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Recommendations for Implementing Radiotherapy with Negative Pions at LAMPF

UNITED STATES
ATOMIC ENERGY COMMISSION
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MASTER

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Recommendations for Implementing Radiotherapy with Negative Pions at LAMPF

by

C. Richman
D. E. Groce *

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FRONTISPIECES

- Fig. 1:** The layout of the Los Alamos Meson Physics Facility on La Mesita de Los Alamos.
- Fig. 2:** Aerial view of the Meson Facility.
- Fig. 3:** A rendering of the proposed Radiobiology and Therapy Research Facility with a cutaway view of the treatment room showing two beam lines. For the present only one beam line, the forward one, is being designed and planned.

Fig. 1.

Fig. 2.

Fig. 3.

LOS ALAMOS MESON PHYSICS FACILITY
RADIOBIOLOGY AND THERAPY RESEARCH FACILITY

DEDICATION

These recommendations are dedicated to the memory of Dr. Wright Haskell Langham (1911 - 1972), who served as the Associate Health Division Leader for Research at the Los Alamos Scientific Laboratory and as our own Alternate Chairman at the time of his death. For more than twenty-five years Wright built a home and strong foundation for radiobiology and radiological health research at LASL. The memory of his sincerity, cheerfulness, and dedication will continue to be with us in this new undertaking.

The Steering Committee

FOREWORD

A little over a year ago, the LAMPF Biomedical Users organized a steering committee to guide and encourage the biomedical work. From the very beginning it was clear that pion radiotherapy was probably the most immediate and most exciting goal. Nevertheless a great deal of basic dosimetry and radiobiology would be necessary to arrive to the point of clinical trials.

The Steering Committee proceeded to organize several subcommittees to deal with the specialties that would be required: It was evident that advice would be needed in dosimetry, in cellular radiobiology, and in radiation therapy proper. To implement these ideas, the beam line and the facility had to be planned and built. Furthermore, the radiobiology with whole animals merited separate consideration; and also the use of isotopes from LAMPF for diagnostic problems could turn out to be very important. In this way six subcommittees came into being to deal with these quite separate problems. Finally a number of people felt that the problem of tumor localization was an essential aspect of this whole endeavor and so a seventh subcommittee is now being organized to study the combined areas of tumor localization and treatment simulation.

It can properly be said that a program leading to radiotherapy with a radiation as unique and as complex as negative pions will require a deep sense of cooperation and faithful dedication to the work. This comes about because it is very unlikely that the knowledge and skill required will reside in one person; rather reliance will have to be placed on groups of experts who have studied the problems for many years. This has already become evident in the work of the subcommittees. Not only have these groups met and gone over the problems in each area, but questions and advice have been sought by one subcommittee from another. This has been especially true of the beam line and facility subcommittee and the radiotherapists and between other groups as well.

The recommendations and discussions presented here are in this spirit. The various subcommittees have traveled far and met and have written down what they believe will be necessary to inaugurate work with patients. The document presented here is the progress of this effort - - it is not meant to be complete or polished but simply the various needs of the work as seen at this time.

It is a pleasant feeling to express at this point how much the program of the Users and the radiotherapy program at Los Alamos have been enlightened and enriched by all of the committees; and the Users hereby express their appreciation to the chairmen and members of all of the committees for the generous spirit which made these recommendations come into being.

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INTRODUCTION

The preparation and utilization of a new modality for radiation therapy is a rare occasion and of great significance for improving the therapy of cancer. For many years now, the principal modalities for therapy have been Co-60 gamma rays, supervoltage radiations from various machines, and high energy electrons; all of these are what can be designated as radiations of low LET.

The recent reexamination of neutrons for therapy at Hammsmith Hospital in London and elsewhere is a forward step into the high LET region. The studies so far have shown that such a high LET radiation leads to survival curves with less of a shoulder, therefore less sublethal damage, and lower oxygen enhancement ratios. While neutrons do produce these effects, it must be said that from the physical point of view they leave much to be desired: Neutrons are uncharged particles and as a result their depth dose properties are of the same general type as x rays and gamma rays.

The reason for going to the negative pion is that it is essentially a lightly ionizing particle with a well defined range, which features a release of high LET radiation at the end of its range. Such a radiation combines the advantages of a low LET region, with a high LET region in the treatment volume and no exit dose.

In view of these characteristics the radiation of a treatment volume with negative pions becomes a more delicate matter than the interposition of the tumor in a stream of quanta or of uncharged particles. In essence the goal with pions is to place a high LET, high RBE region in a volume undergoing treatment with little or no dose anywhere else.

The work begins with making a beam line or channel that fulfills this purpose for patient irradiations - - such a channel consists of a series of focusing and bending magnets that in the first place collect a sufficient number of pions from the target and then delivers the star region to the desired treatment volume in the patient.

There are many questions that need to be answered for this radiation: Clearly the spatial and dynamic characteristics of beams produced in this way must be measured and be reproducible at any time; furthermore, the physical dosimetry must be determined. And it can be added here that further knowledge of the attenuation properties of these beams in tissue is needed.

These physical parameters form the basis for the radiobiological studies. Here we have an area for basic cellular studies, and also for the study of the response of various organized tissues such as skin, gut, cartilage, spinal cord and others as well. The RBE of pions under various regimes of fractionation will provide the essential knowledge needed for treatment planning and treatment problems.

The carrying out of these programs and the interrelationship of these problems is the subject and purpose of the following recommendations.

RECOMMENDATIONS
made by the
SUBCOMMITTEE on FACILITY and BEAM LINE
Initial Meeting in Albuquerque, January 22, 1971

I. Beam Line

- A. Consult further with the therapy subcommittee concerning:
 - 1. Dose rate requirements.
 - 2. Significance of electron and muon contamination.
 - 3. Parallel beam requirement.
 - 4. What is an acceptable total dose of nontherapeutic radiation.
- B. Calculate muon contamination for 3-bend channel.
- C. Make a more detailed study of the source of electron contamination.
- D. Calculate flux of neutrons "streaming" through a 3-bend channel.
- E. Estimate a time schedule for beam line design, magnet design and fabrication, and channel installation.

II. Stubout

- A. Remove two support columns which appear in the original design.
- B. Relocate thin floor slab areas and make them as large as possible.
- C. Provide easier access between power supply area and control room area in stubout structure.

III. General Facility Considerations

Assure frequent interaction with other subcommittees so that we remain aware of their evolving requirements both with respect to the present and also with respect to the future.

RECOMMENDATIONS
of the
FACILITY and BEAM LINE SUBCOMMITTEE

Los Alamos Meson Physics Facility
October 4, 1971

Recommendations Relevant to the Design and Development of the Biomedical Pion Channel and its Associated Shielding and Instrumentation

1. There is no well-established empirical data on the production of electrons within pion production targets. Therefore, it is difficult to predict for this proposed channel and target configuration to what extent electron contamination will be present and to what extent this contamination can be eliminated from the proposed pion beam.

For this reason it is vital that the Therapy Subcommittee review and clarify the importance of the magnitude of the electron contamination in the various cases encountered in clinical situations.

It must be kept in mind that electrons will contribute a uniform, low LET dose extending from the entrance surface of the patient to the exit surface as shown on page 41 of the Biomed Facility Proposal (LA-4490-P) and having a lateral extent approximately the same as the primary pion beam.

2. Any pion production target is a copious source of high energy (several hundred MeV) neutrons, from which the patient must be shielded. The shielding will cost on the order of hundreds of thousands of dollars so it is essential that no more is spent than absolutely necessary.

Not only do the neutrons penetrate shielding, they stream down the pion channel contributing a dose in the general area of the target volume of the order of tens of rads per hour. These neutrons also scatter and, along with the neutrons from the pion stars, give rise to further whole body dose of, as yet, unknown total magnitude.

It is recommended that calculations of shielding, neutron streaming and scatter, and star neutron production proceed as rapidly as possible.

Further, it is recommended that the Therapy Subcommittee specify maximum acceptable neutron doses both to various possible target volumes and to the whole body. These tolerance levels will affect the amount of shielding provided and possibly the exact bend magnet configuration in the pion channel.

3. It is recommended that the people involved in the pion channel design and instrumentation meet soon with the Physical and Biological

Dosimetry Subcommittee to establish definite recommendations as to dosimetry and instrumentation needs and development.

4. As additional base for the design of the computer system and computer I/O, it is important to start as soon as possible the development of treatment planning techniques and computer programs appropriate to the unique characteristics and capabilities of pion beams. It is expected that the control computer (a DEC PDP11/45 with 24K memory and disc) will be utilized for some treatment planning and that a data link to the LASL central computing facility will become available. So that the development of treatment planning techniques unique to pion therapy can begin, it is recommended that the Therapy Subcommittee suggest and define in detail some typical clinical cases for early consideration in treatment planning.

5. This subcommittee re-emphasizes the importance of redundancy in dose monitoring and beam turnoff instrumentation.

6. Since it is absolutely essential that patient treatment proceed smoothly and with an absolute minimum of delay and uncertainty in treatment scheduling, it is strongly recommended that the accelerator operations procedures and biomedical pion channel operations procedures incorporate a mechanism by which decisions are made quickly as to whether downtime faults are probably of short duration or are of indefinite or long-term duration so that the therapists and experimentalists can make appropriate changes in their various patient and experimental schedules.

Recommendations Relevant to the Design of the Biomed Facility Building and Services

Because of the schedule by which projected appropriations for future years are reviewed and formulated at LASL, it is important that the needs for space and equipment in fiscal year 1974 be considered soon. It is recommended that the projected space needs for the various programs be studied by the subcommittees involved at the first opportunity.

Operational requirements for personnel, supplies, etc., must also be considered.

General Recommendations

1. The following lists the minimum projected needs for operational personnel during initial two years' usage of the facility and beam line:

Senior Staff (Physics and Instrumentation)	2+
Programmer (Control Systems)	1/2 - 1
Electronics Technician	1
Mechanical Technician	1
Operator	1
Total	<u>5 1/2</u> - 6

2. Other subcommittees have made personnel recommendations involving a sizeable number of people. Some subcommittees have not done so yet but will undoubtedly do so soon.

This subcommittee is seriously concerned that, if the situation continues as it has, all these people of widely varying backgrounds and immediate interests will be falling together into a program without clearly defined and agreed upon programmatic goals.

We recommend that every effort be made to designate some person, who is conversant with the problems of facility and beam line development and with the needs and purposes of the various programs, as presented by the subcommittees, to: (1) be responsible for pulling the biomedical program together into a more coherent whole, and (2) see that, as the facility comes into use, a well-ordered program of research and development is outlined and scheduled in some detail so that the facility will be used in the most productive way possible.

If one person is designated to spend essentially full time at this, the biomedical program will tend to progress more rapidly.

As it stands now, every person who is involved in the project on a full time basis, namely those people at LASL, have specific interests and responsibilities whether it be pion radiobiology or instrumentation or something else, and cannot devote full time to detailed program planning and development.

We also recommend that a clearly defined administrative structure for the conduct of the biomedical program and the operation of the facility be established as soon as possible.

