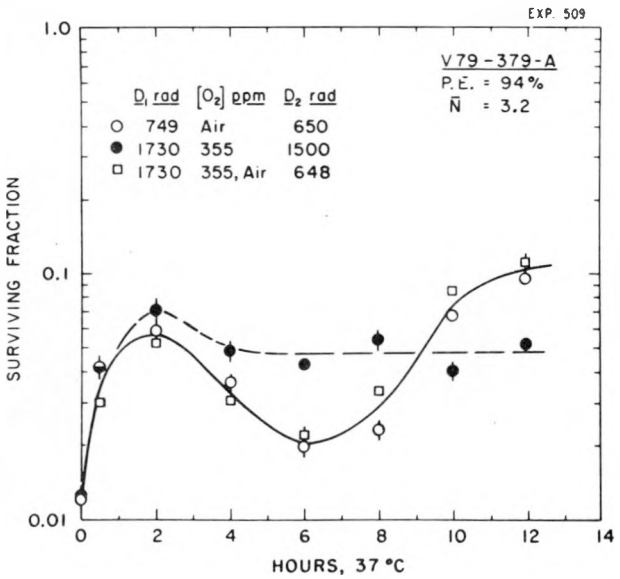


Figure 10.

One of the important questions that comes up relative to tumors, is whether those cells, which are hypoxic but viable, can also repair sublethal damage. If they can, they are spared not only because they are hypoxic but also because they repair. Thus, they would shed at least some degree of the damage that is registered in them every time an interval is allowed to elapse between fractions. The set of data indicated by squares in Fig. 10,

shows cells irradiated while hypoxic, with 355 ppm of oxygen. Then air was promptly admitted to the vessels. We see that the fractionation curve lies superimposed on the air-throughout curve. This means that the dose sparing effect of hypoxia, which was present for the first dose, had nothing to do with the course of events thereafter. Cells were able to repair damage, which is evident by the prompt increase in survival to begin with, and to do other things indicated by the structure of the curve, just as would cells treated in the presence of air throughout.

If cells are maintained hypoxic during the entire treatment, the result is traced by the closed circles. There is still a prompt increase in survival, but the minimum seems to be much reduced, if not absent. Therefore, while hypoxic cells can repair damage, they appear to be doing things that are different in the interval between the two exposures. What they are doing differently, as we shall discover in a moment, has to do with their ability to grow and progress in their growth cycle in the fractionation interval.

An understanding of repair of sublethal damage becomes intimately involved with another major topic in cellular radiobiology, i.e., the variation in the survivability of cells as they progress through their life cycle. Figure 11 shows a sketch that many of you may be familiar with. It indicates the major features of the cyclic properties of the mammalian cell. When cells go through division, they enter a period called G_1, in which they do not synthesize DNA, then a period in which they do called S, and this is followed by a second period of no DNA synthesis denoted by G_2. This particular age cycle has as its major dimension, the DNA cycle of events. Other parameters can be used to denote age but this is a convenient one, and one of the most important.

Methods exist for examining radiation and other properties of cells as they progress through their growth cycle. Figure 12 shows one example of this for Chinese hamster cells insofar as concerns radiation survivability. At zero time on the abscissa, we synchronized cells at the border between the G_1 period and the S period, that is, just at the end of their pre-DNA synthetic phase. Then, they progressed into the S phase, and were

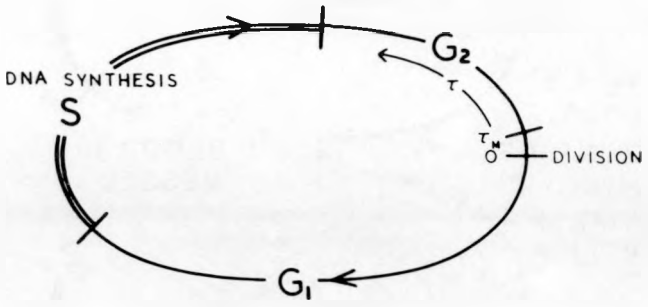


Figure 11.

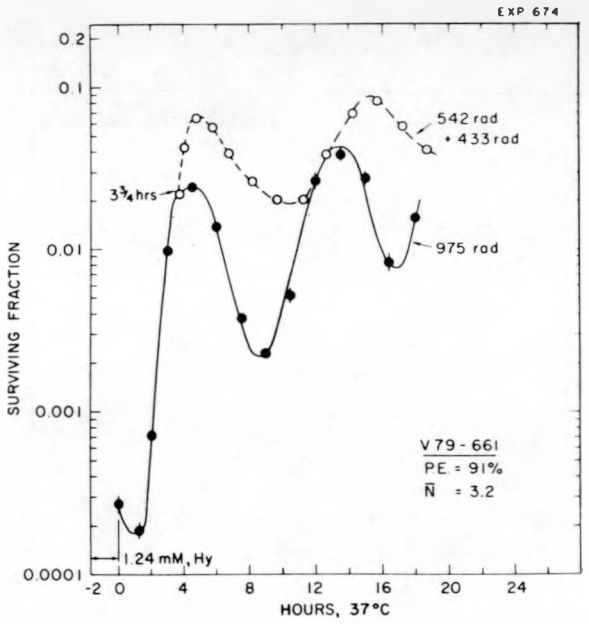


Figure 12.

irradiated with a fixed dose of radiation at various times. The closed circles trace out the variation in survival that was observed. This is by itself an important biological effect. Radiobiologists don't have an adequate explanation for it as yet, but the fact is that the survivability of cells depends very much on where they are in their growth cycle when they are irradiated.

We know from the work of Sinclair and Morton that the peak in this cycle corresponds to cells in the latter part of their DNA synthetic phase. Therefore, if an asychronous population of such cells is irradiated, the fact that there is this

variation of sensitivity will automatically select out the most resistant cells, or cells in the bottom half of S. In the fractionation experiment that is shown here, the series of fractionations was started at the peak in the age response pattern in order to see whether these cells would show a similar kinetics to those from asynchronous populations in view of the selection for resistant cells which radiation imposes. The results are traced by the open circles. There is prompt increase in survival, a drop to a minimum, and additional structure. The minimum comes from the fact that cells which survive at 3-3/4 hrs and begin to age during intervals between exposures must progress into a region of greater sensitivity, and, therefore, in addition to their repairing damage they are becoming more sensitive. Thus, the structure shown results during short intervals in a fractionation sequence.

It is important to know something about the age response patterns of cells in general. Figure 13 shows three simplified sketches, from three more or less distinctly different types of cultured mammalian cells. The age response pattern of Chinese hamster cells is one which is characterized by essentially a single maximum. For HeLa cells there appear to be two maxima. The patterns for mouse L cells depend very much at what level of damage the assay is performed, because at a high level of survival there is very little structure and at a low level a very significant amount of structure.

Figures 14-17 show some examples of repair of sublethal damage relative to important cell systems in the body. Till and McCulloch in Toronto, performed an experiment similar to ones already discussed, using an assay system devised for assessing

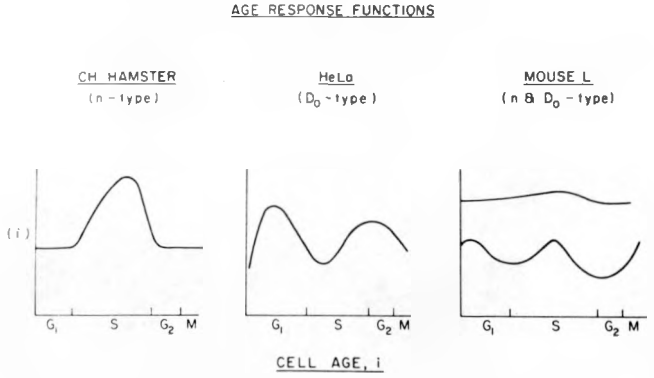


Figure 13.

proliferation ability of stem cells in bone marrow (Fig. 14). You can see that the curve has structure similar to the fractionation curves for Chinese hamster cells (Fig. 10). The magnitudes of the changes are considerably smaller. But, except for the fact that the time scales are different, the curves are very similar in shape.

To be sure that a curve such as the one in Fig. 14 represents a repair process, it is important to look at the overall fractionation survival curve. Figure 15 shows this for mouse marrow cells once again. The single dose survival curve is traced by the line without data. The fractionation curve for cells given a first dose at time zero, and then 12 hours later given graded second doses, is traced by the open and closed circles which come from two different experiments. There is a small shoulder which reappears in the time interval which elapsed, about 5 hrs. The point to be stressed is that the displacement of these curves from one another is small. The reason is the extrapolation number of the curve, or the quasi-threshold dose, is small, i.e., 40 or 50 rads, which is a rather small threshold for mammalian cells.

The reality of this last is evident from a comparison of the fractionation response of marrow cells to the fractionation response of stem cells of the mouse small intestine. Some experiments by H. R. Withers, involving the delivery of two fixed doses as a function of time between the doses, are shown in Fig. 16. For stem cells of the gut of the mouse, there is a very large increase in survival followed by a decrease once again and some additional structure at later times. The ratio of survival is not about 2 as it is for mouse marrow; it is a factor of 40 to 50.

Figure 17 shows portions of single-dose and fractionation survival curves. The curve on the left in each case is the same and results from single-dose data. All the curves are compared in the lower right panel. Aside from secondary qualifications (required for a complete discussion of these results relative to those in Fig. 15), it is clear that stem cells in the intestine have a much larger capacity to repair sublethal damage than do marrow stem cells.

The ability of cells to repair damage and the variation in this ability depending on cell type are

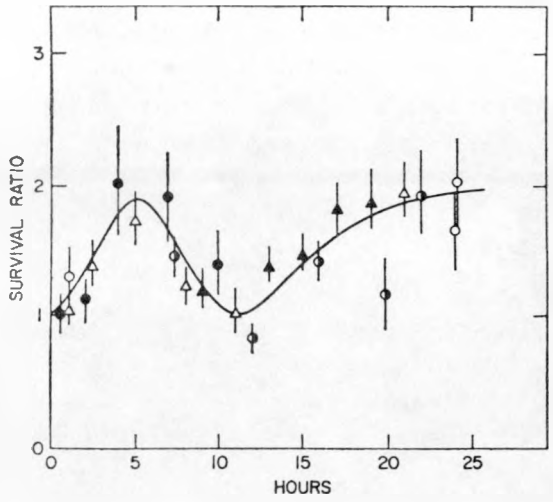


Figure 14.

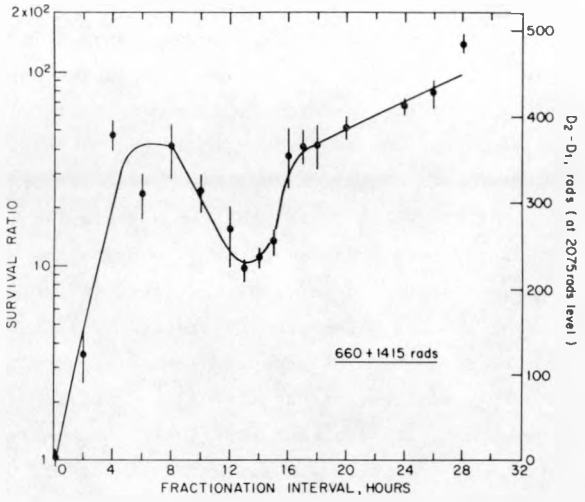


Figure 16.

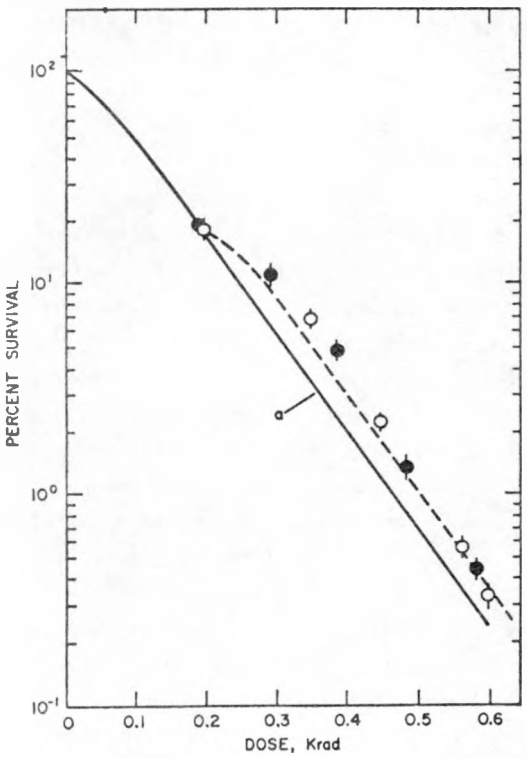


Figure 15.

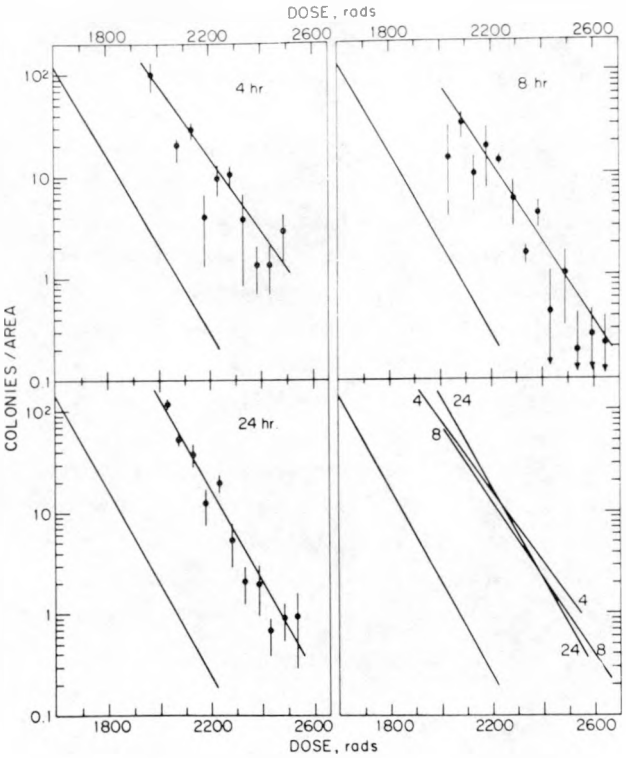


Figure 17.

very important considerations in radiotherapy. Figure 18 shows what the consequences might be over many fractions. Curve A is the single dose survival curve for the target cells involved. If we fractionate the treatment of these cells, and if we have a long enough interval for complete repair of damage between fractions, the survival to graded second doses of those cells that survived D_1 would be curve B. Those cells that do survive D_1 have a survivability which is displaced upward from curve A; curve B represents A redrawn from the new origin. If we continue our fractionation procedure after dose D_2, curve C would obtain following repair; after dose D_3, curve D; and so on. Line F results on the assumption of complete repair of damage between fractions and is exponential in theory.

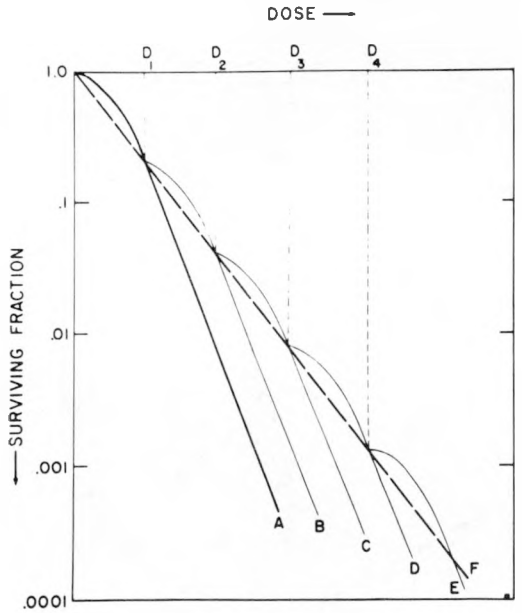


Figure 18.

The effect of fraction size, when complete repair of damage between fractions obtains, is sketched in Fig. 19. In the limit of very small fractions, theory and some data suggest that the slope of the fractionation curve should approach a small negative but non-zero value.

Thus, for a given total dose, the level of survival depends very much on the repairability of the cells involved. In addition to the predictions

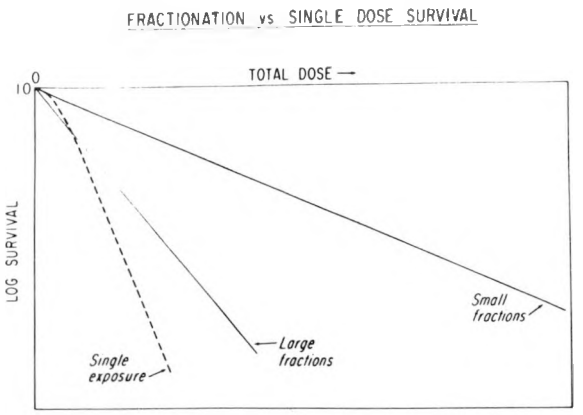


Figure 19.

of the survival curve itself (and the modification of these which depend upon the oxygen concentration) we have now another major factor, i.e., the ability of cells to repair sublethal damage. This can have very strong effect on the level of survival that is reached with a given total dose. To this point, I have said nothing about high LET radiation, and of course, it is highly apropos to get into that subject. Neutrons, and particularly fast neutrons, are a modality of radiation that has received considerable attention. In a broad sense, the LET spectra which result from fast neutron beams have a similarity to pi meson beams, and therefore we should consider some of the data relative to fast neutrons.

Barendson and associates performed neutron experiments dealing with different kinds of radiation (Fig. 20). As plotted, the curves form a series one below the other and having somewhat steeper terminal slopes, although this is not a very marked effect. They certainly have narrower shoulders, i.e., smaller extrapolation numbers and smaller D_q's. In general, fast neutrons are a form of high LET radiation, and give rise to relative biological effects greater than one because the survival curves involved fall off more rapidly.

Barendson has performed a number of experiments to measure things like the oxygen enhancement ratio for different neutron radiations. In Fig. 21 x rays are compared to 15 MeV neutrons, i.e., deuterons on a tritium target. The x-ray curve for aerobic cells, human kidney cells grown in culture, is curve 3. When these same cells are exposed under hypoxic conditions, curve 4 results; 15 MeV neutrons and

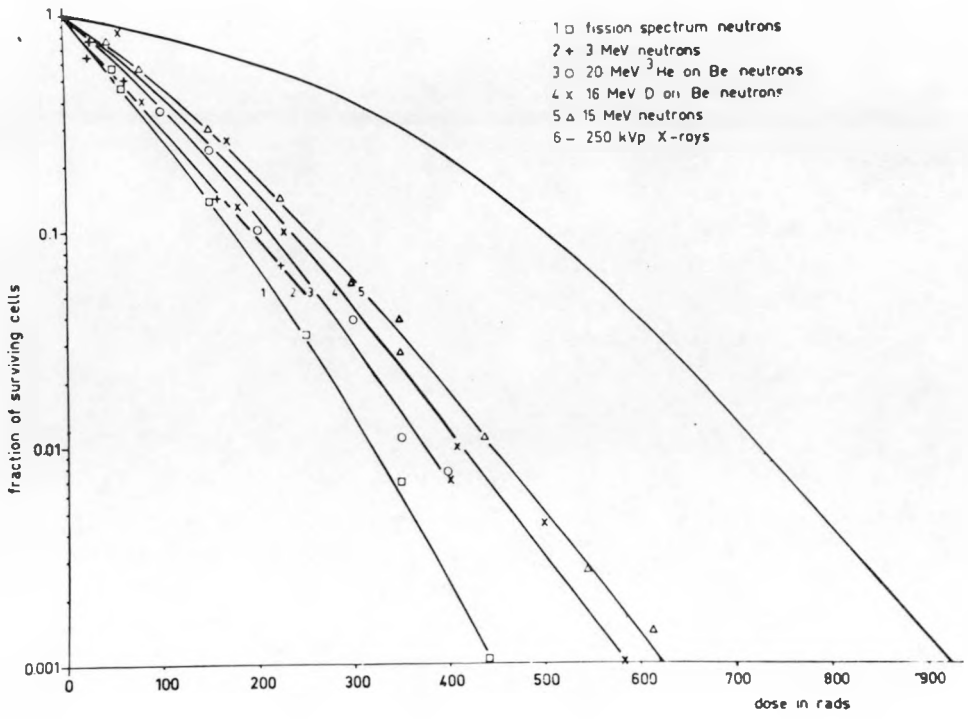


Figure 20.

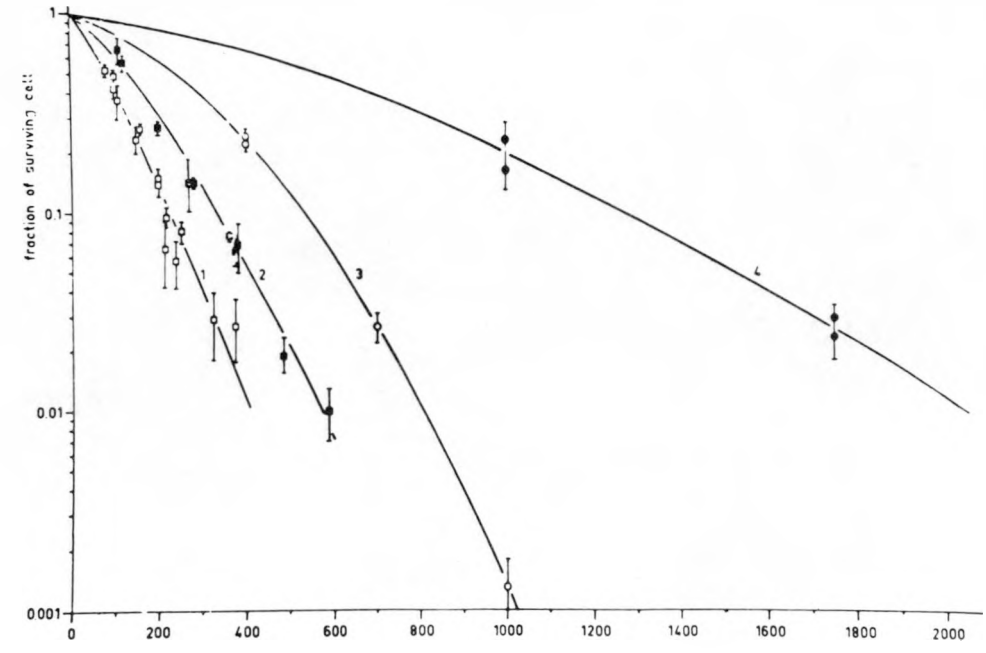


Figure 21.

hypoxic conditions yield curve 2; aerobic conditions, curve 1. In addition to the strong relative biological effectiveness made evident by the curve shifts for a given oxygen status, there is also a much reduced oxygen enhancement ratio.

Data of this type are summarized in the review by Langham and Groce (Fig. 22). Track segment data of Barendson et al. yield oxygen enhancement ratios traced by the closed circles; the open triangles are from their neutron experiments. You can see that the OER does not seem to drop very much until somewhere in the region of about 30 keV per micron, and at about 100 keV per micron it is down to 1. For neutrons, however, the OER's remain in the region of about 1.5. The two squares for pi mesons are in part the result of inference. For pi mesons in the plateau it is known that LET's are low and, hence, an OER comparable to those obtained with x or γ rays is assumed. The point for pi mesons at the Bragg peak comes from the measurements of Raju, Richman, and their associates using the pi meson beam available in Berkeley and several biological systems. Recently Raju has made measurements with human kidney cells using the Berkeley pi meson beam, and in spite of the low dose rate and other technical difficulties, the OER is similar to OER's for the fast neutron data.

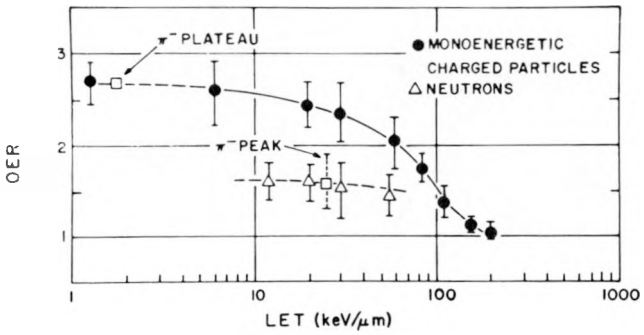


Figure 22.

So it appears that we have a fairly coherent picture with neutrons but unfortunately not enough data with pi mesons. The picture is somewhat more complex, however, as the examples to follow indicate.

Figure 23 is an experiment of Schneider's and Whitmore's performed at the Toronto Cancer Institute. They compared the survivability of a line of Chinese hamster cells to x rays and fast neutrons of model energy 3 MeV. A fairly typical shift in the curve

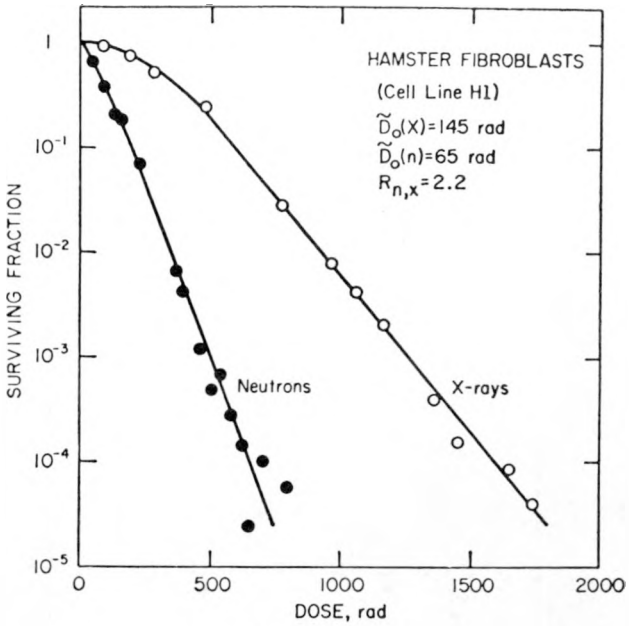


Figure 23.

results. There is a reduced D_0 and a much reduced extrapolation number. One would think, therefore, for this particular spectrum of fast neutrons, that there would be a very small fractionation effect because there is a very small capacity for sublethal damage, and that is, indeed, what they found. In Fig. 24 there are only a few data but nevertheless the result is quite clear. As a function of time between two neutron doses and with the same line of cells, Schneider and Whitmore found essentially no increase in survival, no fractionation sparing. All of this is quite consistent, but unfortunately with the same neutron spectrum and another line of Chinese hamster cells (Fig. 25) irradiated under oxic conditions, a rather substantial shoulder was observed and the nitrogen curve is shifted only slightly. Compared to OER values of 1.5-1.6 in Fig. 24 the OER is more like 1.1-1.2. This illustrates an inconsistency in two regards.

Here are some data of Hornsey and Silini (Fig. 26) having to do with mouse ascites cells irradiated in vitro and assayed for proliferation in the groins or axillae of mice, the end point being the production of tumors. When these cells are irradiatd with fast neutrons (modal energy 8 MeV), they yield a survival curve that begins with a very substantial shoulder, a good indication of a requirement for sublethal damage. Their fractionation response

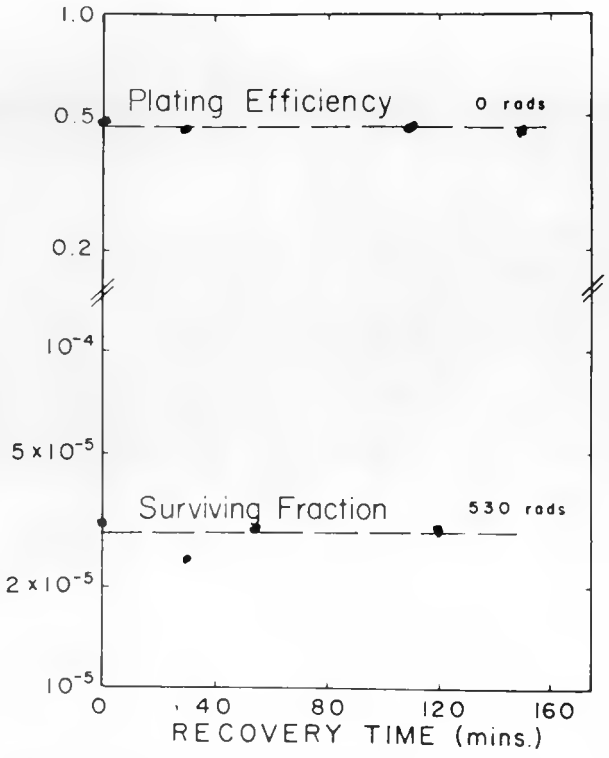


Figure 24.