TABLE I

CHARACTERISTICS of the BIOMEDICAL CHANNEL¹

<u>Design Characteristic</u>	<u>Numerical Value</u>
Angle of Pion Beam to the Proton Beam	~ 60°
Length of Channel	~ 10 meters
Solid Angle Accepted	~ 30 msr
Momentum Bite Accepted	$\frac{\Delta P}{P_0} = \pm 8\%$ at $P_0 = 202.5 \frac{\text{MeV}}{c}$
Field Size	15 cm x 15 cm (nominal maximum)
Dose Rate (assumed for 15 x 15 x 12 cm ³ treatment volume)	20 rads/min (nominal)
Uniformity of Dose Distribution	± 5% (± 3% desirable)
Maximum Depth of Distal Surface of Treatment Volume	25 cm
Minimum Depth of Proximal Surface of Treatment volume	0.5 cm
Maximum Treatment Volume Thickness	12 cm

¹R. L. Hutson and M. Jakobson, The LAMPF Biomed Pion Channel:
A Preliminary Report MP-7-34.

DRAWINGS of the BIOMEDICAL FACILITY

- Fig. 4:** The biomedical beam line is shown: it consists of seven quadrupoles and four bending magnets.
- Fig. 5:** Plot plan and location plan of the biomedical experimental area - - TA-53.
- Fig. 6:** Elevation and section views of the research facility.
- Fig. 7:** Room layout of the research facility.

Fig. 1

FIG. 7

LEGEND

- EJF EYE SAFETY FOUNTAIN
- EDF ELECTRIC DRINKING FOUNTAIN
- CA COMPRESSED AIR
- V VACUUM
- G NATURAL GAS
- O₂ OXYGEN
- DWS DISTILLED WATER SYSTEM
- HW HOT WATER (POTABLE)
- CW COLD WATER (POTABLE)
- FHC FIRE HOSE CABINET (150' HOSE)
- AS ACID SINK
- LS LABORATORY SINK (TWO COMPARTMENT)
- N LABORATORY FUME HOOD (CW, HW, G, & AS)
- L LAVATORY
- WC WATER CLOSET
- U URINAL
- HS HOSPITAL SINK
- SH SOLDERING HOOD
- WDE WASH DOWN EQUIPMENT
- FD FLOOR DRAIN
- DS DARK ROOM SINK
- PS PLASTER SINK

SERVICES GROUPING

- ◆ G, C.A.

FIRST FLOOR MECHANICAL SERVICES

GRAPHIC SCALE 0 5 10 20

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GENERAL RECOMMENDATIONS
of the
SUBCOMMITTEE on PHYSICAL and BIOLOGICAL
DOSIMETRY

Initial Meeting in Chicago, December 2, 1970

1. The purpose of the Committee is to point out the areas that need work and to recommend an experimental program for the work. It is not the purpose of this Committee to do the work. A working group dedicated to pion dosimetry must be established.
2. The Committee strongly recommends that a senior radiological physicist with a thorough understanding of radiation biology and therapy problems be appointed to establish a group at LASL to carry out the pre-clinical and clinical dosimetry program. He should be given a position of responsibility and authority commensurate with this task. This should be accomplished as soon as possible.
3. A vital part of any good clinical radiotherapy program is a continuing program of radiation dosimetry. Because of the experimental nature of the use of negative pions at LAMPF, such a component is even more of a necessity.
4. The development of dosimetry techniques for radiobiology shall have first priority, and a comprehensive program must be initiated soon to take advantage of facilities such as the 184-in. cyclotron at Berkeley, the NEVIS cyclotron of Columbia University, and others before the LAMPF accelerator becomes available.
5. In order to terminate a patient treatment rapidly or to stop a physical or biological experiment, a mechanical beam shutter should be incorporated to intercept the pion beam.
6. The biomedical group must be able to remove or interchange targets at will. This capability must be verified by the following groups:
 - a. Health physics.
 - b. Downstream users, including beam dump.
 - c. Proton beam line transport people.
 - d. Target designers.
7. The beam line must have a capability of reducing the intensity of the pion beam by at least a factor of 100 with minimal effects on beam characteristics such as spatial distribution, energy spread, etc. The beam transport designers should be asked to assess what minimal effect may be attainable.
8. On-line measurements of the pion beam will require routine measurements of:
 - a. Beam characteristics (spatial distribution, energy, etc.).

- b. Depth-dose distribution.
- c. LET distribution.
- d. Localization of stopping region.
- e. Contamination.

9. Beam monitors used during treatment will require a fail-safe system with independent redundancy.

10. The pion dose rate during patient treatment or critical radiobiology experiments must remain constant within $\pm 20\%$. These periods of required stability would be 10 to 15 minutes maximum. It would be desirable to have the same stability over a period of several hours.

11. The design of the beam line will be such as to assure reproducible conditions on all aspects of the pion beam over a period of several years. Even if changes are made in the accelerator that will upgrade the performance or reduce the pion beam contamination, the ability to return to previous, possibly less desirable, beam conditions is required.

12. There will be a requirement for absolute dosimetry with a local absolute standard referenced to the NBS standard. Development of absolute dosimetry techniques should be started at the NEVIS cyclotron.

13. Organized archival documentation shall be required of the measurements of beam parameters and dosimetry.

MANPOWER RECOMMENDATIONS
of the
SUBCOMMITTEE on PHYSICAL and BIOLOGICAL DOSIMETRY

1. Most of the members may not be familiar with the activities, facilities and expertise of H Division and MP Division and hence it is difficult to make recommendations regarding the specific duties to be performed in the dosimetry program. This is the matter to be decided by MP Division and Health Division leaders.
2. The biomedical program at LAMPF should be considered as one group, although, for administrative purposes, the participants may belong to different divisions and possibly institutions. Dosimetry is a branch where extensive coordination is vital with various activities such as beam line design, radiobiology and radiotherapy. The location of specific activities in specific divisions is less important than the question of their ability to work closely together. Beam diagnostics and particle counting equipment are routine pieces of equipment in Intermediate Energy Physics and hence can very effectively be built at MP Division. Measurements of dose, LET, location of stopping power region, etc., and exposure gadgets need effective collaboration. It is very important for the staff in all divisions and groups working in the biomedical program at LAMPF to have complementary training and experience.
3. The development of physical and biological dosimetry programs is extremely important because the very promising physical advantages of π^- mesons will not be realized unless the entire physical and biological dosimetry and treatment planning procedures are sophisticated and realistic.
4. The physical and biological dosimetry program may be classified into the following categories for the purposes of planning and recommending the size of senior staff, although the actual work will not divide so neatly.
 - A. Physical Dosimetry -
 - Understand physical processes.
 - Calculate dose and LET distributions.
 - Design, construct and calibrate dosimetry probes.
 - Design, construct and calibrate external monitors.
 - Design, construct particle counting equipment, time-of-flight systems, etc.
 - Verify calculated distributions by measurement.
 - Establish and maintain local standards.
 - B. Biological Dosimetry -
 - Obtain biological weighting functions.
 - Calculate effect distributions.
 - Verify by biological measurements.

C. Therapy Technique -

- Decide on spatial coordinate system.
- Calculate treatment plans.
- Select or reject treatment plans.
- Design, construct and test beam-handling devices.
- Design, construct and test patient-handling devices.
- Design, construct and test coupling devices.
- Develop target identification and aiming procedures.
- Develop verification devices.
- Verify treatment plans.

D. Initial Therapy -

- Document procedure.
- Monitor patient exposure dose.
- Monitor effects on patient.
- Revise treatment plans.

E. Clinical Trials -

- Standardize treatment planning.
- Inter-compare dosimetry.
- Document procedures.

F. General -

- Records, documentation, analysis.
- Planning, scheduling, accounting.
- "Health-physics" monitoring.

SENIOR MAN YEARS OF EFFORT (CALENDAR YEARS)

Physical and Biological Dosimetry Program for LAMPF

	<u>1971</u>	<u>1972</u>	<u>1973</u>	<u>1974</u>	<u>1975</u>	<u>1976</u>	<u>1977</u>	<u>TOTAL</u>
1. Physical Dosimetry	1.0	2.0	2.5	2.5	2.0	1.0	1.0	12.0
2. Biological Dosimetry	0.5	1.0	1.5	1.5	1.5	1.0	1.0	8.0
3. Therapy Techniques		0.5	1.0	1.0	1.5	1.5	1.5	7.0
4. Initial Therapy				0.5	1.0	1.0	1.0	3.5
5. Clinical Trials					0.5	1.0	1.0	2.5
6. General	0.5	0.5	0.5	0.5	0.5	0.5	0.5	3.5
TOTAL	2.0	4.0	5.5	6.0	7.0	6.0	6.0	36.5

**PHYSICAL and BIOLOGICAL DOSIMETRY
PROGRAM at LAMPF**

CALENDAR YEAR	1971	1972	1973	1974	1975	1976	1977	
<u>PION BEAMS</u>								
NEVIS		—————						
LAMPF (B.J. Channel)			—————					
LAMPF (BioMed. Channel)				—————				
<u>DOSIMETRY PROJECTS</u>								
1. Physical Dosimetry			-----					12.0
2. Biological Dosimetry			-----					8.0
3. Therapy Techniques					-----			7.0
4. Initial Therapy				-----				3.5
5. Clinical Trials					-----			2.5
6. General		-----						3.5
Senior Man Years	2.0	4.0	5.5	6.0	7.0	6.0	6.0

TECHNICAL RECOMMENDATIONS
of the
SUBCOMMITTEE on PHYSICAL and BIOLOGICAL DOSIMETRY

Los Alamos, January 13, 14, 1972

The purpose of this committee is to make recommendations, not to prepare a detailed experimental program. That responsibility rests with the Los Alamos Scientific Laboratory. The committee cautions that the physical dosimetry program should be completed to the satisfaction of the dosimetry personnel before therapy begins. It is the experience of most medical physicists that the routine use of complex systems such as the negative pion beam line is almost universally premature. The committee recommends that the following projects be undertaken in essentially the order in which they appear, although many of them must run concurrently.

I. Before a Low-Level Negative Pion Beam is Available

A. Design, build, and check out dosimetry equipment.

1. Large, parallel plate ionization chambers for beam monitoring.
2. Quadrant chambers.
3. Dose integrators.
4. Acquire thimble ionization chambers (Shonka or Baldwin-Farmer) and calibrate to Co-60 as well as at the National Bureau of Standards.
5. Acquire semiconductor probes.
6. Acquire a Rossi-type proportional counter for LET measurements and, hopefully, get Rossi and Shalek to help make the measurements.
7. Investigate the recombination technique of Sullivan and Baarli as a measure of radiation quality.
8. A thin, parallel plate proportional counter.
9. Calorimetry to be undertaken in collaboration with the National Bureau of Standards, Memorial Hospital, and M. D. Anderson (not a high-priority item for early completion).
10. Miscellaneous equipment.
 - a. X-Y-Z positioners and isodose plotters.
 - b. Film devices.
 - c. Computer interface equipment.
 - d. Beam diagnostic equipment (beam composition monitoring).
 - e. Phantoms.

B. Initiate a theoretical dosimetry program.

1. A simple computer program needs to be developed locally that can calculate LET, dose, and dose-equivalent beam characteristics for a particular beam (including contamination, detector response, etc.). This should use data derived from Monte Carlo-type codes and any available experimental data.

II. Dosimetry for Radiobiology

- A. Be able to predict theoretically and verify experimentally the depth-dose pattern and LET distribution as a function of beam-line settings for specific experiments. The reproducibility of dose rate, dose distribution, and LET distribution must be verified. All measurements should be made to the best accuracy attainable within the constraints of time, equipment, personnel, and funds.
- B. Methods must be developed for proper collimation and alignment procedures. Special attention should be given to requirements for special facilities and equipment for animal and cellular radiobiology.