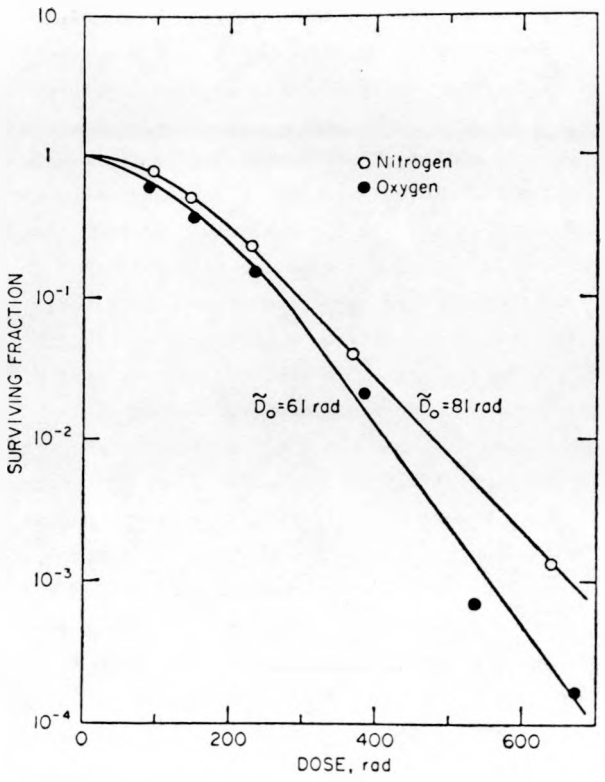


Figure 25.

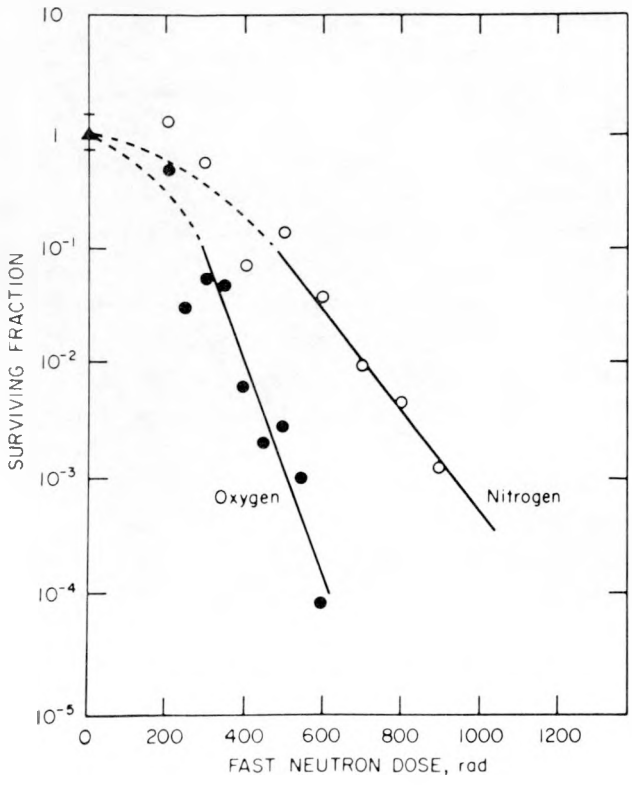


Figure 26.

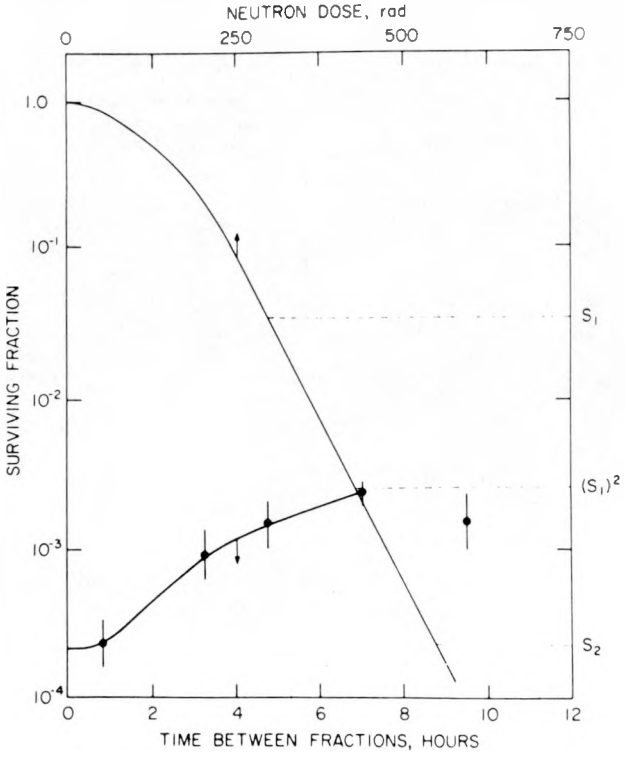


Figure 27.

is consistent with this (Fig. 27). The experiment in Fig. 26 also shows that the OER is of the order of 1.8-2.0 for these neutrons as opposed to 1.5-1.6 which would be expected from the data already presented. The survival increase in Fig. 27 is quite similar in magnitude to the increase found with fractionated x irradiation by Hornsey and Silini.

Figure 28 is an experiment of Withers' and illustrates what might be another exception to expectation in this case, having to do with the fractionation response of the stem cells of the mouse gut when they are irradiated either with x-rays or with fast neutrons (14 MeV). These cells, in spite of the fact that they are being irradiated with a presumed high LET radiation, have the capacity to repair sublethal damage. The main reason seems to be that they have such a broad shoulder for damage accumulation to begin with (x irradiation) that even though they are exposed to a reasonably high LET radiation, they still have a capacity for sublethal damage.

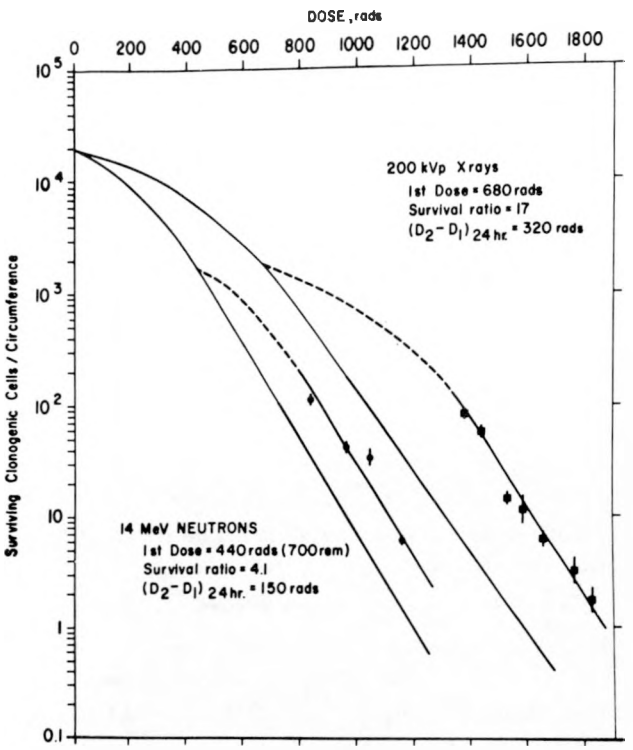


Figure 28.

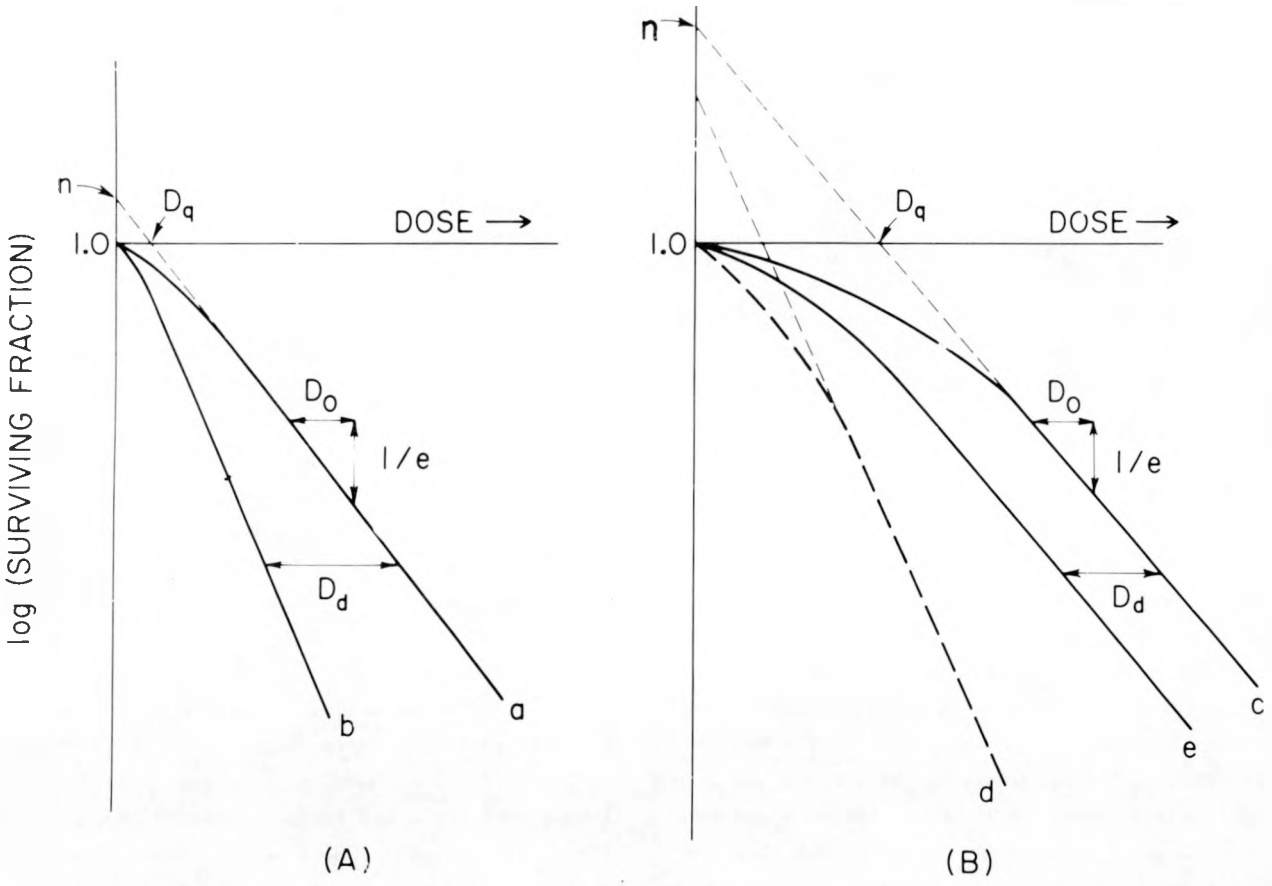


Figure 29.

Relative to therapy, Fig. 29 illustrates at least one last point which has to do with the question of differential effect; a question that is paramount not only in the case of low LET treatment of tumors but high LET as well. By differential effect, I mean that in order to adequately treat a tumor, it is important to maximize the damage to the tumor vs damage to normal tissues. Insofar as is known, any tumor can be sterilized. The problem is to sterilize it and still maintain the host in an overall state of viability and vigor consistent with life and the enjoyment of it. To optimalize a differential effect, one must optimalize damage in the tumor vs normal tissue. This is the name of the game for both low and high LET radiation. If we consider, for example, two cell systems, one being the tumor system and the other a normal tissue system that incidentally gets irradiated, we might characterize the situation by these two extreme cases. Figure 29a shows a cell system in which the shoulder is small, the capacity for sublethal damage is small, and we would expect a high LET radiation to shift the curve from curve a to curve b. The major effect would have to be a D_0 change because there is not much shoulder on which the radiation can work. There is very little capacity for sublethal damage and in an absolute sense, it cannot be reduced by very much. On the other hand (Fig. 29 b), if we have another line of cells which has a broad shoulder and a large capacity for sublethal damage, we could expect then that a high LET radiation would produce not only a D_0 change but also a decrease in the capacity for sublethal damage as well. This is pretty much what is demonstrated in many instances; that is, a shift from curve c to curve d.

Now, if d describes the effect of a high LET radiation on tumor cells and b on normal cells, we would then have a potentially significant benefit just on the basis of considerations of sublethal damage repair to begin with, because we not only achieve a change in D_0 but also a reduction in capacity for sublethal damage and therefore the ability to repair that damage. But if the reverse were true, if b corresponds to tumor cells and d to normal cells, using a high LET radiation would be disadvantageous because now we would find that the ability of our normal tissue to repair damage would be compromised by the fact that these cells have a reduced capacity for sublethal damage. So it would depend very much on which cells are the target cells and which are the incidentally irradiated cells, whether or not a benefit from a particular radiation modality is to be expected.

Summary

In summary here are some of the measurements we should have to help assess the potential usefulness of pi mesons in radiotherapy. To begin with most of the high LET data available relate to only a few types of mammalian cells, largely human T-1 cells, from the work of Barendson and his associates. They are good experiments but should be repeated and extended. They should be repeated with slow growing and rapidly growing cells. They should be repeated with cells which are sensitive and cells which are resistant. And they should be repeated with cells that have a small capacity for sublethal damage like mouse marrow cells, for example, and cells which have a large capacity for sublethal damage like stem cells in the gut.

Secondly, all of these measurements should be done using both the plateau and Bragg regions of a pi meson beam. We want to know what the high LET and low LET effects are because we are not sure which kinds of cells are going to be the normal and which the malignant cells. Further, we want to know what are the RBE effects with these different kinds of cells. We want to know the OER and we want to know things about the ability of cells to maintain their viability, in spite of depleted levels of oxygen. If, for example, cells can be viable, when anoxic and able therefore to demonstrate a full oxygen sparing effect and such cells characterize the tumor, we would have one situation. But quite another situation obtains if the same degree of hypoxia is not consistent with cell viability since then a full reduced sensitivity should not be expressed.

To elaborate on this last point, I note again that one of the principal advantages that we associate with pi mesons is the reduced OER at the Bragg peak. Further, we have evidence from experimental tumors that there are zones of reduced oxygen tension. If, however, some types of tumor cells cannot sustain viability under degrees of hypoxia corres-

ponding to a full radiation sparing effect, the advantage of treating such cells with a high LET radiation like neutrons or pi mesons would be reduced.

In addition to the oxygen effect, there are a number of additional cell-based properties that should be studied as a function of LET like age-response patterns, division delay, survival independence, and so on. However, some additional considerations relative to tumors are in order.

When one goes through a gamut of experiments with cells in culture, the next logical step in building the framework for dealing with human situations is to consider animal tumor systems. A number have been examined. But unfortunately, insofar as the radiation therapy is concerned (as well as other areas of cancer therapy such as chemotherapy or even immunotherapy), most of the animal tumor systems that we have available are not similar at all to the human tumors that have to be treated. There is one principal difference, i.e., most animal tumors grow rapidly relative to chronological time. Most human tumors have cell cycle times of days if not weeks, while most animal tumors have cell cycling times of the order of a fraction of a day. If we contemplate daily fractions as the scheme to be examined, insofar as an animal tumor system is concerned, we must realize that we are treating relative to a biological time scale which is not the same as it would be for humans. So what we really have to be concerned with is the ratio of the fractionation interval to the cell cycle time and the question of whether this is or is not similar to the situation in the human tumor in question. If we want to treat daily, and we have tumors that may divide once a week, for example, we can expect one set of properties to dominate as opposed to treating daily when the tumor might divide every 12 hours. I think work done with animal tumor systems is important if only because it demonstrates that a lot of the cell work that has been done is really borne out in in situ situations. We do not yet have well-developed animal tumor systems which simulate adequately enough the situation in human tumors. Experimentation with human tumors may still have to be resorted to until such systems are available.