III. Dosimetry for Human Radiobiology

- A. Develop simulator and localization techniques. The timing of this development depends on whether or not these techniques will be necessary for the first patient exposure.
- B. Calculations of dose patterns must be shown to agree with experiment to a degree consistent with the requirements of the particular exposure.
- C. Extensive feedback from the radiobiology program relevant to therapy must be incorporated into the treatment-planning effort.
- D. Collimation, alignment, and immobilization techniques must be perfected.
- E. The dose to parts of the body outside the treatment volume should be calculated and verified experimentally to within 20 percent.

IV. Dosimetry for Therapy

Recommendations for the therapy program will be made at a future meeting.

TABLE I. Man-Power Requirements*

Task		Man-Years
<u>Phase I:</u>		
A. Design, build, and check out dosimetry equipment		
1.	Beam monitors	3 man-months
2.	Quadrant chambers	2
3.	Dose integrators	1
4.	Thimble ionization chamber	1
5.	Semiconductor probes	1
6.	LET monitoring (Rossi-type)	6
7.	Radiation quality (recombination)	6
8.	Proportional counter	6
9.	Calorimetry	2
	Total	28
B. Theoretical dosimetry		2.4
<u>Phase II:</u>		
A. Calculate and measure dose distributions		1.5
B. Collimation and alignment procedures		1.0
<u>Phase III:</u>		
A. Simulator and localization		1.0
B. Calculations for therapy		1.5
C. Radiobiology feedback		- -
D. Collimation, alignment, and immobilization techniques		1.0
E. Dose to body outside treatment volume		0.5
Phase I		4.4 man-years
Phase II		2.5 man-years
Phase III		4.0 man-years

*The manpower requirement is listed separately for each task. Some tasks will have to be performed simultaneously. Consequently, the manpower requirement will be different for each year.

RECOMMENDATIONS
of the
SUBCOMMITTEE for CELLULAR RADIATION BIOLOGY
Meeting held in Boston, May 10, 1971

This report was prepared by the cellular radiation biology subcommittee of the LAMPF biomedical users steering committee and is directed toward recommending a cellular and tumor radiation biology program to precede the use of negative pions on cancer patients. A preliminary report was circulated among the subcommittee members, and most of their modifications were incorporated into this final report, which embodies five aspects of the pretherapeutic pion program: (1) general policy and facility recommendations, (2) recommendations of the therapy subcommittee that are pertinent to cellular radiation biology, (3) recommended research at other accelerators before pions are produced at LAMPF, (4) recommended research at LAMPF, and (5) a guess of manpower requirements.

1. General Policy and Facility Recommendations

The general spirit of the subcommittee's consensus at its meeting in May of 1971 indicated that the mission orientation of the pretherapeutic program will only succeed under close coordination between the Los Alamos workers and expert outside users. The following paragraph adequately summarizes our recommendation in this regard.

An effective well-supported resident staff program should be established at LAMPF to ensure maximum efficiency in acquiring critical information as early as possible. This will preclude exclusive dependence upon outside users for early results. Since it is unrealistic to assemble a staff capable of working in each of several areas where pretherapeutic experimentation must now be done, the in-house staff will collaborate with outside users wherever necessary to carry out the recommended pretherapeutic program. Further, the in-house program should have enough funding to invite expert users capable of answering with great certainty the questions most important to therapeutic trials.

From the practical standpoint, the two types of visiting investigators can be expected to participate - - those who are eager to carry out research in their own areas of specialty and will apply for beam use at LAMPF and those who must be actively sought and financially supported in order to perform a critical aspect of their areas of great proficiency.

While the biomedical facility is still in the design stage, it is clear that some effort must be made to provide biomedical users, including cell biologists, with adequate laboratory space and basic laboratory equipment.

It would be advisable to include 4 - 6 full-sized chemistry-type laboratories, including full utilities (gas, distilled water, vacuum, compressed air, floor drains, fume hoods, work benches, refrigeration, drying or sterilizing ovens, etc.). As the therapy subcommittee recommends, these laboratories should be some distance from patient staging and treatment areas. Experimenters can be expected to bring a certain amount of supplies and unusual, specialized equipment with them.

2. Pertinent Recommendations of the Therapy Subcommittee

The therapy subcommittee held its first meeting very recently, and its recommendations are now being distributed. Our recommendations are, to some extent, influenced by their deliberations. Pertinent aspects of their reports are as follows:

Scanning in depth in order to utilize the maximum number of incident protons to cover a target volume should be employed if it can be determined that this method results in satisfactory dose uniformity throughout the target volume at each treatment session. The effect of this approach on the RBE variation across the target volume should be investigated, especially at the proximal surface and proximal portions of the target volume where high LET effects may be present for only a fraction of the treatment time.

Building design of the biomedical facility at LAMPF should be such as to ensure maximum separation of patient areas from those devoted to animal experiments, medical physics, and cellular radiation biology.

Cellular and tissue radiobiology form the basic knowledge to which therapeutic studies must be related. Knowledge of these effects which can be obtained before availability of the beam at LAMPF would be beneficial.

It is very strongly recommended that statistically significant studies with concurrent RBE adjusted photon irradiated controls be performed at NEVIS.

Biological dose-fractionation experiments at NEVIS should utilize as many fractions as practical for the specific experimental system; then a smaller number of fractions for comparison. A suggestion was made that fractions be given every 48 hours, which may be close to clinical projections.

It is suggested that the consideration of normal tissue systems, which can be assayed by skin or gut cell cloning or spleen colony forming units, is appropriate for the Cellular Radiation Biology Subcommittee.

No OER vs. depth studies should be undertaken at NEVIS.

Recommendations for priority of cellular studies at NEVIS.

- a. Mammalian Cells (human, hamster, mouse).
 1. Survival vs. depth.
 2. Split dose studies.
- b. Skin and gut colonies.
- c. Slow growing mouse tumor system with fractionation.

3. Recommended pre-LAMPF cellular studies

It has become known that a pion beam line capable of producing intensities of up to 10 rads/min will be available in a few months at the NEVIS synchrocyclotron of Columbia University and a second line may become available at the Berkeley bevatron. Due to the anticipated difficulties of working with animals at the NEVIS site, it is recommended that pathological studies with animals be performed in Berkeley if possible, where excellent animal facilities are available; additionally, the whole animal radiobiologists are concentrated in the West. It is therefore recommended that cellular and tumor studies be conducted at NEVIS, as the experimenters are within easy reach of the site; it is further recommended that a physicist be maintained for the NEVIS physical research and dosimetry. Research at these two sites will be termed the "pre-LAMPF program."

The following experiments have been proposed for performance in the pre-LAMPF program and represent what the cellular subcommittee considers high-priority experiments.

- (1) Peak and plateau survival and OER of Vicia faba roots will be determined. This test material yields good quantitative data and is easy to deoxygenate. It is a standard and reliable test object in radiation biology, particularly for the measurement of OER.
- (2) Survival of cultured Chinese hamster cells (well-characterized lines such as CHO and V79) will be determined as a function of depth in tissue-equivalent material. A continuous depth-survival profile for these cells will yield a pertinent biological characterization of the beam profile.
- (3) Survival of human kidney T-1 cells at various depths in the pion beam will provide a meaningful comparison of pions with the numerous other high-LET radiations to which this standard cell line has been exposed.
- (4) Split-dose survival of cultured human and hamster cells in the pion stopping region will reveal the relative roles of single-hit inactivation and accumulation of sublethal injury.

(5) Survival experiments with mouse ascites tumors irradiated in vivo will extend the work of Feola et al. to higher doses and higher dose rates. They found an RBE of 5 for this system, and it needs to be ascertained whether or not this high RBE resulted from the low dose rate used in their experiments. New (aerobic) and old (hypoxic) tumors will be irradiated by stopping and plateau pions using the higher dose rates available at the NEVIS cyclotron.

As the LAMPF pion beam is expected to be an order of magnitude more intense than the NEVIS or Berkeley pion beams, it is anticipated that many of the above cellular experiments will be repeated at LAMPF. It should be pointed out, however, that additional projects are essential at Los Alamos which would not be feasible at NEVIS.

4. Cellular and tumor experiments having high priority for the LAMPF program

The higher dose rate and the existence of an in-house cell biology group makes the rapid performance of significant experiments possible at LAMPF. In addition to repeating much of the work to be done at NEVIS, the following experiments are recommended:

(1) Depth-survival profiles of cultured Chinese hamster cells growing in semi-solid methylcellulose medium. This system is in operation in the H-4 group at Los Alamos and is capable of providing important results not available with other cell-culture techniques. First, depth-survival profiles can be determined directly, as a column of cells can be irradiated in a large cylinder oriented along the axis of the pion beam. Secondly, the cultures are easily made hypoxic and can provide reliable OER's. Thirdly, the cells grow in three-dimensional microcolonies so that daughter cells are always adjacent to one another; this feature can be exploited to determine whether, in the pion stopping region, single capture events lead to inactivation of more than one cell in a significant number of cases.

(2) Age response of cultured human and hamster cells irradiated with stopping pions. During some parts of the cell cycle and in plateau phase (which may characterize most tumors) mammalian cells have periods of reduced capacity for sublethal damage. With high LET radiation, extremes in age-dependent sensitivity are less apparent.

(3) Mammalian-cell survival curves in tailored beams. The effect of beam tailoring on biological effectiveness and OER in the broadened stopping region would be most expeditiously and meaningfully evaluated by obtaining survival curves for a standard cultured mammalian cell line. Such studies should continue through the therapy program.

(4) In vivo survival of a mammalian stem-cell system. A thorough set of experiments (OER, split-dose, dose-rate, etc., should be done on one of the proliferating in vivo stem-cell systems for which good quantitative end-points exist (skin, gut, or lung). A thorough study of one of these systems is better than a collection of a small amount of information about each.

(5) A study of the more sensitive spleen-colonizing cells from bone-marrow, lymphatic organs, and spleen is already planned and is very pertinent, as many advanced cancer cases are in marginal condition with respect to blood cells and immunological competence.

(6) Solid tumor control doses in hypoxic rodent tumors. Fractionated-dose survival (tumor control) studies should employ two types of solid tumors that proliferate under similar hosts: one that undergoes "reoxygenation" after the first exposures(s) to radiation and one that does not. The possible existence of analogous conditions in irradiated human neoplasms indicates that the increased efficacy of stopping pions in non-reoxygenating cases could be important. Slowly-growing tumor cell lines should be used in these experiments.

(7) Chromosome damage in vitro and in vivo. Most studies to date indicate that chromosome damage by radiation parallels reproductive lethality. This is true for other high-LET radiations, and it should be demonstrable for pions. Reproductive lethality is difficult to measure in some tissues in vivo (most, in fact). Reproductive lethality RBE's in the stem cells of some tissues should be estimable by the evaluation of chromosome damage.

5. Time-table and manpower requirements

At this stage it is difficult to assess the number of principal investigators who will actually be doing experiments and the extent of their involvement. The outline that follows is therefore, if anything, an under-estimate of the anticipated manpower and time requirements.

- 1972: Experiments at NEVIS
3 principal cellular investigators, 1 - 2 helpers each
4 - 6 months' work in each case
Senior man-years: 1.5
- 1973: Continuing experiments at NEVIS, similar requirements
Senior man-years: 1.5
- 1973: Initiation of cellular studies at LAMPF
3 - 4 principal investigators
2 - 4 helpers each
6 - 8 months' work in each case
Senior man-years: 2.0 - 2.5

- 1974: Peak year for cell studies at LAMPF, emphasis on continuing in vivo work.
6 - 7 principal investigators, including LASL personnel, 2 - 6 helpers each six months to full year on pion studies.
Senior man-years: 4.0 - 5.0
- 1975: Mostly effect of beam tailoring on cell survival, OER etc.
3 - 4 principal investigators, mostly in-house, 2 - 4 helpers each.
Senior man-years: 2.0 - 2.5
- 1976: Continuation of 1975 work, extension of experiments where indicated.
Senior man-years: ca. 2.0

It should be pointed out that senior man-years may not represent total labor force, as some experiments require more technical assistance than others.