In addition to tumor properties, there are, of course, questions of differences in damage in normal tissue elements. When you irradiate a tumor you also irradiate its blood supply, stromatous elements, and incidentally, perhaps marrow, blood vessels, skin, and so on. You irradiate pieces of organs, and perhaps areas of the body involved with immune responses. We do not know, in detail, how low LET radiation affects these normal tissue elements. We certainly do not know how high LET radiation affects these same types of structures and tissues. Some of these data will come from neutron experiments to be sure, but that may not be enough, because after all, there are some uniquely important differences between neutron experiments and those contemplated with pi mesons. For example, the LET spectra are not the same, certainly not on a microdosimetric basis. Secondly, most of the neutron beams which will be available will be, by and large, low dose rate beams compared to the beam anticipated at LAMPF. The machines which are currently being talked about for neutron therapy are expected to have dose rates, initially at least, of 5 to 10 rad per minute. LAMPF dose rates are expected to be 100 rad per minute. Thirdly, there is always the possibility that unexpected things may result from new modalities. We do not have a set of first principles by which to guide ourselves in many areas of biology including radiobiology and often we have to resort to the pragmatic approach.

In spite of qualifications and reservations, I would like to conclude by just reviewing for you, and repeating in part what you will find so well laid out in the Proposal* by Wright Langham and David Groce, strong points which favor pi mesons. They are: (1) the favorable difference in depth dose vs surface dose, i.e., the difference between the Bragg peak dose and the plateau dose; (2) the reduced OER associated with the Bragg peak and not expected in the neighborhood of the plateau; and (3) with this reduced OER, a reduced capacity for sublethal damage and this implies a reduced fractionation sparing effect. For deep-seated tumors, therefore, I think there is a fairly good

*"A Proposal for a Biomedical Addition to the Los Alamos Scientific Laboratory's High-Flux Meson Physics Facility," W. H. Langham and D. E. Groce, LA-4490-P.

likelihood that a net advantage can be scored, at least in some instances, with the use of pi mesons.

Figure Credits

Fig. 1. T. T. Puck and P. I. Marcus, Proc. Nat. Acad. Sci., 41:452-437 (1950).

Fig. 2. M. M. Elkind.

Fig. 3. M. M. Elkind, H. R. Withers, and J. A. Belli, Frontiers in Radiation Therapy and Oncology, 3:55-87 (1968).

Fig. 4. M. M. Elkind, R. Swain, T. Alescio, H. Sutton, and W. B. Moses in Cellular Radiation Biology, Williams and Wilkins Company, Baltimore, pp. 442-466, 1965.

Fig. 5. L. M. Van Putten and R. F. Kallman, J. Nat. Cancer Inst., 40:441-451 (1968).

Fig. 6. J. A. Belli and J. R. Andrews, J. Nat. Cancer Inst. 31:689-703 (1963).

Fig. 7. W. Powers, L. A. Palmer, and L. J. Tolmach, J. Nat. Cancer Inst., Monograph 24, pp. 169-185 (1966).

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Fig. 9. M. M. Elkind and H. Sutton, Nature, 184: 1293-1295 (1959).

Fig. 10. M. M. Elkind. T. Alescio, R. W. Swain, W. B. Moses, and H. Sutton, Nature, 202: 1190-1193 (1964).

Fig. 11. M. M. Elkind.

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Figs. 18 and 19. M. M. Elkind.

Figs. 21 and 21. G. W. Barendson in Current Topics in Radiation Research, North-Holland Publishing Co., Amsterdam, pp. 293-365 (1968).

Fig. 22. W. H. Langham and D. E. Groce, "A Proposal for a Biomedical Addition to the Los Alamos Scientific Laboratory's High-Flux Meson Physics Facility," LA-4490-P, July, 1970.

Figs. 23, 24, and 25. D. O. Schneider and G. F. Whitmore, Rad. Res., 18:286-306 (1963).

Fig. 26. S. Hornsey and G. Silini, Int. J. Rad. Biology, 4:135-141 (1961).

Fig. 27. S. Hornsey and G. Silini, Rad. Res., 16: 712-722 (1962).

Fig. 28. H. R. Withers, J. Brennan, and M. M. Elkind, Br. J. Radiology, in press.

Fig. 29. M. M. Elkind, European J. of Cancer, in press.

BIOMEDICAL
SESSION II

1. Minutes of the Business Meeting of the LAMPF Biomedical Users Group
2. P. N. Dean, "Pion-Stopping Region Visualization Experiments"
3. M. R. Raju, "Present Status of Biophysical Experiments with Pi Mesons at Berkeley"
4. H. A. O'Brien, "Radionuclides from LAMPF for Medical Uses"
5. R. L. Hutson, "Biomedical Beam Line Status Report"
6. D. E. Groce, "Biomedical Facility Status Report"
7. A. S. Lundy, "Possible Diagnostic Uses of Muons"

Minutes of the Business Meeting of the
LAMPF Biomedical Users Group

At the Second Biomedical Session of the Fourth Annual LAMPF Users Group meeting held at Los Alamos, New Mexico, on Saturday, October 31, 1970, a business session of the LAMPF Biomedical Users Group took place under the Temporary Chairman, Stanley L. Whetstone (LASL and the University of Texas, Dallas), and General Chairman, David E. Groce (JRB Associates).

A proposed Charter for The Organization of the LAMPF Biomedical Users was presented. After due discussion, it was moved and seconded that the Charter be adopted. A motion to amend the Charter by the addition of Article III relating to changes in the Charter by a majority vote of those members attending an Annual Biomedical Users Meeting was moved, seconded, and passed. As amended, the Charter was then adopted by a majority of those present.

Nominations were requested by the temporary chairman for the position of Chairman of the LAMPF Biomedical Steering Committee. Chaim Richman (University of Texas, Dallas) was nominated from the floor. A motion to close nominations was moved, seconded, and passed. Chaim Richman was then elected Chairman of the LAMPF Biomedical Steering Committee by a majority of those present.

Under the Chairmanship of David E. Groce, nominations for the Biomedical representative for the Technical Advisory Panel (TAP) of the LAMPF Users Group were opened. Positions on TAP are filled by the Executive Committee of the LAMPF Users Group, but nominations were requested from each organized specific users group. The following were nominated:

R. J. Shalek, M.D. Anderson Hospital
L. H. Lanzl, University of Chicago
W. R. Hendee, University of Colorado Medical Center
M. M. Elkind, Brookhaven National Laboratory
Max Boone, University of Wisconsin Hospitals.

It was generally felt that the biomedical representation on TAP should consist of a radiation therapist and a nontherapist.

The business portion of the LAMPF Biomedical Users Group was then adjourned.

Respectfully submitted:

David E. Groce

David E. Groce

Pion-Stopping Region Visualization Experiments

Phillip N. Dean

Los Alamos Scientific Laboratory

A potential advantage of using negative pi mesons as a modality for radiation therapy is the possibility of *in situ* monitoring of the treatment volume. When a negative pion loses enough energy in passage through tissue to be captured by an atom, it goes into orbit about the nucleus. The particle then cascades down through the various atomic levels, emitting characteristic x rays just before capture by the nucleus and subsequent production of stars. Since these x rays originate at the point where the mesons stop and/or interact, a collimated position-sensitive detector with good spatial resolution can, in principle, be used to locate the point in two dimensions. There are also nuclear gamma rays produced in the stars, and these can be used for the same purpose. A report was presented at the Users Group meeting in Boulder last year on an experiment performed at Berkeley by Sperinde *et al.* on the measurement of nuclear gamma rays. It was a very successful experiment.

We have recently measured the pi mesic x rays in an experiment at Berkeley. The procedure was as follows: A pi meson beam is brought down a channel through three plastic scintillators and into an absorber, a tank of water in this experiment. A fourth scintillator is positioned behind the absorber. The pion beam had an energy of 70 MeV and a range of about 16 cm in water. The momentum dispersion was ± 3%. There was a contamination of 10% muons and 25% electrons in the beam. The electrons would pass completely through the absorber and be negated by the last scintillator. An attempt was made to trigger the electronics on pions only by making a time-of-flight measurement. As will be seen later, this was only partially successful.

A relatively small Anger camera, 6-1/2 in. in diameter, was positioned at the side of the absorber, centered at 16 cm from the beam entrance end. The front section of the Anger camera consists of a lead collimator 4 in. thick with 1/8-in. diameter holes. Positioning of the equipment is shown in Figure 1.

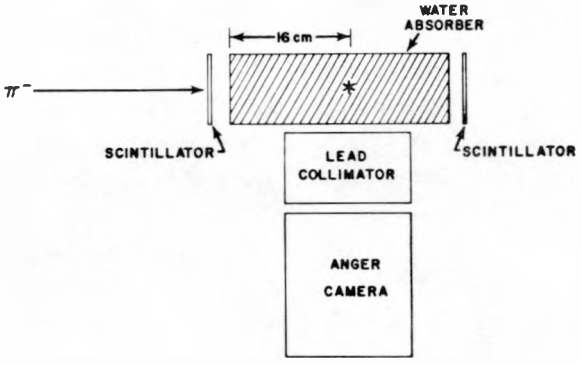

Figure 1.

Results of the measurement are plotted in Figure 2. A muon of the same momentum as the pion has a higher energy, in our case 84 MeV, and consequently a greater range, 21 cm. Muons also produce x rays when they are captured by an atom. The energy of the most abundant muonic x ray, 134 keV, is only slightly less than the energy of the pionic x ray, 160 keV. The muonic x ray is also about 10 times as abundant as the pionic x ray. Consequently, the 10% muon contamination could produce as many x rays as the pions. In the graph, the peak at 16 cm is due to the pions and the one at 21 cm to the muons. The energy acceptance window in the Anger camera was set at 100 to 200 keV to get as high a counting rate as possible. The dashed line represents the

distribution of Y coordinates. Since the beam is 4 in. square in cross section when it enters the absorber, we would expect to see a peak about 4 in. wide. The pion peak is about 3 cm wide, which is about what is to be expected from the momentum dispersion of ± 3%. The spatial resolution of the Anger camera is about 1.8 cm, full-width at half-maximum.

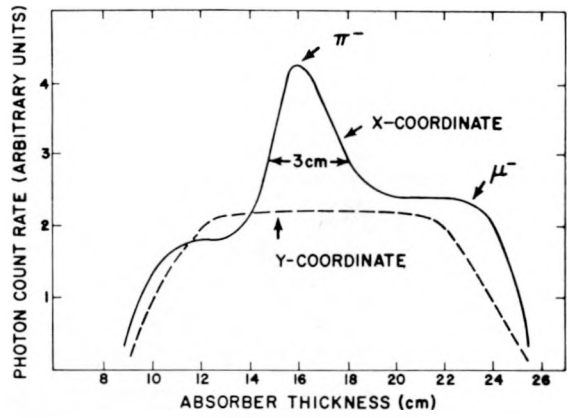

Figure 2.

We had another detector which we had hoped to use to detect the x rays. It is a multiwire proportional counter with a wire spacing of 3.8 mm. Two of these wire planes are mounted at right angles so that we can get both X and Y coordinates from a single counter. When an event triggers the counter, we can read the wire numbers directly into a computer. We did not have enough time to try this counter for detecting the x rays, but we did put it in the pion beam to see whether or not it could be used to look at the intensity profile of the beam. In this application it worked very well.

In summary, it now appears that it will be possible to monitor in situ the treatment volume in pion radiotherapy using either pionic x rays or nuclear gamma rays.

Question: What were the beam intensities and number of counts that you got?

Answer: About 3000 pions per second and about 20 good events per minute.

Present Status of Physical and Radiobiological Experiments with Pi Mesons at Berkeley

M. R. Raju

Lawrence Radiation Laboratory

I will just give you a short summary of what we have done all these years. Most of this information is published and, if you'd like the information, please write to me.

Measuring doses with an unconventional source like this is always difficult in the beginning. We try to get the basic information, but some of the main problems of dosimetry have not been solved. For example, if you want to measure the dose due to high-energy charged particles, the wall material of the ionization chamber is not critical, because the ionization is directly in the gas.

But, on the other hand, if you're measuring dose from, let us say, fast neutrons, then the interaction in the gas is very small and in the wall material is large, and hence the composition of the wall material of the ionization chamber is very important.

In the case of mesons, you get both situations. In the region where mesons do not stop, the wall material is not critical, but in the region where mesons stop and produce stars, wall material is important. In addition to this, the use of the Bragg-Gray relation in estimating the doses is also questionable for this application. So I cannot say the doses we have measured are absolute doses, but they are perhaps within 10%.

We tried to solve the problem in the following way. We measured the depth-dose distribution of mesons using tissue-equivalent ionization chambers where the question of wall effect would come into play. We also measured the depth-dose distribution using semiconductor detectors made of silicon. There is no wall effect in case of silicon detectors and the energy is deposited directly in the detector. When we used the ionization chamber, the interaction was in the wall, and we compared the depth-dose distribution of these two, and there is a good agreement between them. Now what does it mean? Does it mean that the Bragg-Gray relation is nothing to worry about? Does it mean that the interaction in silicon is the same as in tissue-equivalent material? Does it mean that the combination of these two effects cancel each other? I wish I could answer that question, but we do not know. But what I can say is that from what we know, the interaction in silicon may not be significantly different from that in oxygen, because silicon is an alpha structured nucleus, like oxygen. So if we accept this fact, then perhaps the Bragg-Gray relation might be applicable.

And then the second question is, how important is tissue-equivalent material? As you all know, tissue-equivalent material is not really tissue equivalent, because you cannot make a plastic that is exactly like tissue. Since you cannot load as much oxygen in a plastic as there is in tissue, then you always make some sort of compromises, taking the interactions into consideration so that the interaction in plastic from the radiation would be quite similar to that in tissue.

The result is we have different tissue equivalent plastics for gamma radiation, and neutrons, and so on. I am very sorry to hear that Dr. Shonka, who has contributed so much to this field, unfortunately is not with us any more. This could have a very bad effect. Dr. Shonka prepared a special plastic for me taking π meson interaction into consideration. The hydrogen content in this plastic is less that of

tissue. This does not make significant difference because the stars form from heavier elements in tissue. The composition of this special plastic is adjusted so that in addition to being quite close to π^- interactions in tissue, its response is the same for $^{Co}60$ gamma rays as I.C.R.P. muscle-equivalent plastic. Dr. Shonka also kindly made one set of thimble type ionization chambers with the special plastic and another set with I.C.R.P. muscle-equivalent plastic.