**An EXPERIMENTAL PROGRAM in
WHOLE ANIMAL RADIATION BIOLOGY and PATHOLOGY**

Meeting in Albuquerque, January 25, 1971

The pre-therapeutic experimental program at LAMPF should provide the radiotherapists with enough information about the effect of negative pions on various tissues and with enough comparisons with conventional radiations so that this new modality can be applied promptly and with minimal hazards to human cancer patients.

The definition of "enough" is not precise and is known to vary greatly among radiotherapists. The scope of the program, therefore, must be worked out in close collaboration with the radiotherapists who will be responsible for the initial patient treatments and subsequent clinical trials.

As a starting point for discussion, the following overall plan has been proposed:

To determine (a) early, (b) late effects of negative pi mesons in the (a) plateau, (b) peak regions in (a) whole animal, (b) organized tissues compared to conventional radiation under conditions of (a) single dose, (b) split dose exposures and (a) large, (b) small treatment volumes.

A proposed schedule follows:

NEVIS, 1972

1. Studies of LD-50 in mice following whole body exposure.
2. Carcinogenesis in young female Sprague-Dawley rats.
3. Skin response in rabbits.
4. Local exposures of normal tissues in large animals for studies of late effects.

LAMPF, 1973

1. Some or all of the above should be repeated using the more intense LAMPF pion beam.
2. Local exposures of normal tissues and tumors in large animals should begin as soon as possible so late effects can be studied. Participation of radiotherapists in planning these exposures and observing these effects is essential.

LAMPF, 1974

1. Continuation of above.

LAMPF, 1975

1. Continuation of above.
2. The design of the initial therapy studies and subsequent clinical trials should include a protocol for careful pathologic studies of all autopsy tissues obtained from patients treated with pions.

RECOMMENDATIONS
of the
SUBCOMMITTEE on WHOLE ANIMAL RADIATION BIOLOGY
Meeting at Los Alamos, November 10, 1971

The LAMPF Biomedical Users Group Subcommittee on Whole Animal Radiation Biology and Pathology met at LAMPF on Wednesday, November 10, 1971.

It was noted that an almost limitless number of animal experiments with pions could be performed, but the programmatic goal of early safe use of pions in cancer therapy should be the main focus of the committee. Although "programmatic" experiments have priority, "elective" experiments should be encouraged as there is likely to be beam time available especially at "off hours."

The Radiation Therapy Subcommittee at the July 1971 meeting, considered priorities for the proposed preclinical program at NEVIS and recommended the following:

1. Studies be designed with sufficient numbers to give statistically significant results.
2. Exposures be made with as many fractions as practical (48-hour intervals), which will then be compared with a smaller number of fractions.
3. Long-term normal tissue effects be studied in systems in which there is considerable past experience and which can be quantitated.
4. The most important tissue systems are: skin, spinal cord, cartilage and heart.

Since it is not likely that preclinical experiments will be funded at NEVIS or the Berkeley Bevatron, the therapists' recommendations should carry over into the preclinical program at LAMPF, but there are additional items that need to be added:

1. Determination of RBE, using some of the classical systems such as LD50-30, decrease in spleen and thymus weight at 4 - 6 days, decrease in testicular weight at four weeks, should be performed because there is a large body of information with many different radiation modalities and these early RBE estimates can be utilized in the design of the more tedious and sophisticated experiments.
2. The list of four important tissues listed by the therapists should be the starting place, but studies of other tissues, such as lung, gut, oral mucosa, kidney, urinary bladder, etc., should be anticipated.
3. Plans should be made for treatment of spontaneous tumors in dogs to gain familiarity with the clinical responses of tumors and normal tissues.

4. Since carcinogenesis has been noted with quite small doses of high LET radiations, studies of carcinogenesis following pion exposures should be initiated as soon as practical after the beam becomes available.
5. Wherever possible, existing experimental models for which there is already considerable information relating to other radiation modalities, should be adapted for the early pion experiments at LAMPF.
6. Statistical consultation should be sought during experimental design, not after data are collected.
7. New end points should be explored for use in later experiments. An example is the application of new techniques and equipment for quantitation of histopathologic features in numerical terms, more precise than the classic mild, moderate and severe or 0 to 4+.
8. There is a problem in determining tolerance of normal tissues to pions, when tolerance to x rays (in use for 75 years) is not well known. The existing experimental models referred to above often relate to small rodents and their extrapolation to larger animals and man is uncertain. On the other hand, to irradiate localized regions in dogs or other animals for long term observation becomes a large and expensive chore if sufficient animals for statistically significant observations are utilized.
9. Organizational and operational matters need to be clarified.

RECOMMENDATIONS
of the
SUBCOMMITTEE on RADIATION THERAPY
Meeting at LASL, July 14 - 17, 1971

A. Recommendations Regarding Pion Beam and Beam Line Parameters

In response to specific questions regarding beam line, the parameters defined below were suggested from the viewpoint of their desirability for radiotherapy. It is recognized that certain of these requirements may be mutually incompatible. For this reason, it is hoped that designers of the beam line may subsequently define for us any required trade-offs in quantitative terms, so that compromises in these important parameters, if they must be made, can be decided on the basis of a maximal amount of information.

For purposes of pion radiotherapy, the following definitions are recommended and used hereafter in this report:

Tumor Volume is that volume of tissue which the radiotherapist has identified as constituting the primary volume of tumor involvement.

Target Volume is that volume of tissue which the radiotherapist wishes to treat with high dose in order to encompass all known and suspected tumor areas with an appropriate margin of safety.

Treatment Volume is that volume of tissue which the radiotherapist must treat with high dose to insure that the entire target volume has been encompassed.

For pions, the target and treatment volumes should be nearly equivalent.

1. Dose uniformity within the target volume should be such that the variation in absorbed dose within the volume shall be no greater than $\pm 5\%$. A variation no greater than $\pm 3\%$ is considered highly desirable.

2. It was emphasized that further planning of beam line and beam parameters should be used on detailed considerations of the actual geometries which will be encountered in tumor therapy. A comprehensive program of detailed three-dimensional treatment planning based on typical target volumes is deemed essential.

Only in this way can maximum flexibility and utility of the beam channel design be insured. Such a program should be undertaken as soon as possible, using cross-sectional anatomical diagrams with representative tumor volumes identified thereon.

3. In order to accomplish the above program prior to availability of experimental data on the LAMPF beam, isodose curves generated by computational techniques of the type presently being explored by Turner, Wright, Hamm, and others at Oak Ridge should be encouraged and expanded.

If these techniques are successful, they will make possible an enormous reduction in the amount of experimental dosimetric data required before initiating clinical trials.

4. The Committee noted that better cross-section data for plateau and stopping regions are required for the elements found in tissue for pion energies from a few MeV to slightly over 100 MeV. These will be especially important in generating dose distributions reflecting the extent of perturbations from tissues of different densities and compositions (tissue heterogeneity). Distributions should be calculated in three dimensions and compared with experiments when the latter are possible. Ultimately, it will be desirable to generate dose distributions in (a) absorbed dose, (b) LET distribution, and (c) (RBE x dose) distribution.

5. A minimum pion peak dose rate of 40 rads/min for a 15 x 15 cm field was considered highly important and nearly essential.

6. The maximum short-term and long-term variation in dose rate due to fluctuations beyond the control of the therapist should be as recommended by the Physical and Biological Dosimetry Subcommittee, i. e. less than $\pm 20\%$ for any given field.

7. As a major priority item, a second pion beam line should be constructed before 1975.

8. Requirements for beam boundary sharpness -

The following definitions are to be used:

Edges - those portions of the target volume, or high-dose region, which are oriented roughly parallel to the beam direction.

Proximal Surface - that surface of the target volume or high-dose region which lies roughly normal to the incoming beam direction and is most distant from the entrance port.

a) The absorbed dose at the edges of the target volume should decrease from 90 to 10% of maximal dose in less than 1.0 cm for a mean stopping depth of 20 cm.

b) The absorbed dose at the proximal surface of the target volume should decrease from 90 to 60% of maximal dose in less than 1.0 cm.

c) The absorbed dose at the distal surface should decrease from 90 to 60% of maximal dose in less than 1.0 cm and from 90 to 30% in less than 1.5 cm.

9. The muon contamination in the pion beam should be less than 4%. The electron contamination in the pion beam should be less than 10%.

10. The Committee agreed that scanning in depth in order to utilize the maximum number of incident pions to cover a target volume should be employed if it can be determined that this method results in satisfactory dose uniformity throughout the target volume at each treatment session. We understand that this will result in an increase in dose rate by a factor

of approximately two compared with selecting a broad momentum distribution in order to spread the peak dose over the target volume. The effect of this approach on the RBE variation across the target volume should be investigated, especially at the proximal surface and proximal portions of the target volume where high LET effects may be present for only a fraction of the treatment time.

11. Other beam parameters were discussed and are virtually unchanged from those given in LA-4490-P:

<u>Design Features</u>	<u>Maximum Value</u>	<u>Minimum Value</u>
Field size*	15 x 15 cm**	4 x 4 cm
Maximum depth of distal surface of high-dose region	30 cm	
Minimum depth of proximal surface of high-dose zone without using bolus		0.0 cm
Peak width	12 cm	1.5 cm

*For fields up to 10 x 10 cm a nearly parallel beam is desired. For therapeutic purposes, this means a beam divergence at the treatment volume no greater than that from a point source of radiation viewed at a distance ≥ 5 meters for a 10 x 10 cm field. For a field size of 15 x 15 cm, the beam divergence at the treatment volume shall be no greater than that from a point source of radiation viewed at a distance ≥ 3 meters. For fields larger than 15 x 15 cm, the divergence should be capable of being increased to that equivalent to a point source viewed at a distance of 50 cm.

**Without employing appreciable beam divergence and consequent reduction in dose rate. Geometric sharpness of the target volume should be preserved for field sizes larger than 15 x 15 cm, however, by use of the method of scanning in depth with essentially monoenergetic pions.

B. Recommendations Regarding the Biomedical Facility

The following recommended facility criteria are those necessary to carry on a clinical investigation program utilizing negative pi mesons. It is recommended that LASL personnel consider the design of the radiation therapy and radiobiology support areas based upon these criteria and to interact with the Radiation Therapy Subcommittee if trade-offs or compromises need to be made.

1. The Biomedical Facility should be oriented out of the congestion developing at and near the beam stop.

2. A staging room should be provided adjacent to the treatment rooms to handle the prestaging of four patients. There should be straight-line access from the staging area to each treatment room.
3. A 16 x 18 ft simulator room should be adjacent to the staging room.
4. A 20 x 18 ft mold room should be adjacent to the simulator room.
5. The control room should be close to the exposure rooms.
6. Design should be such as to ensure maximum separation of patient areas from those devoted to animal experiments, medical physics, and cellular radiobiology.
7. Five examining rooms of approximate size 10 x 12 ft should be available. One should be set up as a photographic facility and examining room.
8. Six offices should be provided:
 - Physicians, 2 each, 8 x 10 ft
 - Chief technician, 1, 8 x 10 ft
 - Head nurse, 1, 8 x 10 ft
 - Social service, 1, 8 x 10 ft
 - Receptionist, 1, 8 x 10 ft
 - Transportation, 1, 8 x 10 ft
9. One 15 x 10 ft records office is required.
10. One 15 x 20 ft conference room is required within or at least a short distance from the facility.
11. The facility should be pleasant looking, perhaps with decorations by local artists.
12. Stored equipment should not be readily visible to the patients.
13. Planned expansion of the above facility should be considered initially. For example, facilities for conventional X-ray and electron therapy for treatment of control patients in a meson trial will be necessary. The latter facility will need to be designed to accommodate a high-energy accelerator of the type recommended by the Committee on Radiation Therapy Studies (NCI) survey on the new generation of medical accelerators.

C. Recommendations Regarding Cellular and Animal Radiobiology

Cellular and tissue radiobiology form the basic knowledge to which therapeutic strategies must be related. Knowledge of these effects which can be obtained before availability of the beam at LAMPF would be beneficial.

1. It is strongly recommended that support be given to preclinical biological studies including the effects on normal tissues which can be carried out using the π meson beam at NEVIS because of the tremendous importance to the studies to be undertaken at LAMPF. Even though the dose rate is lower, these studies will provide useful information and give

valuable experience in techniques and methods of study for those who will later undertake these investigations using the more intense beam at LAMPF.

2. It is very strongly recommended that statistically significant studies with concurrent RBE adjusted photon irradiated controls be performed at NEVIS.
3. No studies should be undertaken at NEVIS using combined modalities.
4. Fractionation of biological experiments at NEVIS should utilize as many fractions as practical for the specific experimental system; then a smaller number of fractions for comparison. A suggestion was made that fractions be given every 48 hours, which may be close to clinical projections.
5. RBE's for fractionated meson doses may be reasonably close to those encountered for fast neutrons as reported by Stanley B. Field (Radiology 93, 915-920, October 1969).

Recommendations Specifically for Cellular Work

6. It is suggested that the consideration of normal tissue systems, which can be assayed by skin or gut cell cloning or spleen colony forming units, is appropriate for the Cellular Radiation Biology Subcommittee.
7. No OER vs Depth studies should be undertaken at NEVIS.
8. Recommendations for priority of cellular studies at NEVIS:
 - a. Mammalian cells (human, hamster, mouse)
 1. survival vs. depth
 2. split dose studies
 - b. Skin or gut colonies
 - c. Slow growing mouse tumor system with fractionation.

Recommendations Specifically for Animal Radiobiology:

9. It is recommended for the program at NEVIS that long-term normal tissue effects be studied in systems for which there is a considerable past experience and which can be quantitated.
10. The most important tissue systems to be studied at NEVIS are:
 - a. Skin
 - b. Spinal cord
 - c. Cartilage
 - d. Heart
11. The study of LD 50 following whole body irradiation in mice was felt to have low priority at NEVIS.

D. Recommendations Regarding Isotopes and Diagnostic Applications

The LAMPF facility will have the unique capability of producing large amounts of isotopes which have not been previously available or available in only very limited quantities. Exploration of these new resources for nuclear medical applications should proceed without delay. It is strongly recommended on the basis of general medical considerations and those related to the use of isotopic methods of tumor localization, that the production and use of the new isotopes to be available from spallation reactions be given strong support at LASL.

Areas of immediate importance for development are:

- a. Visualization of the pion stopping region
- b. Tumor localization
- c. Isotope production and development of new radio pharmaceuticals.

The diagnostic uses of mesons is recognized as being extremely important to the entire sphere of diagnostic medicine; however, it is felt that such techniques are not within the scope of the Radiation Therapy Subcommittee even though they are of a personal interest to individual members of the Committee.

Routine X-ray and nuclear medical services to support the clinical trials might best be purchased under contract from the local hospital. New development techniques should be done elsewhere at institutions willing to undertake studies of new and improved methods of tumor localization.

E. Recommendations Regarding Physical and Biological Dosimetry

The fields of radiologic physics and dosimetry are extremely important in radiation therapy because they provide the knowledge of quantity, quality, and distribution of the deposited dose. Besides the obvious efforts in dosimetry and beam diagnostics, there are several other areas in clinical physics that should be stressed:

- a. Absolute dosimetry-calorimetry
- b. 3-D distributions of absorbed dose, LET and (RBE x dose)
- c. External visualization of pion stopping region or tumor-seeking isotope distribution
- d. Dosimetry in body cavities and regions of tissue heterogeneity
- e. New basic physical information such as improved cross sections for tissue elements, interface effects, investigation of a possible buildup region for pion ionization and/or protons at the skin surface, etc.

Visualization of the pion stopping region should have effort devoted to it by the Physical and Biological Dosimetry Subcommittee in order to coordinate studies of tissue heterogeneity, dose-depth distributions and other dosimetry areas.

F. General Recommendations

The Committee felt that since the overall goal for this effort is the utilization of negative pi mesons for radiation therapy, it is incumbent to develop plans for the ultimate clinical trials as soon as possible. This will enable the other efforts in dosimetry, radiobiology, etc., to coordinate closely with the radiation therapy effort. The following set of recommendations related to clinical trials are by no means complete but represent a substantial start towards defining the ultimate program.

1. The Committee felt very strongly that, in addition to the pre-clinical studies, an organized clinical evaluation of pi mesons is required. It is important that when these clinical trials are undertaken, they be accomplished by staff and investigators who have spent considerable time in other more conventional clinical investigation or cooperative clinical trials, and that there be adequate patient control populations available. Thus, an institution with a history of excellence in clinical trials should undertake the coordination of the clinical investigations, and organize mobilization of the population of patients required for the clinical trials.

These clinical trials should be national in scope and should be organized through the Radiation Therapy Oncology Group, which has established mechanisms for setting priorities among the different national trials. In this way, effective cooperation between multiple institutions should be facilitated and ensured. It is, of course, necessary that the principal investigator conducting the clinical trials be fully aware of the preclinical biological and physics implications of pi meson therapy, and that a specific team under his direction be charged with direct responsibility for care of the patients and proper conduct of the clinical trials, with advice provided by this Committee (Radiation Therapy Subcommittee) or other duly constituted advisory group.

2. Effective communication with other groups interested in pion radiotherapy should be maintained with coordination in both preclinical stages and later clinical trials. Such groups include those associated with TRIUMF in Vancouver, British Columbia, SIN in Zurich, Switzerland, Stanford University in California, Brookhaven National Laboratory, New York, and others interested in newer radiations such as fast neutrons, heavy ions, etc.

3. It was unanimously agreed that eventual clinical trials must include the availability of a modern mega-voltage unit located on site in the Los Alamos area with the same team working on conventional and pion radiotherapy, thereby ensuring homogeneity of staging, care, observation and follow-ups.

4. Patient treatment will start at LAMPF when the radiotherapists have sufficient information. This may occur in 197? Human radiobiology will start earlier.
5. The Users Group concept does not appear to be an appropriate mechanism under which clinical trials can take place. It was designed for physics investigators who come for a time to perform specific experiments.
6. During the clinical trial phases, support should be sought for medical and other costs, including living expenses and transportation, over and above third party coverage.
7. During Phase I trials, patients rejected from other clinical trials should be sought as well as other referrals.
8. Phase II trials should receive support from the Radiological Physics Center, as do other national clinical trials coordinated by the Committee on Radiation Therapy Studies and/or the Radiation Therapy Oncology Group.
9. Fractionation schedule for clinical treatment may be 3-5 fractions per week over a 6- week period. The exact schedule will be determined after examination of data from experimental animal tumor systems, spontaneous tumors in animals and normal tissue responses in patients. The fractionation schedule need not be the same as for conventional radiations during the randomized prospective clinical trials phase.
10. Further recommendations for types of cases to be included in clinical trials will be forthcoming at later Committee meetings. Meanwhile, reference should be made to LA-4490-P, "A Proposal for a Biomedical Addition to the Los Alamos Scientific Laboratory's High-Flux Meson Physics Facility," pp. 132-134.
11. Recommendations for clinical staffing are given below:

	<u>FY 73</u>	<u>1974</u>	<u>1975</u>
Radiotherapists	1*	2	3-4
Radiologic Physicists (M. S. and Ph. D.)	1	2	3-4
Social Workers	0.5**	1	2
Secretaries	2	4	6
Treatment Planning Technicians	0.5	1.5	2
Nurses	0.5	1.5	2
Treatment Technicians (including mold room)	0.5	1.5	4
Transportation Arranger	0.5	1	1
Orderlies	0.5	2	4
Clinical Photographer	0.5	1	1

*Two beginning January 1973.

**One beginning January 1973.

G. Other Recommendations

1. Program plans and recommendations in all areas related to pre-therapeutic and therapeutic work with negative pi mesons be published in order to elicit comments or criticism by other investigators.
2. It is recommended that Peter Fowler be invited to Los Alamos.

INFORMAL DISCUSSION
by the
SUBCOMMITTEE on RADIATION THERAPY
Meeting held at LASL, November 8 - 9, 1971

Introductory Remarks - Louis Rosen

A proposal to AEC - NCI for pre-LAMPF work was written but withdrawn because it did not go far enough. Where do we go from here? There are funds from NCI for the channel, funds for A & E on building (OMB) and funds for planning (H-9). Biomed building could be available the end of CY 73. Control room, animal facilities and lab space to be placed in trailers. With funds in hand and committed, there is the capacity to proceed with radiobiology and animal experiments early in CY 73.

Biomedical Users form the largest group with the fewest proposals. Because of the AEC - NCI interagency agreement, the first priorities on the beam must focus on clinical trials. Two things are needed:

1. Overall program - basic research.
2. Structure for program - how to utilize talents to get clinical trials going?

We need an overall proposal that goes up to "clinical trials" that separates DBM and NCI responsibility. But individual project proposals to be accepted from anyone. The low energy pion channel will be available before biomed channel.

Powers: CRTS recommendations on mesons:

1. Clinical aspects only.
2. Trials national in scope.
3. Neutron studies can help pion program.
4. Need interactions between groups of people towards a programmatic approach.

Rosen: No one in the Biomedical Users group comes to LAMPF to work for weeks at a time as on other beam lines.

Kligerman: Last meeting was good but we all went home. We need to spend sabbatical leaves here and get started now.

Powers: Chronic and acute animal experiments for neutrons are needed now. Utilization of neutron sources at LASL in these areas would:

1. Get people at LASL.
2. Get program going.
3. Would provide useful data and experience for work with mesons.

Facility and Beam Line - R. Hutson

Neutron dose in patient may be a problem; it comes from three sources:

1. Pion stars.
2. Transmission through the shield.
3. Scattering along the pion beam channel.

Fluxes are unknown. Transmission through shield has $1/E$ spectrum. Scattered beam through the ducts has spectrum. We need to know how much neutron dose is tolerable. Electron contamination is expected to be 5 - 15% of pion flux; tradeoffs can reduce the amounts of contamination.

Oliver: M. D. Anderson and Rice have a proposal in to measure these contaminants.

Boone: The real problem with neutrons is fractionated RBE. Also, RBE's are very high for low dose levels.

Informal survey of those present on maximum allowable whole-body neutron dose:

Powers: <1% of pion dose.

Chahbazian: 5 rad/week.

Boyd: 10% of star neutrons.

Wiley: 10 rads total overall fractions.

Johnson: $\leq 5\%$.

George: 0.5% bad; 5% impossible.

Nickson: Problems of uniformity of whole-body dose.

Kligerman: <0.25%.