I measured the depth-dose distribution of π^- mesons using ionization chambers made of these two plastics. I did not get any significant variations. The beam that we used had nearly 25% electrons and 10% μ mesons. But anyway, what I am saying about the contamination is: the dose at the peak is not all due to the stars, but some of it is due to the contamination too. For the contamination part of it, the material used really does not make too much difference.

The calculations of the depth doses and the comparable experimental values would become reasonably close if you apply an important correction in the calculation. And that important correction is: all the mesons do not reach the region corresponding to the range of the pion. Some of them interact on the way in, and they get lost. Nearly 40% of the particles are lost so that only 60% remain by the time they come to the peak and give you stars, for the beam that we used, which is about 90 MeV. If you apply this correction for calculated depth-dose curves, then what you measure would be reasonably close to what you have expected from the calculations.

And I must say that, as far as solving these dosimetric problems are concerned, we really do not have to wait till a beam will be available here. Dr. Richman pointed out, and as Phil Dean's and other results indicate, we can do most of the dosimetric problems with existing beam at Berkeley. In some cases intense beams are a problem, because if you want to do pulse analysis, we already have about 10^6 particles per second, and you cannot handle too well intensities that are much higher than that. But, however, high intensity beams are very useful for absolute dosimetry such as calorimetry, which cannot be used now with the current beams because of low intensity. We also measured LET distributions in collaboration with Art Lucas and obtained fairly reasonable agreement with the theory although there is also a lot of room for improvement there too. And those results indicate that at the peak, nearly 20% of the dose is due to events greater than about 50 keV per micron. The rest of the dose is due to π mesons passing through and the low LET components in the stars.

In addition to this, in collaboration with John Sperendi, Perez-Mendez, and others, we have also looked at the gamma rays coming out of the stars, similar to the experiment that Phil Dean has described to you. Nearly 1 or 2% of the stars give high-energy gamma rays. By looking at these high-energy gamma rays, using spark chambers, you can pinpoint the region where the mesons stop. Our results clearly indicate that this can be done in practice.

I will just give you a short summary of the radiobiological experiments. It was felt that the presently available pion beam at Berkeley is not suitable for radiobiology, but with the motivation from Dr. Richman and Dr. Lawrence, we went ahead and tried to do the best we could. Depending on the way you focus the beam, the dose rate we obtain is anywhere from about 5 rads per hour to about 70 rads per hour. This 70 rads per hour is delivered over a region of 2 by 3 cm. Various biological systems were used. In one of our earlier studies we measured anaphase bridges in bean roots--this work was done by Dr. Richman's son, who showed that the anaphase bridges at a peak region are more than at the entrance. Ascites tumor work was done by Jose Feola, who measured the biological effect at the peak region. He got an RBE of about 5. This increase in RBE is due to two factors: (1) his system is an anoxic-cell system, that means he is measuring not only RBE but RBE times the OER, with the result that the RBE of his system is higher; and (2) the dose rate being low, the recovery factors being different with conventional radiations and mesons.

Mr. Loughman from the Donner Laboratory looked at the chromosome aberrations of these ascites tumor cells, and he estimated an RBE of about 2.5.

I have done some experiments with bean roots in collaboration with Mrs. Gnanapurani and Dr. Amer. The RBE that we obtained was about 3, and the OER that we obtained with that system is about 1.5.

Recently, we also measured arginine reversions in yeast cells, and again we did measure both RBE and OER with that system. We also measured RBE and OER with the tissue culture. A summary of this was very well presented by Dr. Elkind in yesterday's slides. The RBE values were about 2.5 and the OER about 1.6.

Now remember that we measured the effect only at the peak point. We are at present planning to do experiments at points across the star region and see how much variation in RBE we would get over the pion stopping region. You can expect high RBE at point 3, slightly lower at 2, and even lower at 1 (Fig. 1). This is because a pion has to pass through regions 1 and 2, and that particle deposits a dose at lower LET in this region as compared to region 3. So that means that the LET increases with depth.

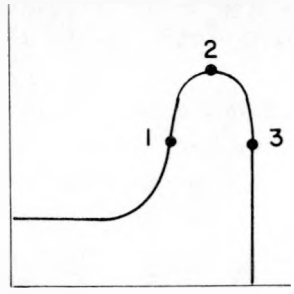

Figure 1.

These measurements are very important because of variations of LET distribution--the dose in the tumor volume may be the same but the biological effect would be different. The biological effectiveness at the tumor volume decreases with increasing size of the tumor. We are also planning to measure the radiosensitivity (pion sensitivity) as a function of cell cycle.

Question: Aren't you surprised that there's 40% loss in the primary pion beam in that area?

Question: I was going to ask you that also. Is that for the 70 or the 90 MeV? That seems high for the 70 MeV beam; I think that's for the 90.

Answer: It's about 90 MeV. However, I would imagine that you should expect a loss of between 25 and 40%, depending on what depth you are treating.

Comment: You must remember that this beam goes a distance of 8 inches. That's a long way, 8 inches of tissue. It's no wonder that the loss is that great.

Raju: Also the problems of multiple scattering come into play and some particle loss would be due to particles being scattered out of the beam. What we measured is really the combined effect, and we should expect something like 30 to 40% particle loss depending on what depth we are treating. It is not really surprising, but it is slightly higher than the numbers used in the calculations. This is why there is a difference between the calculated depth dose and the experimental values.

Question: What happens to the energy of the scattered particles?

Answer: Some of them undergo nuclear reactions. A considerable fraction of the dose due to these events will be deposited outside the beam path.

Radionuclides from LAMPF for Medical Uses

H. A. O'Brien

Los Alamos Scientific Laboratory

Introduction

We are planning to utilize the residual proton beam from LAMPF to produce a variety of radionuclides primarily from proton-induced spallation reactions. Efforts in this area were initiated about a year and a half ago, and I reported on this at the last Users Meeting in Boulder. Rather than discuss any parts of this program in any detail, I will summarize briefly our concept of what the irradiation facility will look like, several examples of specific radionuclides that may be of interest, our experimental program planned for next year, and, finally, what you can do to help us get this program going.

Spallation Reactions

What takes place during a spallation reaction? How do the products from these reactions differ from those obtained from present nuclear installations?

When the bombarding particle possesses a kinetic energy of about 100 MeV or greater, spallation reactions are induced. These are characterized by the ejection of many nucleons from the target nucleus. The types of particles ejected during the spallation reaction include pions, neutrons, protons, deuterons, and heavier fragments. Also, the residual nucleus is usually left in a highly excited state and will de-excite by the evaporation of a similar spectrum of particles. These ejected and evaporated particles can, in turn, interact with other target nuclei, resulting in an increase in the yields of products relatively close in mass to that of the target. This latter phenomenon has been called the thick-target buildup effect.

The radionuclide products from a reactor are most generally neutron-rich nuclides of relatively low specific activity. To a lesser extent, the fast component of the reactor neutron spectrum has been used to prepare carrier-free products by the (n,p) and (n,α) reactions.

Low-energy accelerators are used to produce a variety of generally neutron-deficient radionuclides. The radionuclide products from both these accelerators and reactors are fairly close to the line of stability, because the kinetic energy of the bombarding particle is insufficient to reach farther out.

On the other hand, by using 700- to 800-MeV protons as the bombarding particle, products typically from 10 to 20 mass units away from the target can be obtained in good yields. The significance of this is that soon we will have the ability to reach essentially any nuclide of interest.

Isotope Production Facility

The Isotope Production Facility will be located downstream from the biomed target, and just in front of the main beam stop (Fig. 1).

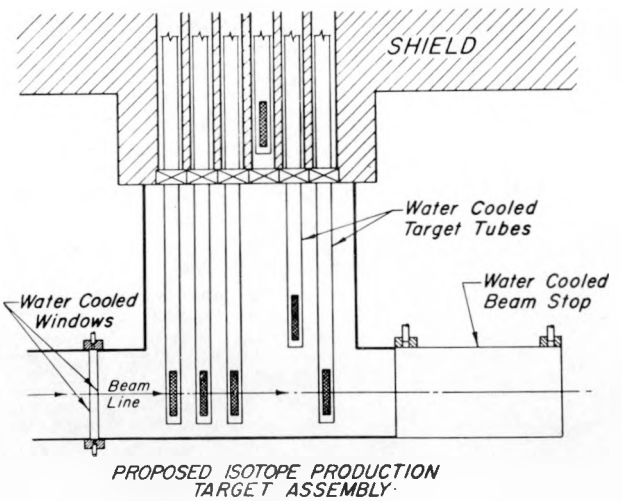

Figure 1

The target assembly will have six target stations, each of which is independently operated. This gives us the flexibility for choosing the optimum irradiation time for each target-product combination. Each station will accommodate a target or combination of targets up to one inch thickness, and will have provisions for cooling, instrumentation, and retraction mechanism so the tube can be withdrawn from the beam when not in use. We are also planning to equip one of the target stations so that we can continuously remove gaseous products during irradiation, such as for the removal of 2-hr Xe-123 for I-123 production.

Recent estimates show that if all of the target stations ahead of this facility were loaded, a 1/2-mA beam of 700- to 750-MeV protons will impinge on our first target. Taking into account both beam attenuation and scattering, we calculate that the last target will see about 25% of the initial beam. We estimate that a 50-μA beam of about 500-MeV protons will emerge from our last target.

All of the calculated yields I will present later are based on the assumption that the target was in the first target station, and that it will see a 1/2-mA beam of 750-MeV protons. As far as we know now, these are realistic yields.

Radionuclide Products

Figures 2 and 3 show a representative list of some of the radionuclides we expect to make, together with their yields. These are intended to give you an idea of the variety of products that could be produced.

SPALLATION-PRODUCED RADIONUCLIDES OF INTEREST FROM LAMPF
(ASSUMED: 750 MEV; 1/2 MA; 1 IN. THICK TARGET)

PRODUCT	DAUGHTER	TARGET	YIELD (CI)	COMMENT
^{67}GA(78H)	---	AS	68/D	SOFT TISSUE TUMOR SCANNING AGENT
^{68}GE(280D)	^{68}GA(68M)	AS	0.32/WK	SHORT-LIVED POSITRON EMITTER FOR MULTIPLE APPLICATIONS
^{72}SE(8.4D)	^{72}AS(26H)	NB	8.7/WK	^{72}AS HAS SHORTER $T_{1/2}$ AND EMITS 3 TIMES AS MANY POSITRONS AS ^{74}AS
^{82}SR(25D)	^{82}RB(75S)	NB	26/WK	SHORT-LIVED RB FOR RAPID DYNAMIC FLOW STUDIES
^{83}RB(83D)	^{83M}KR(1.9H)	NB	15/WK	KR FOR LUNG AND BLOOD DYNAMIC STUDIES
^{123}I(13H)	---	LA	27/D	ABOUT 1% THE DOSE TO PATIENTS AS ^{131}I
^{172}HF(5Y)	^{172}LU(6.7D)	TA	3/MO	GENERAL PURPOSE RARE EARTH TRACER
^{194}HG(700D)	^{194}AU(39H)	TL	0.21/WK	LONG-LIVED PARENT OF USEFUL GOLD ISOTOPE

Figure 2

Gallium-67 has recently been shown by Hayes and Edwards of the Medical Division at Oak Ridge to be a valuable agent for localizing soft-tissue tumors, such as lymph-node tumors in Hodgkins disease. It decays entirely by electron capture, and its principal gammas of 93, 184, 296, and 388 keV are all within the energy range of conventional scanners. The 78-hr half life is convenient for shipping, but not too long to preclude its use on a routine basis. Since the other radioisotopes of Ga have much shorter half lives, we should be able to make this nuclide radiochemically pure. Our yield of 68 Ci/day should be more than adequate for all future demands for this nuclide.

Gallium-68 should be re-investigated for a number of reasons. It is a one-hour, positron-emitting nuclide which is available from a long-lived parent. With the new tagging procedures that have been developed in recent years, this nuclide may become a valuable, general purpose diagnostic agent. The main drawback to the use of this nuclide in the past was the low yield and high cost of the Ge-68 parent. With our yield of 320 mCi/week, this should no longer be a problem.

Rubidium-82 is an example of a very short-lived isotope that may be of value in repeated, rapid dynamic studies. It decays 96% of the time by positron emission to stable Kr-82, so it could be followed either by coincidence counting or by counting the single 511-keV gamma. It can be milked from a 25-day parent that can be made in high yield.

Iodine-123 is familiar to all of you. The problem with this nuclide up to now has been producing it free of I-124 contamination. We propose to isolate 2-hr Xe-123 from an irradiated La target, and to subsequently recover the I-123. Because Xe-124 is stable, no I-124 contamination would be present. However, I-125 from the decay of 17-hr Xe-125 will be present. We have calculated that, at best, we could produce an I-123 product with a 0.7% I-125 contamination. This product would be a great improvement over the currently-used I-131.

Figure 2 shows that three products, Se-72, Sr-82, and Rb-83, can all be produced from a common Nb target. This illustrates that each target will yield several useful radionuclides in substantial quantities. For example, the total yield of just these three is 50 Ci/week.

LONG-LIVED SPALLATION-PRODUCED RADIONUCLIDES OF INTEREST FROM LAMPF

(ASSUMED: 750 MEV; 1/2 MA; 1 IN. THICK TARGET)

PRODUCT	DAUGHTER	TARGET	YIELD (MCI)	COMMENT
$^{26}Al(7.4\times10^{5}Y)$	---	SI	0.026/MO	ONLY NUCLIDE SUITABLE FOR EXTENDED AL TRACER STUDIES
$^{32}Si(500Y)$	$^{32}P(14D)$	V	0.74/MO	LONG-LIVED SI TRACER
$^{42}Ar(33Y)$	$^{42}K(12H)$	V	6.0/MO	PARENT OF USEFUL K NUCLIDE
$^{60}Fe(10^{5}Y)$	$^{60M}Co(10.5M)$	CU	0.007/MO	A PRACTICAL USE?
$^{44}Ti(47Y)$	$^{44}Sc(4H)$	V	25/MO	POTENTIAL BONE SCANNING AGENT
$^{88}Y(107D)$	---	NB	20,000/WK	HIGHER ENERGY PHOTONEUTRON SOURCE
$^{202}Pb(3\times10^{5}Y)$	$^{202}Tl(12D)$	BI	0.036/MO	SOURCE OF USEFUL TL TRACER; YIELD MAY BE TOO LOW

Figure 3

Figure 3 shows that we will also be able to make usable quantities of long-lived radionuclides. The ones of most interest perhaps are Ar-42 and Ti-44. Both are long-lived parents from which useful daughters can periodically be milked. Potassium-42 applications in medicine are well known. The possibility of generating it in your own laboratory would be a significant advancement.

Scandium-44 decays 95% of the time by positron emission and 5% by electron capture. In addition to the 511-keV annihilation gammas, there is also a 1.15-MeV gamma given off per disintegration. Dr. Helen Woodard at Sloan-Kettering disagrees with the possible use of this nuclide as a bone scanning agent, but instead, believes it holds promise as a soft-tissue tumor agent. I don't know, perhaps she is right.

Experimental Program

Between now and the time the facility is available, we have planned a series of experiments using the 600-MeV protons available at the Space Radiation Effects Laboratory in Virginia. There are two major problem areas we would like to work on; namely, gathering experimental data on the thick-target buildup effect and initiating chemical separation studies.

As I mentioned earlier, the buildup effect occurs in thick targets and results in an enhancement of the yields of products relatively close in mass to that of the target. However, little experimental data are available. Thus we cannot take this effect into account in our calculations. We hope that our experiments will provide these data.

The chemical recovery of the products from these spallation targets will not be a trivial matter, because essentially every element below the target will be present in varying amounts following the irradiation. We are planning to select several targets now and carry out long bombardments. With these targets, we will begin working out the chemical flow charts for specific product recoveries.

Conclusion

We anticipate that isotope production could begin in January, 1973, or roughly two years from now. There is one minor problem: the AEC has not yet allocated funds for the target assembly. However, we are confident the funds will be made available when they are needed.

In the meantime, you can help us by supplying information as to which isotopes will be important to your work and why. This input will be used in our justification for the facility to the AEC. With the money as tight as it is today, gentlemen, we need every bit of help you can give us.

Biomedical Beam Line Status Report

R. L. Hutson

Los Alamos Scientific Laboratory

My responsibility is to initiate the design of the pion channel for the Biomedical Facility.

Biomedical Pion Channel Criteria

1. Capability of irradiating volumes up to 10 cm thick at mean depths up to 25 cm. Momentum acceptance of channel - 0.1856 MeV/c ± 8%.
2. Capability of irradiating a 10 x 10 cm field with a parallel beam, and a 15 x 15 cm field with a diverging beam.
3. Dose rates > 35 rad/min, uniform to ± 3% over the irradiated volume.

It is not clear at this point how much above 35 rads/min will be the capability. We'd like, optimistically perhaps, to shoot for dose uniformities of ± 3% over the target volume.

Figure 1 reviews some close distribution calculations done by Arch Thiessen 2 or 3 years ago, and it outlines what needs to be done with a pion beam to effect a desired dose distribution. His calculations show that if you had a pion energy distribution as shown at the upper left, then the depth dose distribution would be as shown on the lower left. Now this is certainly not a uniform dose distribution, but by shaping the energy distribution in a different way, we should be able to effect more flat-topped dose curves. So the problem with the pion channel is one of getting a configuration with which you can control the number of pions of a given energy over a prescribed energy range.

Let me say briefly how one goes about designing pion channels. You define your problem, then using your basic intuition of what can be done with a pion channel as far as control of the flux distribution and the momentum or energy distribution, you draw pictures of possible configurations which you think might be feasible for doing what you want to do. Then you go through pencil and paper calculations which are similar to any calculations you might do with a light optics system and determine whether you can really hope to do what you want to do within the limits prescribed for the channel.

After that things get more complicated. Here at LAMPF there is a computer program available, first developed at SLAC, which allows you to optimize beam channel designs using a first order approximation. This program uses some simplifying assumptions which allow you to arrive at a first-order design rather rapidly. After that you study second and higher order effects and see how far away you really are from what you want, and make the appropriate corrections.

What's being done now at LAMPF?

In consultation with Arch Thiessen and other people here at LAMPF, who have had a lot of experience in designing pion channels, and also in some conversations with Karl Brown at SLAC, we've arrived at two possible configurations which we hope will lead to a usable biomedical pion channel.

Figure 2 is a scale drawing of two preliminary designs to give a feeling for what the configurations look like. The first type is a simple two bend system. The slits shown at the center allow one to define the momentum bite of the pion beam. Another set of slits at the same position but in a plane perpendicular to the plane of the figure allows one to control the pion energy distribution.

The problems with the first type of channel are that there are second order effects arising

which one might not be able to correct easily. For this reason, we are also looking at the second type, a slightly more complicated system suggested by Karl Brown at SLAC. It's a three bend system with the center bend split into two pieces so that there will be space for the slits. We feel more optimistic about the possibilities for this design although both designs are being studied.

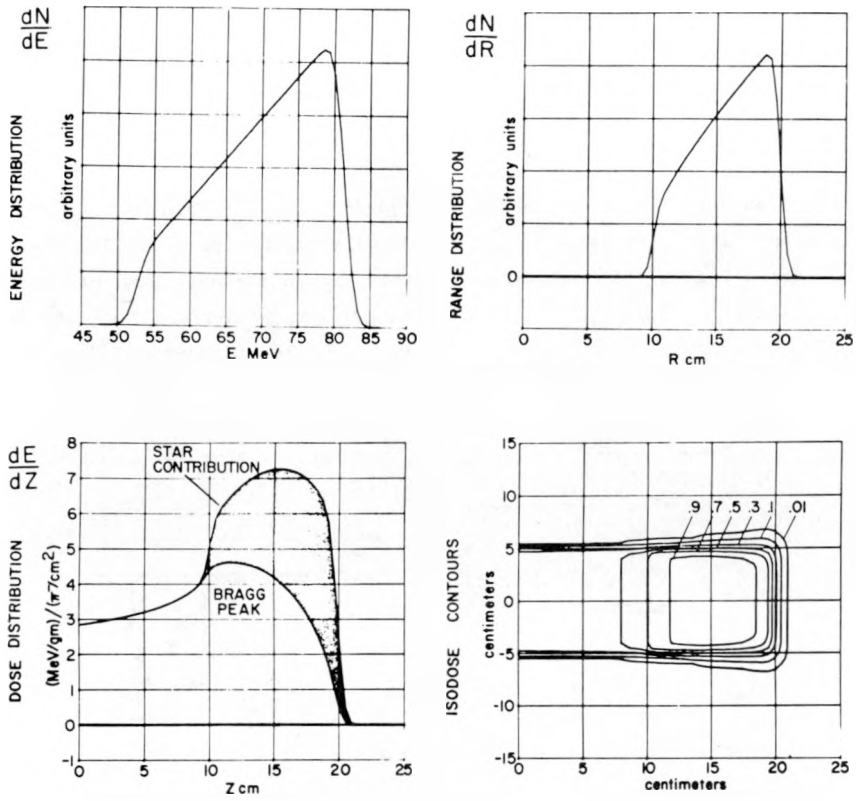

Figure 1. π^- stopping in H_2O; 30 MeV energy deposit/star; 26% $\Delta P/P$.

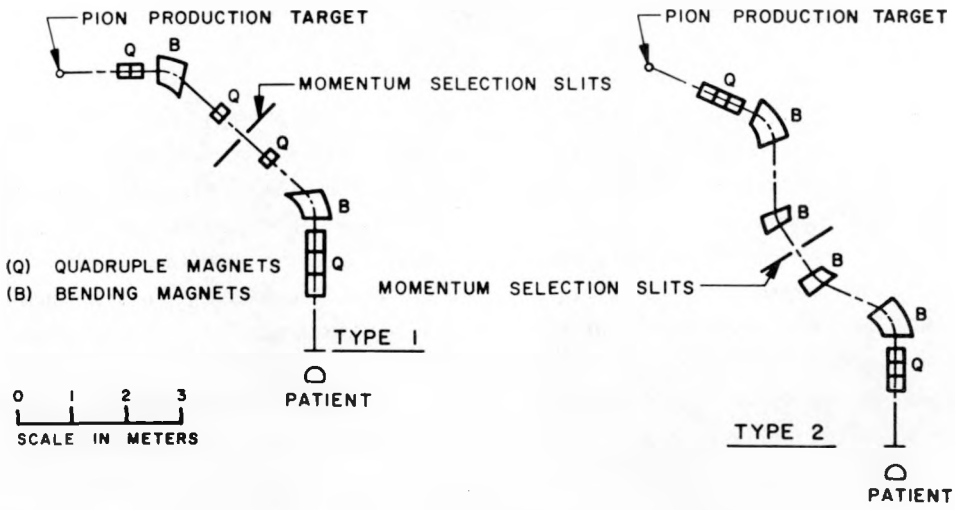

Figure 2. Two designs for Biomedical pion channel.

Biomedical Facility Status Report

David E. Groce

Los Alamos Scientific Laboratory*

I would like to tell you a little about the status of the biomedical facility. For those of you who haven't been here before, Figure 1 shows where the facility will be located.

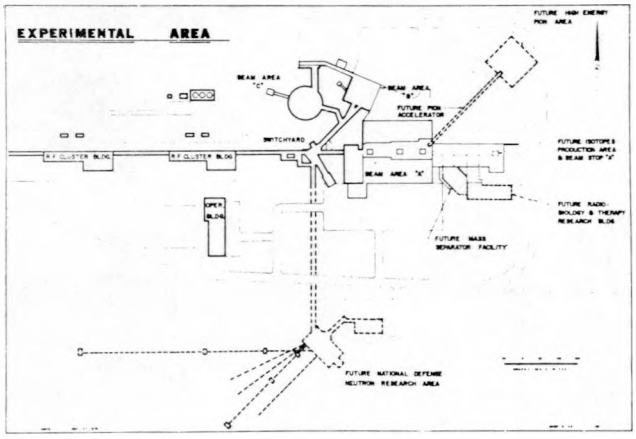

Figure 1

The main accelerator, of course, is a half-mile long and terminates in the switchyard. Here the beam is transported into several experimental areas, each with their specific physics uses. On the main high-intensity proton beam line two meson physics targets are planned initially, with a possible third added later. Next downstream will be a thin target used at an on-line mass separator for short-lived nuclear species studies. Finally, comes the biomed target and lastly Hal O'Brien's isotope production target at the beam dump. So the biomedical facility is near the end of the line with four targets ahead of it. Some of the proton beam will be lost before reaching us, but we will still have something like 700-750 MeV and, perhaps 1/2 to 2/3 of a milliampere. We will operate on a non-interference basis. Anything happening upstream, other than the beam being turned off, will not affect us, except that our dose rate may fluctuate up and down on, perhaps, an hourly or daily basis. It will be extremely important to monitor this dose rate as we operate.

Figure 2 shows a plan view of the proposed facility.

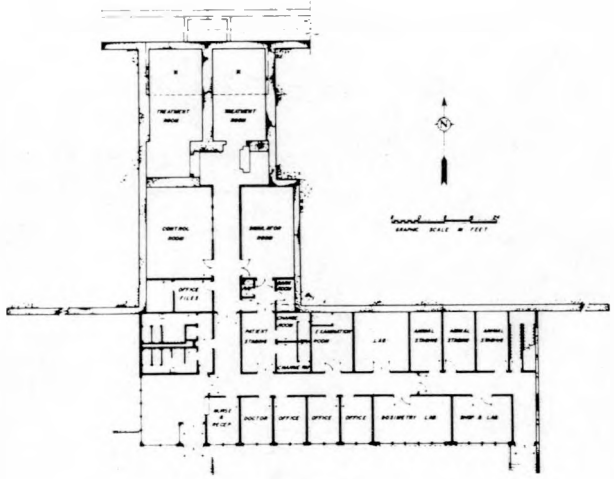

Figure 2

In the Ad Hoc Steering Committee meeting held this summer, it was proposed that we try to build into the facility enough flexibility so that two treatment rooms could be used some time in the distant future. We plan to build the shell of the facility next to the beam line first and then to add the internal shielding walls later -- either portable or temporary shielding. This would allow us to have two beam lines coming from the same target, one at 60° and one at 120° to the beam.

*Permanent address: JRB Associates
La Jolla, California

One room can be lengthened to allow room for a short muon channel for possible diagnostic uses of muons.

As some of you may know, we have not yet received funds for the biomedical facility from the Division of Biology and Medicine of the Atomic Energy Commission. However, at the last meeting of the Joint Congressional Committee on Atomic Energy, Dr. Rosen testified and requested that a certain portion of the money for the main construction be diverted for the basic frame and shell of the biomedical facility. This is in order not to delay the biomedical facility by having to shut down all of LAMPF for a period of possibly three to six months when funds do become available. The Joint Congressional Committee gave Dr. Rosen authorization to divert $300,000 for this purpose. Plans now are to form the basic shell of this facility to include all of the target handling areas, the therapy cell, the control room, and what is presently labeled 'simulator room' but which may have other uses as we go along.

As of now, we have preliminary plans for the basic shell in the hands of Giffels and Associates, the architect-engineer in Detroit. They will be starting preliminary engineering before the end of the year. We still do not have all of the exact configuration within this area defined as of this moment. For example, the floor height is one of the things we must be concerned about because it will depend on the particular beam transport system used. So we must either make decisions on items affecting the building design very quickly or design enough flexibility into the system to accommodate various schemes. We are awaiting input from several people, which may decide some issues.

With our present schedule, construction of the biomedical stub-out will start sometime in late spring or early summer of 1971. So time is getting very short, and we must make a number of decisions soon.

Figure 3 shows a section view of the facility with the main proton beam line at right angles to the biomedical channel, which is bent over and down into the patient position. The amount of shielding that will be required is tremendous.
In order to accommodate a patient in one treatment cell while the main proton beam strikes a target, and yet be able to occupy an adjacent treatment cell, shielding requirements will be something like nine and a half feet of solid steel and two feet of concrete. This gives you an idea of the potential of this proton beam. It is far beyond anything that has ever been built in terms of this type of accelerator, so we will have many problems that people have not had in the past.

In addition to a biomedical staff, we will require a beam transport system to get us on the air. Louis Rosen has stated officially that, if we have to use tents as offices outside the stub-out, or if we have to move in Butler buildings or trailers, we will do it. The planned set of offices, laboratory space, and so forth, is not totally required. The main portions that we could not get along without would be the exposure cells and the control room. The physical facilities for those are now under way.

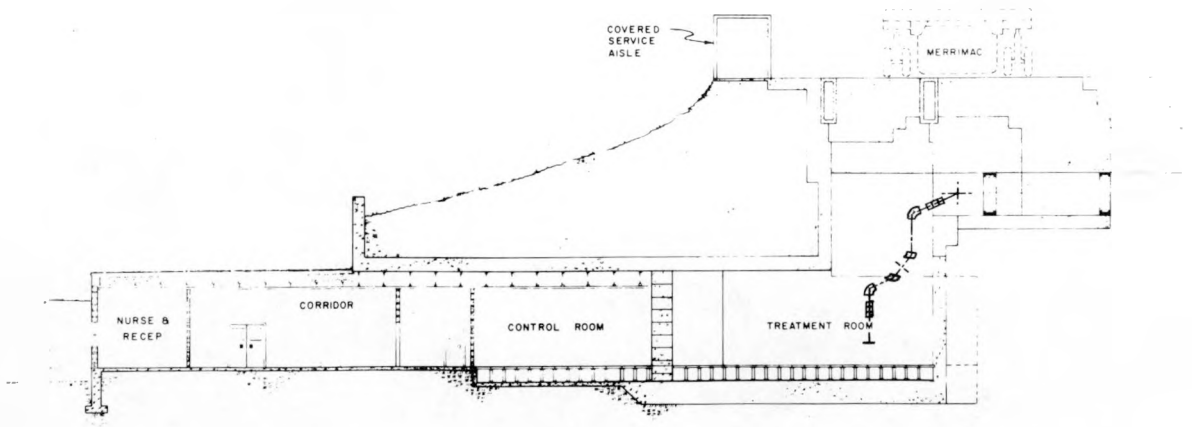

Figure 3

We are trying to maintain as flexible a layout as possible with the capability of a second beam being horizontal if necessary, or a second vertical beam. These decisions will be made later.