Groce: "Whole body" dose is very nonuniform -

1. Stars - $1/r^2$ dependence.
2. Background radiation will be less collimated than the pions.
3. Radiation penetrating the shielding will result in a uniform whole body dose.

Boyd: Dose from stars goes as treatment volume.

Recommendation passed: Total neutron dose to "whole body" should be kept below 0.5% of pion tumor dose. Above 5% would be impossible to do therapy.

Program at Stanford - Douglas Boyd

Superconducting linac and spectrometer are being built. The linac is a physics machine, 600' long, and will produce 2 BeV or 8 BeV electrons.

We now get 1.4 MeV/ft.

A future medical machine would give 1 mA of electrons at 500 MeV.

Target will be 1/4 radiation length of high Z material followed by 2 1/2 cm of graphite.

Spectrometer details: $\Delta\Omega = 1.5$ steradians; 60 sectors; 10^{15} n/cm²/year neutron flux for purposes of radiation damage; cost for spectrometer to be ~\$300K; time to build 1 1/2 years.

Purpose of the project is to test feasibility. Some radiobiology may be done. Four spectrometer units would go into Stanford University Hospital with a special accelerator.

Sixty radial overlapping beams will be used in a scanning mode. Monitored by multiwire proportional counter. Five feet of lead will be used to stop the neutrons.

NAL Protons and Pion Program - J. Nickson

Advantages for these programs at Chicago:

1. Large population base.
2. Many radiotherapists.
3. Injector at NAL only used 3% for physics.

Lester Skaggs, Warren Sinclair and others put together planning grant. Injector for protons; injector plus new accelerator sections for mesons.

Other Programs

TRIUMF - Proceeding one year behind LAMPF. Money may be a problem.

BNL - Hal Atkins - Proposal is complete. SIN - ?

Mercado - Lots of things could be started before January 1973. Proposals are needed as soon as possible.

Specific Clinical Problems

Powers - Phase I - Accessible lesions; multiple incurable lesions at different doses; patients not expected to live long but see degree of local control. Long term radiation response on animals needed: skin, kidney, gut, lung, brain, soft tissue, bone marrow, bone.

Phase II - Lesions in known volume that can be encompassed by beam; primary inoperable breast cancer.

Chahbazian: Agrees with Powers. In addition:

1. Tumors not dependent on oxygen factors.
2. Combined treatment and boost treatment.

3. Low dose levels for whole body irradiation.

Nickson: Phase I - Visible lesions; skin primary or secondary; head and neck nodes.

Phase II - Treatment volume well known; at least one year life expectancy; common tumors: advanced cervix, advanced bladder, breast(?).

Phase III - Common tumors: cervix III_B or maybe III_A; T3N2 tumors of head and neck.

Also uncommon tumors for Phases II and III on mid-line that are not handled well: pancreas, inoperable renal, esophagus, brain(?).

Kligerman: (Has list at home.) Phase I - Accessible and multiple lesions, lung (normal structure also), any incurable single lesions, soft tissue sarcoma.

Phases II and III - Bladder, prostate, cervix III and IV with lumbar irradiation, brain, stomach (not have to randomize everyone).

Phase III - Stage II tumors; lots yet to be done even for those which can be controlled when Stage I. Why do they fail?

Lower equivalent doses to treat regional metastasis.

Johnson: Additional thoughts:

1. Normal tissue response on hopeless individuals.
2. Better techniques - treatment table, immobilization and support techniques, patient data system.
3. Better methods of tumor localization.

Simmons: What to exclude from list: End point patients for Phase I. Not define Phases II and III programs yet.

George: Innovative patient handling systems for repositioning, immobilization and support, automation techniques.

Phase I - Neglected far-advanced lesions, i.e., head and neck, skin.

Phase II - Pions even used on lesions where good control now.

Others - Lymph node extensions; massive tumors.

Boone: Earlier list in LA-4490-P (green book); osteosarcomas and soft tissue tumors.

George: Dogs with advanced sarcomas; work at TAMVEC - fifty-five dogs already on neutrons.

Hutson: There is a stepwise sweep in depth. Average dose rate <20 rads/min; local dose rate higher, i.e., ~100 rads/min. A safe statement would be:

Over 15 x 15 x 12 cm³ ~20 rads/min.

Treatment Planning

Boone: Specific clinical situations and need to converse with channel people.

Hutson: Monoenergetic beam; pseudo-isotope curves.

Boyd: Calculated curves are OK.

Lundy: Computer control. Let's try to get work going; no existing system suitable. There are programming problems, i.e., what hardware to be there?

Powers: Dynamic treatment planning, i.e., 3-D planning?

Lundy: 2-D to start; 3-D later with optimization.

Kligerman: Plan for each possible problem. Some places have treatment records. Send all possible cases to LASL.

Lundy: This will be a full-time job; we have no manpower now. Perhaps in order to get the program working we need to get someone to come here.

Kligerman: Perhaps we can send someone from Yale.

Lundy: Treatment planning around the lung may be difficult because of variation in densities.

Powers: We'll need a sales job to get patients here. Lung patients might be willing to come. Planning should include: (1) hardware determinations; (2) how to treat patients. 42-MeV pencil beam at Chicago. We should check into how they do planning because it is analagous to our situation. We'll need to know what dose profiles we want across the tumor; two lesions with single plane. Tradeoffs: can't identify what we really want.

Kligerman: What dose do I want in the tumor; and where don't I want the dose to go?

Boone: We need a treatment plan with pions to do a better job.

Hutson: What is the ideal dose distribution?

Powers: Solution in therapy; optimization is better than criterion, but no good because of other things. We haven't defined what we really want.

Boone: We need a base line for comparison.

Kligerman: Let's start treatment planning.

Knapp: With neutrons too?

Chahbazian: This is a new tool and it will be more demanding in what to spare and what not to spare.

Lundy: RBE's complicate the case, plus fractionation.

Kligerman: UNM and LASL - still early. October 25 - seven days. No separation. Center construction grant November 1. H-Division needs to write proposal in better form. Must go further. Projects from recommendations for LRL and Nevis. December 1, 2, 3, 4 - Saunders January 1, late application for March council.

Hope to Do: Go further with recommendations in two ways -

Key and Kligerman from UNM and much to be done at LASL. Provide funds for other people to come here for two, six, twelve months and get other people to submit requests. Need an overall cover to handle project which should include everybody. Biology grant greater than two years; make it five years; the first year to be preclinical.

Powers: Short term grant should be preliminary to longer grant.

Kligerman: Only one portion of the program. Dosimetry and physics support needed for radiobiology, etc. Not all dosimetry to be on grant. Post care needs more dosimetry.

Mercado: Two - three-year period is better than five years.

Kligerman: Biology even after patients. What is to be covered: Staff has other things to do; more staff needs to be added; extra people should come here for months; should support projects here; should be centered in core people; staff here is the continuum. Should share problems to see how they're done, but get other people involved. Perhaps Voelz could assign a coordinator to resolve problems.

George: What about individual grants from funding agencies?

Kligerman: Users Group - program; Steering Committee - overall program. Priorities need to be assigned.

Knapp: Individual proposals are not enough.

Kligerman: Needs to be in blocks.

Boyd (or Kligerman?): Need a chairman for task force on neutron problem. Subsequent meeting of Therapy Committee; last week in March; card to Max after the 7th.

Lundy: Tumor localization is No. 1 problem in radiation therapy. If you can't identify it, you can't cure it; and if you can't see it, you can't treat it.

Kligerman: Brain tumors: good fixation but localization bad; do not know total extent.

Powers: Recognize microscopic extent not possible by physical means. What are manifestations of failures; what are mechanisms of failures?

George: Ga 100 x in tumors; use for therapy; or better isotope of Ga than ^{67}Ga .

Kligerman: Where to put diagnostic equipment?

Wiley to report to Steering Committee to form an interdisciplinary group.

Kligerman: Do not need interdisciplinary committee; need more innovative areas, i.e., immunochemistry, etc. We must expand existing committees and pump more oil faster over a broader oil field.

Wiley: We need a workshop.

Kligerman: First priority is to get going in other areas; second is workshop.

O'Brien: This group should come up with what areas of competence you want represented here.

Kligerman: This group is not prepared to recommend areas of competence.

SUGGESTION: Small groups on isotopes and therapy to look at problems of tumor localization and to set up workshop. PASSED.

Kligerman: We should use the first patients as sources of data. Ask them if they are willing to be experimented upon. Often terminal patients will say yes because finally they are able to contribute something and do not feel completely wasted; it's excellent psychotherapy.

Nickson: There may be trouble from politics.

Kligerman: We need normal tissue data.

MOTION: I recommend that Stage II preference to begin, rather than Stage I. Start patients very early to save time and money. Let's say plus or minus three months from animal studies; or plus or minus six months. Do not go through Phase I.

Boone: We'll have the channel in early 1973; the building in late 1973. But it will be a long time before parameters are known.

Kligerman: Important thing is do we have enough information so as not to harm patients; but do not start patients after animals, but along with them.

Groce: How about difference in personnel in handling patients and animals.

Kligerman: Presumably there will be no problem because the personnel will be experimentalists and interested in both.

Phase I is important in that it will allow development of fixation and staging techniques.

QUESTION: What about follow-ups? Effects of radiation after treatment?

RECOMMENDATIONS
of the
SUBCOMMITTEE for ISOTOPE DEVELOPMENT
and
DIAGNOSTIC APPLICATIONS

1. General Recommendations:

Subsequent to plenary subcommittee meetings of February 13, 1971 and June 27, 1971, the following recommendations are made:

- A. That the Los Alamos Medical Center radiological and nuclear medical diagnostic facilities be enlarged and equipped to be equivalent to the facilities of the major Albuquerque hospitals (see minutes of February 13, 1971).
- B. That the current state of the diagnostic accuracy of individual primary malignancies and secondary sites be evaluated with special identification of those areas in which diagnosis and/or staging is least accurate. This will create some priority for investigation using new radionuclides or methods.
- C. That spallation production and radiopharmaceutical chemistry of currently available, useful radionuclides (^{123}I , ^{18}F , etc.) be undertaken to identify methods resulting in decreased isotope cost, increased radionuclidic purity, and increased radiopharmaceutical specificity.
- D. That previously unavailable spallation-produced radionuclides be investigated intensively for localization propensity, labeling characteristics, gamma emission spectrum (ease of imaging) and patient dose.
- E. That development of new or improved methods of tumor tissue and meson deposition localization be encouraged (e.g. muonic X-ray emission, image-intensifier-vidicon TV system, multi-wire proportional counter system).

2. Use of NEVIS Facility:

Due to the availability of SREL for at least one further series of target irradiations, and the intermittent availability of the first 100 MeV of the LAMPF beam, and the availability of the LASL multiparticle cyclotron, the NEVIS facility will not be used for isotope investigation.

3. Initial Studies: (1971-72)

Physical interaction studies in thick targets has been and will continue to be done at SREL. This work is almost complete.

4. Intermediate Studies: (1971-73)

- A. Utilization of the multiparticle cyclotron for production of currently available nuclides which can eventually be produced (e.g., ^{18}F) more efficiently by spallation will begin in 1971. This will allow for establishing radiopharmaceutical techniques necessary for achieving credibility with the Food and Drug Administration.
- B. Intermittent utilization of the 100 MeV LAMPF proton beam will allow for testing of target materials, and production of sufficient quantities of certain radionuclides for establishing radiochemical separation and purification techniques. If sufficient material of this type is available radiopharmaceutical studies can be undertaken as well (e.g., ^{123}I).

5. Final Studies: (1972-77)

Utilization of the full LAMPF proton beams for spallation-production of radionuclides:

- A. Measurement of yields of certain radionuclides using various targets.
- B. Chemical separation of radionuclides of interest from the myriads produced.
- C. Establishment of pharmaceutical purity of radionuclide preparations and investigation of their properties.

SENIOR MAN YEARS OF EFFORT (CALENDAR YEARS)

Isotope Development and Diagnostic Applications - LAMPF

	<u>1971</u>	<u>1972</u>	<u>1973</u>	<u>1974</u>	<u>1975</u>	<u>1976</u>	<u>1977</u>	<u>TOTAL</u>
1. Thick target effects	0.8	0.1						0.9
2. Multiparticle cyclotron production	0.2	0.5	0.2					0.9
3. 100 MeV LAMPF beam	0.1	0.5						0.6
4. 800 MeV LAMPF beam	0.1	0.4	1.5	2.0	2.8	3.0	3.0	12.8
5. Muonic X-rays	0.05	0.05	0.1	0.1	0.2	0.2	0.2	0.9
6. Image intensifier TV camera and other imaging devices		0.5	0.5	1.2	1.0	1.0	1.0	5.2
TOTAL	1.25	2.05	2.30	3.3	4.0	4.2	4.2	21.3

DISCUSSION of ISOTOPES
by the
DIAGNOSTIC APPLICATIONS and ISOTOPE SUBCOMMITTEE

Meeting held at LAMPF, February 25 - 26, 1972

After a tour of the LAMPF facility the subcommittee discussed disease states or radiopharmaceuticals that need to be considered first. They discussed strontium (any medium half-life isotope of it); In-111, Fe-52; uses of the rare earth elements (not good for imaging, primarily for investigating the rare earths); possibility of producing a fairly short-lived isotope (400 keV) that would localize in bone.

Hal O'Brien asked the committee if they anticipated saving the Xe-127 when doing pulmonary ventilation studies. Trow said he did not think it would be practical to reuse it.

Shoop suggested that very short $T_{1/2}$ rubidium would be useful in timing of peripheral angiography, especially if one wanted to repeat the procedure. Technetium is used now but one has to wait a long time between repeats.

Discussion of Priorities of Isotopes

1. Iodine-123 seems to be the first priority.
 - a. Would need minimum of .5 mCi to 1.0 mCi to be worth shipping.
 - b. Twenty-six hour interval not necessary between manufacture and use.
 - c. It appears like there could be adequate financial return from making and selling I-123.
 - d. Need to resolve what thyroid looks like with lower energy photons than with I-131.
 - e. How researchers would like the iodine was decided at slightly basic pH 8-9, NaOH and H₂O in as little liquid as possible.
2. Xenon-127
 - a. We would need minimum of .5 millicuries per animal to be worth shipping; would buy if available.
 - b. Canadians have done several studies with Xe-127.
 - c. Everyone has agreed it would be useful.
 - d. O'Brien: We don't know what our yields of xenon will be.
 - e. Very shippable.

3. Gallium-67

- a. Significant amount will not be produced at first because you can buy it (now limited to suppliers and that is very expensive).
- b. Does not look like there would be important financial remuneration; can make gallium pure at LAMPF.

4. Other Isotopes

- a. Production facility should consider expanding list and pointing out all the radionuclides that can be made available. Time to look at radionuclides which we have never been able to get. Tend to look at new nuclides in terms of what we already know - - have to look at things that are most promising and have to stab in the dark.
- b. Los Alamos will have to prove cost benefit. Must determine what things can be produced in high yield like scandium.
- c. Rubidium is potentially saleable but no research has gone into it. This applies to other isotopes on list too.
- d. Anything we use will have to have radionuclidic purity and consistent preparation.
 - 1) Different methods = control problems; solution?
 - a) Make up cold kits so that everybody has the same kit to work with.
 - b) Have UNM make it in a radiopharmaceutical for everyone and ship it out.

5. Isotope Availability

- a. Both companies and individuals should be able to buy small quantities of isotopes.
- b. A broad license will be necessary if one doesn't have one, start working on it.
- c. Will have to have capability to do the separation.
- d. Will have to get clean products in order to do clinical trials.
- e. Will availability be limited to the members of the committee? Some good groups aren't represented. Solution?
 - 1) Could invite these other people to join the committee.
 - 2) Could assign task groups for each radionuclide.

This question led to the following discussion of who should get the isotopes and of setting up a protocol for initial evaluation of LAMPF radionuclides.

6. Isotope Protocol

- a. Individual protocols should include:

- 1) Quantity needed and time scale of need.
- 2) What project planned with it.

- b. Review committee should be set up (should be working group by next time this subcommittee meets).

Brown: Motion that this committee should form another subcommittee with members from this committee and from outside.

O'Brien seconded motion.

Motion passed unanimously.

- c. Isotopes need to be dispensed to people best able to use them - - may have to defend this on some occasion. Review committee would have prerogative to decide.

This committee will suggest to Dr. Rosen that a committee be formed, give him a list of names for staffing it, and let him choose the membership, but it is important to keep the membership national.

Volunteers for membership from this committee: Don Brown, W. Wolf, Hupf, Keese, Mishkin, O'Brien.

Suggested (will have to be contacted): G. Subramanian, Y. Yano, J. Burdine, A. Gottshalk, M. Blau, G. Johnston, Henry Wagner, and W. Nelp.

These names will be submitted to Dr. Rosen, fourteen total, maybe seven of whom will be able to serve.

- d. This new review committee will have prerogative to announce when they are ready to receive protocols. This could be done via advertising in Nuclear Medicine Journal, etc. Review committee could meet in the fall with Users Group. By then they could lay down ground rules.

7. Comments

- a. Several members of the committee expressed concern about getting too formalized. Dr. Shoop pointed out that the structure must be formalized ahead of time for determining isotope distribution so that when the isotopes are ready they can be used. Coordination is also needed for work with the various isotopes - - that also results in formalizing.

- b. O'Brien said he would like to see recommendations to coordinate efforts. For example, three research groups getting equal quantities of an isotope so that work is carried on simultaneously on the same problems with results coming out at the same time.
- c. Shoop suggested that basic ground rules be established:
 - 1) As long as production is sporadic, there will be -
 - a) No cooperative studies established.
 - b) Rotational system of isotope distribution.
 - 2) When production is no longer sporadic, cooperative studies can then be set up, viz, protocols and review committee.
- d. The need for close cooperation and collaboration with Brookhaven was also discussed. Brown made a motion that this committee recommend much closer communication and cooperation between Brookhaven and LASL as far as isotope production is concerned. He suggested that this be initiated with a letter and a meeting between members of this committee and people at Brookhaven, possibly around the time of SNM meeting in Boston, July 11-14, 1972. The motion passed unanimously. As chairman of the subcommittee, Dr. Shoop will write a letter endorsed by the membership of the committee. It will be sent to Lou Stange, head of the hot lab division at Brookhaven with copies to Dr. Rosen, George Vineyard (deputy director at Brookhaven), and to Flairty, assistant general manager of AEC.
- e. Will wait for response from Brookhaven before scheduling next subcommittee meeting, since that will be the next time that some members of the subcommittee will be able to get together. Otherwise, will plan for the committee to meet a year from now.

CALCULATED
ISOTOPE YIELDS FROM LAMPF*

(TARGET 6 in. diam x 1 in. thick; PROTON ENERGY = 700 MeV; CURRENT = 0.40 mA)

Product	Target	Bombardment Time	Yield (Ci)	Comments
13-h ^{123}I	La	2 h	7.6	Lower radiation dose to patients
36-d ^{127}Xe	La	36 d	91.	Better nuclide than ^{133}Xe for lung scans
3.3-d ^{67}Ga	As	3 d	58.	Soft tissue scanning agent
280-d ^{68}Ge	As	36 d	6.7	Parent of short-lived positron emitter ^{68}Ga
105-d ^{88}Y	Mo	36 d	47	New higher energy photoneutron source
25-d ^{82}Sr	Mo	36 d	194.	Parent of short-lived ^{82}Rb for heart scans
83-d ^{83}Rb	Mo	36 d	113.	Useful in muscular dystrophy
120-d ^{113}Sn	In	36 d	2.5	More economical source of proven medically useful nuclide
2-y ^{172}Hf	Ta	36 d	13.	Parent of a general purpose rare earth tracer nuclide
10-d ^{186}Pt	Pb	10 d	86.	Potentially useful medical nuclide

*Calculations were made by Hal O'Brien.

FINAL BEAM LINE DESIGN

R. L. Hutson

1. Physical Description

The biomedical facility stubout structure is located to the east of LAMPF experimental Area A. The biomedical channel pion production target is in the accelerator beam and is centered within the stubout structure. Pions emitted from the target at an angle of approximately 70° with respect to the proton beam are transported to the patient through the quadrupole and bending magnets which constitute the channel. The pion beam will come down from above to irradiate the patient (see Figs. 8 and 9).

A carbon water-cooled pion production target approximately 5 cm long is used and is inserted into the proton beam only during the time that a pion beam is required. The magnets of the channel are tuned to transport pions within a restricted energy range out of the total spectrum of pions being emitted from the target. These pions are focused just beyond the second bending magnet by the first three quadrupoles. The first two bending magnets cause the higher energy pions to be focused at one position, as measured transverse to the central axis of the beam, while the lower energy pions are focused at a different position. In order to reduce the energy of all pions to the same value, a wedge of beryllium is placed at the focus and oriented so that higher energy pions pass through thicker sections of material than do lower energy pions. The variation of thickness passed through as a function of pion energy is adjusted so that all pions come out of the wedge with the same energy. Now it appears that the wedge of beryllium acts as a large source of almost monoenergetic pions. The third bending magnet bends the beam to a vertical direction, and the five quadrupole magnets at the end shape the beam as desired. Having the large number (5) of quadrupoles at the end is necessary to keep the beam relatively small within the magnets so that the beam is not scraped off while shaping the beam.

There is a triple redundancy in the beam cutoff system: Whenever the pion beam is to be turned off, beam stops are inserted ahead of the first bending magnet and after the last one. The pion production target is pulled out of the proton beam at the same time. To shield the control room and adjacent areas from the intense flux of neutrons from the target, approximately 10 feet of steel are stacked around the target.

2. Mode of Operation

For most irradiations the beam will be shaped into a fan, narrow (≈ 1.5 cm) in the direction perpendicular to the plane of the pion channel and wide (≈ 15 cm) in the other direction (see Figs. 10 and 11). Since the beam is approximately

monoenergetic, all pions will stop at approximately the same depth. The result is that the pions will all be stopping in tissue in a sausage-shaped volume approximately 15-cm in length and 1.5 cm in diameter.

In order to distribute the stopped pions over a range of depths, a range shifter will be put into the beam just above the patient. This range shifter is nothing more than a slab of material such as water or Lucite, which will reduce the energy and, therefore, the range of the pions passing through. The thickness of the range shifter can be varied as a function of time such that any desired depth-distribution of stopping pions is obtained. There will also be independently-controlled collimator jaws above the patient to define the width of the fan. Their position will be varied in conjunction with the range shifter thickness so that the width of the pion stopping region can be controlled as a function of depth.

Only a vertical slab-shaped pion stopping volume has been defined so far. To add the third dimension, perpendicular to the slab, the patient will be translated slowly (~ 1 to 2 cm/min) in this direction while the range shifter is adjusted to scan the stopping volume through the required depth interval - - typically every few seconds. With this mode of operation, it will be possible to deliver the pion dose to a volume with complex boundaries. The scheme outlined above is conceptually simple and offers considerable flexibility in dose-distribution control.