Question: Does the $300,000 include shielding?

Answer: Some of the shielding. We have a large stockpile of steel shielding from which we may be able to divert a quantity.

Question: Can you give us some idea of dose rate variation from upstream?

Answer: A maximum of a factor of three; with 35 rads per minute the lowest and, if we have all the beam to ourselves, about 100 rads plus.

Question: Will the beam drop without notice?

Answer: No. We will get notice, as will all users. However, we will not control our own beam lines. We will have a terminal to a local control computer which will then interface with the main accelerator control computer. All control of beam lines and main magnets is through a central operations room.

Question: Is the momentum slit to be variable or fixed and is it to be motor driven? Will the motor be buried in the shielding?

Answer: It will be variable and motor driven. Your last question points at one of extreme problems faced at LAMPF. All areas in primary beam targets are going to be extremely hot. Therefore, everything will have to be designed for minimum maintenance, and where maintenance is necessary a mobile shielded room with manipulators, referred to as Merrimac, will be wheeled down on four B-52 undercarriages, dropped down into place and maintenance done remotely. If we can get the motors into an accessable location, we will.

Question: What are some calculations of probable levels of induced radioactivity? Can you anticipate the increased levels of long-lived radiation?

Answer: Right near the target, it's kilorads per hour, at shutdown with long decay times. Most long-lived radioactivity will be in the vicinity of the target where the neutron energies are high. We'll have to worry about a certain amount of thermal neutrons and thermal neutron capture at the very outer limits of our shield. The patient himself is a very potent source of neutrons which come from the pion stars; hence we will have a source of fast neutrons right within the exposure cell. We will have to make some effort to minimize this activation, perhaps something like a thin absorbing layer on the walls. Calculations of this have not yet been done, but it may be a significant consideration. But, of course, since the neutron source is located at the tumor, it's the best of all possible neutron sources.

Possible Diagnostic Uses of Muons

A. S. Lundy

Los Alamos Scientific Laboratory

Louis Rosen has proposed a scheme for using negative mu mesons diagnostically to determine the elemental composition of tissue. This has had fairly low priority, but it's been proposed that we do an experiment later this year to find out more about this.

Muons are formed when pions decay in flight. So once one has a pion channel, it's a fairly straightforward process to obtain a muon beam. The muon is somewhat similar to a pion and has a rest mass 207 times that of an electron, slightly less than a pion. Its absorption process in tissue is somewhat similar to a pion and, therefore, the stopping region can be well defined.

When a muon enters tissue, it first loses energy by ionization. When the kinetic energy of the muon has been almost totally expended, it undergoes atomic capture into Bohr orbitals similar to the orbitals that hold the electrons of an atom. In this process it cascades down through the various Bohr orbital levels and emits characteristic x rays, or in some cases Auger electrons. These x rays have energies which are characteristic of the particular type of capturing atom. These characteristic x rays are considerably higher in energy than those from an x-ray target because of the higher mass of the muon relative to an electron.

The proposal is to irradiate tissue with a muon beam and look with an x-ray detector at the energy spectrum of the x rays that come off. This then, in theory, tells one the elemental composition of the tissue being irradiated. It turns out that when muons are absorbed, 95-100% of the muons will produce k-shell x rays, and these k-shell x rays are produced virtually instantaneously (within a few pico seconds). If you consider this on a per particle basis, the sensitivity of this technique is higher than that of neutron activation analysis, and correspondingly less irradiation goes to the patient. The x rays are emitted isotropically relative to the incoming muon beam, so there is a problem with geometrical efficiency, i.e., getting a detector surrounding the area.

We might call this technique mu activation analysis, keeping in mind that activation applies to activation of the atom rather than the nucleus. Before discussing some of the physical problems that we see with this technique, I'll talk about some of the ideas which have been generated for using this medically.

In theory, this is a technique for performing, in vivo, precise elemental analysis of the composition of tissue. One could study the variation in the elemental composition of tissue as a function of age, diet, disease, and so on.

Something which comes to mind immediately is the assessment of calcium in bone mineral which, of course, is currently done with neutron activation analysis. With this technique, it could be done in localized regions in bone, and with reduced radiation dose to the patient.

I'll list a number of other things which have been mentioned to me. Nitrogen quantification in certain organs was suggested. Since nitrogen is basic to protein metabolism, it has been suggested that it is probably important in certain disease states. Zinc studies may be done in the prostate for a possible correlation with prostate tumors. Sodium-potassium balance studies are also a possibility. When there is cell damage in tissues, there

is an exchange of sodium and potassium in and out of the cell. The idea is, possibly, in a heart attack victim, that you actually scan the heart with a muon beam and produce a picture of the distribution of potassium in the heart muscle.

Apparently magnesium enters in a number of diseases and might be studied. Spring and Väyrynen reported in the Journal of Physics in Biology and Medicine, changes in carbon concentration in tumors during radiation therapy. It was suggested that this variation in carbon concentration may indicate both the degree of cell-cycle synchronization resulting from fractionated therapy and the cell-cycle time. Obviously if this were true, this would be very useful in radiation therapy.

I might mention in connection with this that, in low Z elements (Z = atomic number) such as carbon, when pions are absorbed, pionic atoms are formed momentarily and characteristic x rays emitted. There is the possibility of doing carbon concentration studies simultaneously with therapy.

In this technique, two physical problems stand out: First, it's necessary to know the mu capture probabilities of various atoms. Unfortunately, in composite materials, this is not well known or understood. In metals, capture probability follows the Fermi-Teller "Z" law and is proportional to the number of atoms times the Z of the atom. In insulators it appears to go directly as N (the number of atoms per unit volume). Further, there's evidence that in chemical compounds, the chemical bonding affects the capture probability. This is not well understood. These effects may, however, be small enough that they're not too serious.

The other problem that is seen is that Compton absorption in the detector from x rays of elements with higher energy x rays will mark out the signal from some elements with lower energy lines. Therefore, we need to look at what sort of a x ray spectra we would get from tissue and see what elements we might assay. We're in the process of doing this. I've plotted line spectra for the k lines and l lines and assigned intensities relative to tables of tissue composition. The radiochemistry group here at LASL (J-11) is in the process of putting spectra together to represent this. They have recorded spectra with germanium-lithium drift detectors from virtually every available gamma emitting nuclide. They're taking spectra from appropriate nuclei, which have gamma lines near these mesic x ray lines, and adding these together with relative intensities for tissue applied. Within a couple of weeks we should have some idea what elements one could assay in tissue with this process.

If this looks promising, we'll probably go ahead and plan to do an experiment on a cyclotron sometime this year to see just what accuracy can be gotten with this technique. At this point, we're interested essentially in people thinking about this: What sort of clinical and biological uses might we put this to?

BIOMEDICAL
SESSION III

The third Biomedical Session was very informal with considerable free exchange of ideas. Hence most of the three-hour session has been summarized for expedience and much duplicate and extraneous material has been deleted.

1. Louis Rosen, "Introductory Comments"
2. R. E. Anderson, "NCI-UNM Planning Grant"
3. M. R. Raju, "Dosimetry"
4. Max Boone, "Hammersmith Clinical Trials"
5. Michael Holland, "Nevis Modification"

SATURDAY AFTERNOON GENERAL SESSION

Introductory Comments

Louis Rosen

Los Alamos Scientific Laboratory

I want to give you some background information so you will know how this over all endeavor stands. First of all, a few words about the news item from San Francisco announcing that a new laboratory has just been built and pions for radiotherapy are imminent. I think this was not a case of misleading the public but simply tremendous confusion between the people providing the information and the science writers for the newspapers. In this country, there is in the offing, in my opinion, no radiation therapeutic facility based on pi mesons unless it uses the LAMPF accelerator. Electron machines, as near as I can tell, will not be able to produce the basic beam parameters which I understand you, as biomed users, want. These are 100 rad/min over something like 1000 cc of tissue volume.

The reason this is so is because of the fine structure constant in nature, which has the value of 137. This means that for the electromagnetic interaction to produce pions requires something like 140 times the beam for a given pion production as is required when protons produce these pions. This is very crude, of course, and there are second order corrections, but what I say is essentially correct.

We know that with LAMPF it will take about 0.5 mA, average proton current, to give you this 100 rad/min over 1000 cc. If you want to do this with electrons, you need roughly 100 times that beam, which is a completely nonsensical type of beam intensity to talk about. So, if there are going to be clinical trials under actual operating conditions using pi mesons in radiotherapy, it will have to be done with proton accelerators. Some things might be done with the Columbia cyclotron, which will have roughly 1/10 or 1/20 of the beam we shall have, and certainly, many radiobiological experiments, even those on small animals, and tissue culture experiments, could be done there. Dr. Lederman, the director of the Columbia Laboratory, a few weeks ago called to advise me that we would be most welcome to set up experiments at Columbia as soon as they have a pion beam available. This is something all of you should keep in mind as you plan your programs. It would be very nice if we could imagine some of the electron machines, which will be on the air in the next few years, helping us in this program. I think maybe they could help in some of the radiobiology and dosimetry if they were so disposed. But, in my opinion, they will not be applicable to clinical trials and certainly not to actual therapeutic treatment.

Secondly, all the work we have done so far at Los Alamos on the biomedical facility has been bootlegged. We made no secret of this. So far we have had not one dime from the appropriate source to carry on the work of designing the building, shielding, and beam channel. The reason we have gone ahead is because I have personally felt for many years that radiation therapy would be one very appropriate utilization of this facility. I cannot guarantee you that we will obtain funds in FY 72 to build that part of the facility which we do not have money to build at this time. What I can guarantee you is that as soon as there is a pion beam anywhere at this

facility, you will have a chance to compete for time on it. And we are going to have pion beams; they may first appear in Area A before they do in the biomedical area, but they will appear. So your immediate programs, which you are discussing here, should not in any way be influenced by whether or not funding is available in FY 72 or 73 for the completed biomedical facility. I think you can rest assured there will be such a facility.

Why can you be so sure? Mainly, just as I told those of you who were in the plenary session yesterday, the Joint Committee of the AEC, upon my request, has permitted us to proceed with the expenditure of $300,000 for the first phase of the biomedical facility. They agreed to permit the use of these funds for the phase which has to do with the penetration of the beam channel and the construction of the exposure room. The logic here is that any postponement of construction would then necessitate a shutdown of the entire LAMPF facility for something like six months when funds finally become available to build your facility. It was on this that we were authorized to proceed, and we are doing that.

One cannot go ahead bootlegging funds for a project this size forever, and the Division of Biology and Medicine realizes that. About two months ago something happened which is almost as rare as a three-legged bird these days. I received a letter from Dr. Totter, Division of Biology and Medicine, in which he complimented us very kindly on the progress we are making, and he told me that he thinks it's time the Division of Biology and Medicine funded a group in my division on the biomedical applications of LAMPF, a group which could take on the chore of designing, building, checking out, and putting into operation, the biomedical facility, in collaboration and cooperation, of course, with all of you, the Users Group, who will be involved and whoever else will have a legitimate interest.

This came none too soon. I will reveal to you that this year our budget for operations was $6.215 million; that was the President's budget. A few weeks ago, Congress finally passed the AEC appropriations bill and that contained a reduction in the research for the Division of Research of several millions of dollars. Our share of this reduction was $215,000. What this would mean, if nothing else were to happen, is that the activities at Los Alamos, in MP Division, would come to a grinding halt about January 1 unless Dr. Totter comes into the picture with funding from the Division of Biology and Medicine. I explained this very thoroughly when I was in Washington last week. I have written a letter to Dr. Seaborg about the entire general problem, and I'm hopeful that they will not let this happen. I hope that this several hundred thousand dollars per year, which we have been using to carry forward the biomedical effort here, will be replaced by the Division of Biology and Medicine and we can proceed.

But an even more serious problem is how fast will we proceed with the remainder of the facility? If the AEC does not succeed in persuading the Bureau of the Budget to include in the President's budget in FY 72 at least $1 million for the biomedical facility, we can still hope that this will be included during the hearings on the Atomic Energy Program by the Joint Committee on Atomic Energy. I need not tell you that the budgetary situation in Washington right now is very grim, more grim than ever I have seen it. However, what you and we are trying to do here is so dramatically necessary and could help so enormously the entire scientific venture in this country, that I think our message is going to get through. I believe we are going to be funded to proceed with this project.

The interest in the biomedical facility here is quite marvelous. We are getting support from every corner of the country. The New Mexico Medical Association, which is meeting in Albuquerque next year is going to spend a half a day to come here and listen and learn about how they can participate when this facility comes on the air. Just recently, Dr. Anderson and I were at a meeting of the senior people of all the Albuquerque hospitals, and they have expressed an interest to use collectively their resources to try to help the medical school bring to bear the resources of the Albuquerque medical community on the application of the modality we are talking about bringing to fruition here.

On December 5th the trustees of all the Albuquerque hospitals, plus the senior medical personnel, will appear, right here where you're sitting, and we will explain in great detail what is being done and invite them to join with the University of New Mexico to develop long range plans, as they've already been invited by the university Medical School.

The thing, I think, which is most needed right now to press ahead convincingly with this venture is a document which outlines in schedule form what needs to be done to bring about clinical trials at the earliest possible date, i.e. who is going to do it, where it's going to be done, and what funding resources and other resources are necessary to accomplish these objectives. A document which details that would perhaps be the most important ally I could now have in my quest in Washington for funds to build the facility.

Recently the Committee on Radiation Therapy of the National Cancer Institute met and they were given a briefing by Dr. Boone on the biomedical aspects of the LAMPF facility. My understanding is that there is a great enthusiasm among the members of that Committee. Recently, also, there met in Seattle, a similar committee of rather broader scope, the Program Advisory Committee of the Division of Biology and Medicine of the AEC. I heard from Dr. Totter early this week, that there was also great enthusiasm in that Committee. That Committee, or a cousin of theirs, is going to meet here the second week of November, and on November 11 representatives of the National Cancer Institute will be here. I have arranged to brief them very thoroughly on what we are doing and how we think they can help.