3. Beam Characteristics

With 0.5 mA of protons incident on a 5-cm thick carbon target, the average dose rate in a 10^3 cm^3 volume is approximately 35 rads/min. Dose rates will be approximately inversely proportional to the volume treated so that extrapolations to other than 10^3 cm^3 volumes can be made readily. There is the capability of treating volumes having field sizes as large as 15 x 15 cm and thicknesses as great as 12 cm.

In addition to the slight spread in stopping depths caused by the small spread of energies, there will be range straggling which will add somewhat more to the range of stopping depths. For example, in a case studied already, if the distal surface of the pion stopping volume is at a depth of 20 cm, the combination of energy spread and straggling will result in a distance of approximately 2.2 cm between the 90% and 10% isodose curves. This distance will be decreased by further optimization of the configuration of the beryllium wedge energy degrader.

The sharpness of the lateral boundaries of the stopping region are limited by multiple Coulomb scattering (MCS) of pions in tissue and by the fact that at any point in the pion beam the pion trajectories have a spread of angles. The latter effect can be determined only through extensive ray-tracing calculations for each case considered. However, this effect alone would typically result in falloff distances between the 90% and 10% isodose curves of approximately

2 cm at the lateral boundaries. MCS alone would result in a falloff distance of 2.8 cm at a depth of 20 cm. The two effects combined result in a falloff distance of the order of 3.7 cm. Electron contamination of the beam will be less than 10%, and muon contamination will be approximately 5%.

DRAWINGS of the FINAL BEAM LINE

- Fig. 8:** The biomedical beam line is shown: It consists of 3 quadrupoles, followed by 3 bending magnets, and ends with a set of 5 quadrupoles.
- Fig. 9:** Selected optical rays of pions are shown going from the target through the channel to the patient.
- Fig. 10:** Treatment volume shaping with the fan-shaped beam.
- Fig. 11:** Schematic drawing showing simultaneous scanning with a variable absorber and a moving couch.

Figure 8

Figure 9

THE LOS ALAMOS MESON PHYSICS FACILITY
BIOMEDICAL PION CHANNEL

Figure 10

TREATMENT VOLUME SHAPING WITH FAN BEAM—A RAPID VERTICAL SCAN OF STOPPING REGION IS ACCOMPANIED BY A SLOW TRANSLATION OF THE PATIENT PERPENDICULAR TO THE PLANE OF THE FAN

Figure 11

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**PION IRRADIATION WITH FAN BEAM
(LAMPF BIOMEDICAL FACILITY)**

ORGANIZATIONAL MEETING
of the
SUBCOMMITTEE on TUMOR LOCALIZATION and TREATMENT SIMULATION

Meeting held at LAMPF, September 21 and 22, 1972

The meeting was called to order and all present introduced. Members of the Subcommittee in attendance were Phillip N. Dean, Alternate Chairman; A. Bertrand Brill; C. J. Karzmark; David Kuhl; Victor Perez-Mendez; Gordon Potts; James J. Reidy; and Chaim Richman, ex officio.

Dr. Morton Kligerman, Assistant Director for Radiation Therapy, LASL, and Director, Cancer Research and Treatment Center, UNM School of Medicine, briefed the Subcommittee on the biomedical program planned at Los Alamos. He pointed out that this Subcommittee was formed at his insistence because of his great concern for the stringent requirements expected to be placed on accurate tumor localization. He feels that the development of methods of accurately localizing tumors is as important as the entire meson biomedical effort. In the past, diagnostic radiology provided tumor localization information. Now reliance is on nuclear medicine techniques. Tumors are not well defined geometrically, and in the past definition of the treatment volume has been rather gross, with the penumbra of the radiation field used to treat filaments of the tumor. The well-defined character of the negative pion beam has forced us to be more careful in defining the treatment volume. Small errors in positioning the beam relative to the tumor could easily result in failure of the treatment. Protection of organs outside the treatment volume also puts stringent requirements on locating not only the tumor but normal structures as well.

Darragh Nagle, Alternate Division Leader, Medium Energy Physics Division, gave a description of physics techniques now in use in biomedical studies. These include nuclear magnetic resonance, electron paramagnetic resonance, etc. He also gave a status report on the accelerator.

Dick Hutson, MP-3, described the physical parameters of the beam. He estimated that 30% of the pions emitted at the target will pass through the beam channel, yielding instantaneous dose rates of about 2000 rads/min in the scanning beam. The only effort to reduce electron contamination was in selection of the production angle. The expected contamination is 10% e^- and 5% μ^- . The geometry of the beam and patient was described, along with the methods expected to be used to vary range and shape of the beam.

A discussion was then held to decide the specific purpose of this initial meeting of the Subcommittee and to set an agenda for the rest of the meeting. It was decided that the meeting was primarily organizational in nature and served to introduce the members to one another. It also could serve to define the scope of the Subcommittee. Topics to be discussed:

1. The job of the Subcommittee.

2. The compilation of a pertinent bibliography.
3. The patient-handling program and its impact on the facilities requirements.

It was decided that before the Subcommittee could act effectively certain information must be provided by the therapists. This information is:

1. Tumor type and site in order of priority.
2. Present method of study for the above tumors.
3. How well things are being done now.
4. Who is going to do the diagnostics and where.
5. Current facility and supporting services.
6. Specific goals from radiotherapists.
7. Histology, who and where.
8. Are metastases to be treated.
9. Localization bibliography - - tumor and beam terminus.

More discussion brought the following comments from the Subcommittee, having to do with facilities requirements and possible new areas of research.

A. Essential items for LASL

- 1) Activation counters (cameras) and counters for beam localization during irradiation.
- 2) Simulator with diagnostic radiographic capability.
- 3) Transverse tomography.
- 4) Emergency care for patients.

B. New ideas that may be useful for plans

- 1) Elemental analysis by mesic (π^- or μ^-) x-rays.
- 2) Transmission and emission transverse section scanning.
- 3) Doping tumors with stable isotopes - - fluorescent excitation.
- 4) High resolution cameras, both spatial and energy.
- 5) A simulator that produces diagnostic information in the actual scales used in planning.

The simulator and treatment table should have the same geometry in great detail. A coordinate system must be selected, with cross-sections of the patient, to get good anatomical detail.

There was much discussion on whether or not LASL should have all of this specialized equipment; obviously it should have some of it. Should the UNM School of Medicine have a full set of all equipment? No present radio-therapy facility specializes in all these fields. The handling of control patients, who will not travel to LASL, must be considered. A decision needs to be made and given to this Subcommittee.

Some discussion was held on specifying the required accuracy in positioning the beam and in localizing the tumor. Again, the Subcommittee needs input from the therapists. The accuracy required depends on the type of tumor and its site. It appears that positioning of the beam is accurate to about ± 3 mm or better. It was felt that no tumor can be located repeatedly to better than about 0.5 cm.

It was a unanimous recommendation of this Subcommittee that the therapists severely limit the types of tumors to be treated and define them as soon as possible. It was further recommended that the therapists be reminded of the increased advantages of multiple ports in reducing normal tissue effects. This is especially true in treating brain tumors in young people.

Question for Facilities Subcommittee: Will we be able to treat a seated patient?

RECOMMENDATIONS of the SUBCOMMITTEE

1. The therapists should severely limit the types of tumors to be treated and define them as soon as possible.
2. The therapists should be reminded of the increased advantages of multiple ports in reducing normal tissue effects, especially in treating brain tumors in young people.
3. The Facilities Subcommittee should investigate the possibility of treating seated patients.
4. A decision should be made as to where diagnostic information (Patient work-up) will be obtained and this information communicated to this Subcommittee. It is required before specific recommendations for facility requirements can be made.
5. The therapists are requested to provide the following information to this Subcommittee:
 - a. Tumor type and site in order of priority.
 - b. Present method of study for the above tumors.
 - c. How well things are being done now.

- d. Who is going to do the diagnostics and where.
- e. Current facility and supporting services.
- f. Specific goals of the radiotherapists.
- g. Histology, who and where.
- h. Are metastases to be treated.

OUTLOOK for the WORK

After all of these meetings and discussions a few final comments are not out of order; especially, about some things that have emerged as being of unusual importance for the program.

It is clear to all concerned that the biomedical beam line is at the heart of the program and it is fortunate that an extensive body of knowledge and experience exists in beam optics and magnet design which will serve to produce a good beam channel. We are on less sure ground on the question of electron contamination, and therefore one of the first objectives of the beam diagnostic experiments will be to study the beam and find ways to minimize the number of electrons if it should turn out to be excessive.

An essential study around any high current machine like LAMPF is the neutron flux around the machine. This is a problem of Health Physics and this flux will be monitored as the proton current is increased from one microampere to one milliampere. An associated question is how many neutrons stream down the open biomedical channel. This has been studied by M. E. Schillaci². For this purpose he has used the Los Alamos Nuclear Monte-Carlo Transport Code (NMTC), and the results are that very few neutrons get to the patient -- about $10^3 - 10^4$ neutrons/second over the entire area of the beam. This number is small compared to the neutrons produced in the patient by the stopped pions and can therefore be neglected.

We turn now from the machine and the beam line to the areas of dosimetry and radiobiology. What stands out here is the fact that the radiobiological data on RBE will depend on how the scanning is done and the fraction of high and low LET dose in the beam. It is important therefore that a monitoring system be available to check the scanning procedure in this respect. This emphasizes the close link that exists here between the details of the dosimetry and the radiobiology.

In the area of cellular radiobiology, the recommendations for pretherapeutic experiments are aligned to conform to the direction provided by the therapists. In general, it has been recommended that (1) Mammalian cells in culture be utilized to confirm the spatial and radiobiological features of pions that have been predicted by physics and dosimetry.

²M. E. Schillaci, Neutron Streaming in Bio-Med Channel, LAMPF Internal Report

(2) The radiobiological responses to pions of an in vivo clonogenic cell system be evaluated in depth. (3) That the response to pions of a slowly growing transplantable solid tumor in rodents be investigated, comparing related tumor types that do and do not reoxygenate and using irradiated tumor-bearing animals for evaluation of normal tissue responses.

In the area of mammalian radiobiology a large program is now envisaged at Los Alamos to study the response of the following tissues: brain and spinal cord, heart, kidney, skin, lung and esophagus, and colon.

In the area of radiotherapy two lessons have come to all of us: The first is the need for better localization of the tumor-bearing tissue. One of the good results of working with pions is that it is forcing us to ask for better information on the location of the tumor. The second lesson is related to the first: We need to know the properties of the tissues between the skin and the tumor, for the stopping of a pion in a given region is dependent on the path it has taken to arrive at the tumor-bearing tissue.

One of the most interesting recommendations made by the whole animal and radiation therapy subcommittee is to have a program for the treatment of spontaneous tumors in dogs. Many canine tumors are also found in humans and this will provide a link between the experiments on tissue response in animals and the treatment of human neoplasms. Such a program has also been proposed by the M. D. Anderson and Texas A & M group studying neutron therapy. At Los Alamos this would mean that a referral arrangement will have to be organized with the small-animal practices in a large surrounding area to provide the clinical material.

We cannot bring these recommendations to a close without a final word about the need for a sense of cooperation and partnership between the off-site user and the staff at Los Alamos: In a program as large and as diverse as this, much of the knowledge and experience needed exists around the country in various laboratories and hospitals. It is the hope and sense of the committees that good working relationships will be established with these places so that this program proceeds easily and effectively toward its goal of improving radiation therapy.