An important point I would relate to you has to do with my conversations last Tuesday with Dr. Totter and his senior people. It emerged that the Division of Biology and Medicine looks upon the LAMPF biomedical facility in the following way: They consider their obligation to be to build the facility and get it started. They intend that from then on the burden will be carried by the National Cancer Institute. So they shall work with the NCI and try to coordinate with them their plans for the next few years, so that when they bow out, the NCI will not have to have an upheaval here and change everything around and discommode a lot of plans and people. I think it is very important, and I was glad to hear from them that they are taking care, to proceed in an orderly and systematic way to develop the facility on the one hand and then turn over the entire operation, the clinical operation, to the NCI. They don't want to be in the position of competing in clinical therapy with the NCI. They will continue to support Dr. Voeltz and Dr. Langham and you people who are doing fundamental radiobiology with pions. I'm sure they consider that their prerogative, but not to treat patients. This they want NCI to do.

This is the story as of this point in time. I have very great confidence that this activity is going to go ahead at a good pace, but a lot of work remains to be done on your part and also on the political side, which I will have to worry about.

Question: This all-inclusive document includes things that might fall into the Agency's realm of interest and might even this early be more appropriate at the NCI. How do we juggle that?
Answer: Fortunately, I don't think you have to worry about it because the Division of Biology and Medicine people indicated that they will coordinate with NCI, and they'll decide between themselves who shall fund what aspects of this work. So they have taken us off the hook, and that's the marvelous thing. We don't have to worry about this problem. They will work it out among themselves. They have very good relations.
Question: So we should define what needs to be done, who may do it, and how much we think it might cost?
Answer: Right, and then we will turn it over to Dr. Totter, and Nat Barr, and Bob Wood and they will meet with their opposites at the NCI and let them decide who funds what. We really shouldn't be involved in that. All we do is spend money, we shouldn't worry about how it comes to us.
Question: The attitude of the AEC is that the maintenance of the facility would pass very quickly to the NCI. Is that the plan?
Answer: Yes.
Question: Does this also mean that a portion of the costs of operating the accelerator ... (unintelligible) ... or merely the direct costs?
Answer: Merely the direct costs. Now this is something no one can give guarantees on; however, beam time is going to be free for all users of this facility, as near as we can now tell. I would imagine having from now on, in our Division a small group

which will maintain the biomedical facility. We're not going to try to have engineers who just worry about the biomedical facility or beam target people who just worry about beam targets. That would be terribly inefficient and inexcusable. We will incorporate these activities in the over all management of the division's work in maintaining and operating the accelerator. We'll try to split out the costs so that they pay their fair share of operating the biomedical facility, not the accelerator proper. The funding situation could cause the Division of Research to say, three years from now, everybody's going to pay their way, and we just can't fund you otherwise. That is not the plan right now, and I hope it never is. It would cause great difficulties and it probably never will be because the Division of Research will get prestige out of this with the Congress that they can get almost no other way. If they are wise, they will gladly pay the cost of providing the beam to the biomedical facility. It's the best investment they can make for their future.

Question: What sort of schedule would you like on this document?

Answer: The schedule I would like to see is one which takes you up to actual clinical trials by the time we get a beam, the first part of 1973. A schedule which is complete as far as it can be completed, in the dosimetry certainly, and some of the other items, radiobiology as well. As Dr. Boone and Dr. Anderson have pointed out, we are moving very slowly. In June we thought we were going to set up these committees to outline the projects to be done and assign them to different groups, but as far as I know, not much has happened. In this respect may I suggest that we consider perhaps bringing in our Canadian and Swiss colleagues, and perhaps divide up the work including those groups ..... The schedule on the document; I'd like that tomorrow!

NCI-UNM Planning Grant

Robert Anderson, M. D.
University of New Mexico Medical School

Robert Anderson, M. D., of the University of New Mexico Medical School, opened a general discussion of the NCI-UNM planning grant and the general status of biomedical program. He echoed the concern of several people that the biomedical activities were not moving ahead rapidly enough to assure the earliest use of negative pi-mesons for therapy. A plan must be developed now for the required preclinical experiments. Funding requests must be submitted soon because of the inevitable delay - delay well evidenced by the NCI-UNM planning grant request, which required one year from inception to funding.

The planning grant will support a radiation therapist and a part-time pathologist in the first year. During the second year, a radiation biologist and a radiological physicist will be added to the program. However, the therapist is not yet on board, and the program cannot wait until the appropriate personnel are obtained and integrated into the program. The present members of the Biomedical Users Group must act now. Even if pre-therapeutic programs were started today and rapid progress was made, we would still not be ahead of schedule.

He indicated that two specific items should be discussed at this session of the Users Group Meeting:

1) Guidelines and outlines of specific experiments in the various pre-therapeutic programs must be developed utilizing the Hammersmith neutron experience as a starting point. Possible funding from NCI, ACS, and NSF should also be discussed.

2) Define which individuals and organizations that are interested in planning and experimentation.

Dosimetry

M. R. Raju
Lawrence Radiation Laboratory

M. R. Raju, of LRL Berkeley, gave an impromptu discussion of some of the aspects of the pre-therapeutic dosimetry program. Some of the items discussed were the on-line dosimetry, the delineation

of the pion stopping regions and absolute dosimetry. Investigation in these areas and others are proceeding at Berkeley and will start at Nevis when that facility becomes available. The Subcommittee on Dosimetry will make recommendations of specific experimentation required before therapeutic trials can proceed.

Hammersmith Clinical Trials

Max Boone, M. D.
University of Wisconsin Hospital

Max Boone, M. D., of the University of Wisconsin Hospital, gave an impromptu discussion of the experience in neutron therapy, both the early trials by Dr. Stone of the University of California at Berkeley and the more recent trials by the group at the Hammersmith hospital.

The misfortunes of the early neutron therapeutic trials indicate the necessity of proceeding cautiously and trying to understand the ramifications of a new therapeutic modality. However, it is not required to understand the radiation response of all normal and tumorous tissues in order to proceed with patient irradiations. These responses are not even known for conventional x rays. But it is important to study the response of representative normal tissues and typical tumor systems.

The failure of Stone's work greatly hindered the further attempts of the uses of neutrons for therapy. The group at Hammersmith proceeded slowly over a period of 12 years with several simultaneous programs of the different aspects of the over all effort. These included dosimetry, accelerator and beam development, cellular and tumor radiobiology, dose control and safety, treatment planning, auxiliary equipment development, isotope production, and other minor areas. Careful measurements found the cause of the difficulty in Stone's fractionation scheme, and they were able to proceed with patient irradiations.

The unforeseen problems with the neutron therapy should forewarn us to amass sufficient evidence in order to circumvent unanticipated difficulties with pi mesons. The surprises that come up during the treatment of patients must be minimized, because then is the wrong time to learn.

Nevis Modification

Michael Holland
Nevis Laboratories

I will describe very briefly to you the experimental facilities that will be available at the Nevis Cyclotron after the modification program is completed in the latter half of 1971.

As some of you may know, the present synchrocyclotron, which is a standard model, is being stripped and will be replaced with three-fold symmetry. It will be a sector-focusing type of cyclotron, will give us a substantially greater increase in proton energy and intensity. In the old configuration, this cyclotron has operated successfully for the past 21 years. In about 1963, it was decided that the accelerator was rapidly becoming obsolete and would either have to be shut down or modified considerably. We received $5 million from the NSF to do this modification. Table I shows the new parameters in comparison with LAMPF.

With the increased energy and the increased proton intensity, we should produce considerably more intense muon and pion beams. Up to the present time Nevis has not had an extracted proton beam. Pions were produced with an internal target and extracted through the fringing field with a magnet. After modification, we will have an extracted proton beam, two secondary beams, and one tertiary beam. The first beam will probably be a muon channel produced at a 3-cm target of Be. At the second target we will have a low momentum two-bend pion channel, bending the pions through two 45° bends to provide neutral particle attenuation. In addition, at this same target, we may have a high momentum pion channel which will also handle a scattered proton beam. The momentum range of the low energy pion beam will be between 0 and 250 MeV/c, and high momentum from 200 - 400 MeV/c for pions (600 - 1200 MeV/c protons).

Table I

NEVIS MODIFICATION

	Nevis		
	Before Modification	After Modification	LAMPF
Proton Energy (MeV)	380	550	800
Proton Current (μA)	2	25^{+25}_{-5}	1000

The low momentum pion beam is capable of being operated in two modes, which are characterized by the optics of the system. One possible mode of operation would be from the target to a point focus between the dipole magnets. Between the dipoles would be a slit system which would define the beam momentum. The other mode of operation would be from the target to a parallel beam at the momentum slits. These two beams are continuously variable over their momentum ranges. Operated in the first mode, from point to point to point in the bending plane, we can expect resolution $\Delta P/P = \pm 1\%$. The second mode of operation would be a possibility of optics of point to parallel between the dipoles and back to point at the end of the system. In this case we would have $\Delta P/P \approx \pm 10\%$.

Table II should allow you to compare the facilities that we will have to those which are currently available in Berkeley and will be in the future available here at LAMPF.

There has been some discussion about the possibility of having a fourth beam at Nevis, which would be a therapy beam, but there is no money available for that.

A word about contamination. At least for the low momentum pion beam, the muon contamination would be 15-20%; the neutral particle contribution is probably of the order of a few percent. The biggest difficulty would be electron contamination. As far as physicists are concerned, we simply put a Cerenkov detector in front of the beam, and by anti-coincidence techniques remove the electrons from consideration. But for the kinds of applications that the people here might have in mind, electrons may be a problem, so one might need some sort of mass separator, which is a device for which we have no money.

Dr. Leon Lederman, the Director of the Laboratory, is especially interested in having people come there and do biomedical pre-therapeutic research. If there are any of you here who would like to submit a proposal, I strongly urge you to do so.

Table II

LOW MOMENTUM PION CHANNELS

Beam Line	Configuration	π^- Energy (MeV)	$\Delta P/P$ (%)	π^- Flux (sec^{-1})	Spot Size (cm)	Divergence (mrad)	Contamination	Operational Date
Nevis (low momentum)	pt-pt-pt	50 (5-105)	± 1	7.5×10^6	H: ± 11 V: ± 10	H: ± 50 V: ± 200	μ ≈ 15-20%	~9/71
	pt-parallel-pt		± 5	2.0×10^7	H: ± 2 V: ± 2	H: ± 50 V: ± 230		
LAMPF (Burman-Jakobson)	Physics Channel	50 (20-300)	± 2	8×10^7	±1.6 x ±1.0 ±8 x ±10	±130 x ±40 ± 21 x ± 2	~10% μ ~20% e $<5 \times 10^{-4}$ n	1/73
Berkeley	Pion Cave	90	± 7	10^6	H: ± 2 V: ± 7		~10% μ ~25% e	current
LAMPF	Biomedical	90	± 7	10^8	H: ± 10 V: ± 10	H: ~ 100 V: ~ 100	~10% μ ~5% e	unknown

Note: Above based upon a 3-cm Be target. Nevis numbers represent an upper limit based on first-order calculations.

Question: To what extent are the beam optics optimized; and what are the muon yields expected?

Answer: All of these calculations are first order calculations, and are not optimized. The muon channel we expect of the order of 5×10^5 muons per sec per MeV, at 100 MeV/c central momentum.

Question: Will just the accelerator come back on in later 1971?

Answer: Our operational date means that everything comes on and magnets, etc., will be in place.

Question: Are the secondary beam lines existing equipment?

Answer: There was never an extracted beam of any sort before and there were no magnets in existence. Our magnets have been designed and ordered and will be in place when the beam comes on.

Question: What do you plan for a beam stop?

Answer: We plan for a beam stop outside of the building, representing an embankment of about 35 ft of dirt and a constant elevation representing an infinite stop of earth. There will also be a beam stop of concrete.

Question: From the table, do you plan two low momentum pion channels?

Answer: The figures in the table represent the two modes of operation for a single low momentum channel. One is a point to point to point, which has ± 1% resolution; the other mode has a ± 5% resolution. The intensities from the high momentum beam will be of a comparable intensity and ± 1% resolution.

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CHARTER

ORGANIZATION OF THE LAMPF BIOMEDICAL USERS

(Adopted October 31, 1970)

Article I. LAMPF BIOMEDICAL STEERING COMMITTEE

A. Function and Responsibilities

1. Represent the Biomedical Users and provide liaison with the LAMPF administration through the Users Group Executive Committee.

2. Ensure that the Biomedical Users are kept informed of the activities in the biomedical area.

3. Seek out, propose, and evaluate general and specific uses of the LAMPF Biomedical Facility.

4. Act in an advisory capacity in support of research, development, and planning activities pertinent to the design and eventual use of the facility.

5. Generate and maintain up-to-date specifications for the initial design and later modifications of the facility.

6. Establish standing subcommittees to assist it in each of the main areas of current interest to the facility.

B. Membership

The Steering Committee will consist of a Chairman, Alternate Chairman, Assistant to the Chairman, Members-at-Large, plus the chairman of each of the currently existing standing subcommittees.

C. Rules

1. The Steering Committee Chairman will be elected by the membership of the Biomedical Users at an annual meeting of the LAMPF Users Group and will serve for a term of two years.

2. The Chairman will appoint members to the Steering Committee and will determine their terms of service. Normally, these terms will be concurrent with that of the Chairman.

3. The Chairman will convene the Steering Committee approximately semiannually, with one meeting to be held each year in conjunction with the LAMPF Users Group meeting.

4. The Alternate Chairman may act in place of the Chairman at the Chairman's request.

5. The Assistant to the Chairman will be responsible for general correspondence, information handling, continuous liaison with the LAMPF project and the LAMPF Users Group, and the planning of meetings for all standing subcommittees, in addition to being an ex-officio member of all standing subcommittees.

Article II. STANDING SUBCOMMITTEES

A. Functions and Responsibilities

1. Standing subcommittees will be established and dissolved by the Steering Committee. These subcommittees will assist the Steering Committee in specified areas of interest.

B. Membership

1. The Steering Committee Chairman will appoint a chairman to head each standing subcommittee.

2. The Chairman of a standing subcommittee will appoint members to his committee, as well as designate his alternate who may substitute for him on the Steering Committee.

3. Membership on a standing subcommittee should be limited to those already actively engaged in the area of concern to the committee. In addition, total membership on each standing subcommittee should be limited to about eight (8) people, with an attempt made to distribute the membership among the many interested institutions.

C. Rules

1. All standing subcommittees will meet each year in conjunction with the LAMPF Users Group meeting.

2. Other meetings may be called by the individual chairman, subject to the approval of the Steering Committee Chairman.

Article III. Any of the previous Articles may be changed by a majority vote of the members attending an annual Biomedical Users Group Meeting.

CM/Ms: 817 (500)